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Research Findings - Basic Neuroscience Research

RGS9-2 Signaling Partners

Regulators of G protein signaling (RGS) are known to bind to G alpha proteins, speeding the process of GTP hydrolysis and terminating the signaling pathway in which the GPCR participates. Based on immunoblotting and immunoprecipitation results, the RGS9-2 protein, highly expressed in the striatum and nucleus accumbens, forms a tertiary complex with the G protein Gbeta5, and with R7BP (R7 binding protein) at distinct binding regions of RGS9-2. Certain details about the stoichiometry of this complex are understood: Gbeta5 is necessary for the constitutive expression of RGS9-2, and these two partners are expressed in direct proportion, i.e., both their expression levels increase, or decrease together, as in the case of R7BP being absent in a R7BP knockout mouse species. The binding of R7BP may aid in targeting RGS9-2 to post-synaptic neuronal regions, and may also contribute to the stability of the RGS9-2/Gbeta5 complex. RGS9-2 has been studied as a regulator of dopamine and opioid (mu receptor) signaling in the animal brain. RGS9-2 levels are decreased in rats chronically self-administering cocaine, and RGS9-2 knockout mice have increased sensitivity to the rewards of morphine (lower doses) in place conditioning experiments, compared to wild type mice. RGS9-2 knockout mice show enhanced withdrawal symptoms following morphine administration. Dr. Martemyanov and his associates at the University of Minnesota have carried out a quantitative proteomics study to detect changes in the proteins that complex to RGS9-2 when R7BP is absent, using the R7BP knockout mouse. Three striatal brain samples were used: a wild type, an R7BP knockout sample, and, for control purposes, an RGS9-2 knockout sample to detect non-specific interactions in the absence of RGS9-2. Following immunoprecipitation to obtain proteins from the samples, each sample was treated with trypsin to produce fragment peptides, which were derivatized with three different isotopically-labeled tags, samples were combined, separated by LC, and analyzed by mass spectrometry. RGS9-2 interaction with Gbeta5 was confirmed, and, in the absence of R7BP in the complex, twenty-one new binding partners of RGS9-2 were identified as being upregulated, including the heat shock chaperone protein Hsc70. Hsc70 was absent (no immunoprecipitation) in RGS9-2 knockout samples, and in R7BP knockout striatal tissue, increasing in amount when R7BP was absent. The binding of Hsc70 protein was found to take place at a C-terminus peptide fragment of RGS9-2. When Hsc70 was "silenced" by siRNA for Hsc70, the RGS9-2 expression increased 17%, based on Western blotting analysis. Therefore, Hsc70 negatively regulated the RGS9-2 expression. Although the mechanism of Hsc70 action is not known presently, Hsc70 may serve to regulate RGS9-2 by targeting a RGS9-2 complex into lysosomes, where it can be degraded. Posokhova E, Uversky V, Martemyanov KA. Proteomic identification of Hsc70 as a mediator of RGS9-2 degradation by in vivo interactome analysis. J Proteome

Res 2010; 9(3): 1510-1521.

Negative Allosteric Modulators that Target Human α4β2 Neuronal Nicotinic Receptors

Allosteric modulation of nicotinic acetylcholine receptors (nAChRs) is considered to be one of the most promising approaches for therapeutics. The present authors previously reported on the pharmacological activity of several compounds that acted as negative allosteric modulators (NAMs) of nAChRs. In this publication the effects of 30 NAMs from the authors' small chemical library on both human α4β2 (Hα4β2) nAChRs and human α3β4 (Hα3β4) nAChRs expressed in HEK ts201 cells were investigated. Using calcium accumulation assays, these NAMs inhibited nAChRs activation with IC50 values ranging from 2.4 µM to greater than 100 µM. Several NAMs showed relative selectivity for Hα4β2 nAChRs with IC50 values in the low micromolar range. A lead molecule, KAB-18 was identified that showed relative selectivity for Hα4β2 nAChRs. This molecule contains 3-phenyl rings, 1 piperidine ring, and 1 ester bond linkage. Structure-activity relationship (SAR) analyses revealed 3 regions of KAB-18 that contributed to its relative selectivity. Predictive 3D-QSAR (comparative molecular field analysis and comparative molecular similarity indices analysis) models were generated from these data and a pharmacophore model was constructed to determine the chemical features that were important for biological activity. Using docking approaches and molecular dynamics on Hα4β2 nAChR homology model, a binding mode for KAB-18 at the α/β sub-unit interface that corresponded to the predicted pharmacophore was described. This binding study was supported by mutagenesis studies. In summary, these studies highlight the importance of SAR, computational, and molecular biology approaches for the design and synthesis of potent and selective antagonists targeting specific nAChR sub-types. Henderson BJ, Pavlovicz RE, Allen JD, Gonzalez-Cestari TF, Orac CM, Bonnell AB, Zhu MX, Thomas Boyd R, Li C, Bergmeier SC, McKay DB. Negative Allosteric Modulators that Target Human α4β2 Neuronal Nicotinic Receptors, J Pharmacol Exp Ther. 2010, Jun 15. [Epub ahead of print].

Molecular Mechanisms Involving Cocaine/Sigma Receptor-Mediated Induction of MCP-1: Implication For Increased Monocyte Transmigration

Cocaine abuse hastens the neurodegeneration often associated with advanced HIV-1infection. The mechanisms, in part, revolve around the neuroinflammatory processes mediated by the chemokine monocyte chemotactic protein-1 (MCP-1/CCL2). Understanding factors that modulate MCP-1 and, in turn, facilitate monocyte extravasation in the brain is thus of paramount importance. These researchers demonstrate that cocaine induces MCP-1 in rodent microglia through translocation of the sigma receptor to the lipid raft microdomains of the plasma membrane. Sequential activation of Src kinase, mitogen-activated protein kinases (MAPKs), and phosphatidylinositol-3' kinase (PI3K)/Akt and nuclear factor kappaB (NF-kappaB) pathways resulted in increased MCP-1 expression. Furthermore, conditioned media from cocaine-exposed microglia increased monocyte transmigration, and this was blocked by antagonists for CCR2 (MCP-1 receptor) or sigma receptor. These findings were corroborated by demonstrating increased monocyte transmigration in mice exposed to cocaine, which was attenuated by pretreatment of mice with the sigma receptor antagonist. Consistently, cocaine-mediated transmigratory effects were not observed in CCR2 knockout mice. It was concluded that cocaine-mediated induction of MCP-1 accelerates monocyte extravasation across the endothelium. Understanding the regulation of MCP-1 expression and functional changes by cocaine/sigma receptor system may provide insights into the development of potential therapeutic targets for HIV-1-associated neurocognitive disorders. These findings have implications for cocaine abusers

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with HIV-1 who are known to have increased risk of stroke and CNS-associated inflammation. These findings suggest that sigma receptor antagonists could be considered as adjunct therapeutic agents for the treatment of cocaine addicts infected with HIV. Yao H, Yang Y, Kim KJ, Bethel-Brown C, Gong N, Funa K, Gendelman HE, Su TP, Wang JQ, Buch S. Molecular mechanisms involving sigma receptor-mediated induction of MCP-1: implication for increased monocyte transmigration. Blood 2010; Jun 10; 115: 4951-4962.

A Programmable Transdermal Patch for Delivering Nicotine Via Carbon Nanotubes (CNT) Membranes

Dr. Bruce Hinds and his colleagues at the University of Kentucky have developed a small skin patch that is cable of delivering nicotine in a controllable manner by turning on or off a minute electrical current across a permeable membrane. The heart of this device is based completely on new nanotechnological approaches. CNTs crossing a solid polymer film are the active layer that can be switched with the voltage. The CNTs are a truly unique material system with atomically flat and chemically inert graphite planes rolled into tubes 1.5-7 nanometers in diameter. Work in the Hinds' group showed that this allowed fluid flow 10,000 times faster than in pores of similar size. In addition, the nanotubes are electrically conductive and a single layer of charged chemistry can be placed at the pore entrance. This closely mimics the principles of ion channel proteins that regulate the flow of ions into and out of cell walls. Constructing robust human-made platforms over large areas with each pore having the same performance as natural protein channels is a grand challenge of nanotechnology with far-reaching impact wherever the control of selective chemical transport is needed (i.e. pharmaceutical synthesis, sensing, drug delivery, energy storage). When connected to a nicotine reservoir, these CNT patches were shown by Dr. Hinds to successfully switch between high and low concentrations on human skin consistent for effective nicotine cessation treatment. These controllable CNT patches have the potential to be developed to deliver other compounds for drug abuse treatments as well as nicotine. Wu J, Paudel KS, Strasinger C, Hammell D, Stinchcomb AL, Hinds BJ. Programmable transdermal drug delivery of nicotine using carbon nanotube membranes. PNAS 2010; 107(26): 11698-11702.

Heroin Use or Heroin Use Plus HCV Infection Impairs CD56+ Cell-Mediated Innate Immune Function

Ho and colleagues examined 37 heroin users with (17) or without (20) HCV infection. In addition, 17 healthy subjects were included in the study. Although there was no significant difference in CD56+ T cell frequency in PBMCs among three study groups, CD56+ T cells isolated from the heroin users had significantly lower levels of constitutive interferon-gamma (IFN-c) expression than those from the normal subjects. In addition, when stimulated by interleukin (IL)-12, CD56+ natural T cells from HCV-infected heroin users produced significantly lower levels of IFN-c than those from the normal subjects. This diminished ability to produce IFN-c by CD56+ T cells was associated with the increased plasma HCV viral loads in the HCV-infected heroin users. Investigation of the mechanisms showed that heroin use or heroin use plus HCV infection induced the expression of suppressor of cytokine signaling protein-3 (SOCS-3) and protein inhibitors of activated STAT-3 (PIAS-3), two key inhibitors of IL-12 pathway. These findings provide in vivo evidence that heroin use or heroin use plus HCV infection impairs CD56+ T cell-mediated innate immune function, which may account for HCV infection and persistence in liver. Ye L, Wang X, Metzger DS, Riedel E, Montaner LJ, Ho W. Upregulation of SOCS-3 and PIAS-3 Impairs IL-12-Mediated Interferon-Gamma Response in CD56+ T Cells in HCV-Infected Heroin Users. PLoS ONE. 2010 March; 5(3): 1-10.

Dopamine Modulates the Action of Endocannabinoids In the Brain (Prefrontal Cortex) Which May Contribute to the Change In Neuronal Activity That Underlies Cannabinoid (THC)-Produced Neuropsychiatric Disorders

Dopamine (DA) and cannabinoids strongly influence prefrontal cortical functions, such as working memory, emotional learning, and sensory perception. Although endogenous cannabinoid receptors (CB(1)Rs) are abundantly expressed in the prefrontal cortex (PFC), very little is known about endocannabinoid (eCB) signaling in this brain region. Recent behavioral and electrophysiological evidence has suggested a functional interplay between the dopamine and cannabinoid receptor systems in mid-brain areas, but it is unknown whether a functional interaction also occurs in the PFC. This paper provides data to support a functional interaction. Using immunoelectron microscopy, it was shown that CB(1)Rs and dopamine type 2 receptors (D(2)Rs) colocalize at terminals of symmetrical, presumably GABAergic, synapses in the PFC. Furthermore, activation of either receptor suppresses GABA release onto layer 5 pyramidal cells. Co-activation of both receptors triggers eCB-mediated long-term depression of inhibitory transmission (I-LTD). D(2)Rs most likely facilitate eCB signaling at a presynaptic site because disrupting postsynaptic D(2)R signaling does not diminish I-LTD. Therefore, facilitation of eCB-LTD may be one mechanism by which DA alters the balance between excitatory and inhibitory neuronal activity in the PFC to produce PFC-mediated behavioral deficits and cannabinoid-induced neuropsychiatric disorders. Chiu CQ, Puente N, Grandes P, Castillo PE. Dopaminergic modulation of endocannabinoid-mediated plasticity at GABAergic synapses in the prefrontal cortex. J Neurosci. 2010 May 26;30(21): 7236-7248.

Repeated Stress Differentially Alters the Signaling of Two Endocannabinoids: Anandamide (AEA) and 2-Arachidonoylglycerol (2-AG) Ligands In the Brain to Regulate the Neuroendocrine Response to Stress

Secretion of glucocorticoid hormones during stress produces an array of physiological changes that are adaptive and beneficial in the short term. In the face of repeated stress exposure, however, habituation of the glucocorticoid response is essential as prolonged glucocorticoid secretion can produce deleterious effects on metabolic, immune, cardiovascular, and neurobiological function. Endocannabinoid signaling responds to and regulates the activity of the hypothalamic-pituitary-adrenal (HPA) axis that governs the secretion of glucocorticoids; however, the role this system plays in adaptation of the neuroendocrine response to repeated stress is not well characterized. Herein, the PIs demonstrate a divergent regulation of the two endocannabinoid ligands, N-arachidonylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG), following repeated stress such that AEA content is persistently decreased throughout the corticolimbic stress circuit, whereas 2-AG is exclusively elevated within the amygdala in a stress-dependent manner. Pharmacological studies demonstrate that this divergent regulation of AEA and 2-AG contribute to distinct forms of HPA axis habituation. Inhibition of AEA hydrolysis prevented the development of basal hypersecretion of corticosterone following repeated stress. In contrast, systemic or intra-amygdalar administration of a CB(1) receptor antagonist before the final stress exposure prevented the repeated stress-induced decline in corticosterone responses. The present findings demonstrate an important role for endocannabinoid signaling in the process of stress HPA habituation, and suggest that AEA and 2-AG modulate different components of the adrenocortical response to repeated stressor exposure. Hill MN, McLaughlin RJ, Bingham B, Shrestha L, Lee TT, Gray JM, Hillard CJ, Gorzalka BB, Viau V. Endogenous cannabinoid signaling is essential for stress adaptation. Proc Natl Acad Sci U S A. 2010 May 18;107(20): 9406-9411.

Extinction Training After Cocaine Self-Administration Alters Glutamate Receptor Trafficking In the Nucleus Accumbens Core To Inhibit Cocaine Seeking

Learning to inhibit drug seeking can be an important strategy for inhibiting relapse, and this can be modeled by extinguishing drug seeking in response to a drug-paired context. Rats were either extinguished or withdrawn without extinction training (abstinence) from cocaine self-administration, and measurements of postsynaptic density proteins in the core and shell subcompartments of the nucleus accumbens (NAc) were compared with yoked-saline controls. Extinguished, but not abstinent, rats had elevations of several proteins, including Homer1b/c that regulates trafficking of the glutamate receptor, mGluR5, in the postsynaptic density of the NAc core. No differences in protein levels were measured in the postsynaptic density of the NAc shell in either extinguished or abstinent rats. Additionally, it was found that surface expression of mGluR5 was reduced only in the core of extinguished animals. Blunted long-term depression (LTD) was also observed only in extinguished rats. These data indicate that the elevation in Homer1b/c in the NAc core may have sequestered mGluR5 away from the membrane surface and that the loss of surface mGluR5 alters neuronal activity. Accordingly, when Homer1c was over expressed in the NAc core of cocaine-naive rats with an adeno-associated virus, long-term depression was inhibited. This mechanism may contribute to the inhibition of cocaine seeking by extinction training because over expression of Homer1c in the NAc core also inhibited cue-induced reinstatement of cocaine seeking. These data identify a cellular mechanism that may contribute to extinction-induced inhibition of cocaine seeking. Knackstedt LA, Moussawi K, Lalumiere R, Schwendt M, Klugmann M, Kalivas PW. Extinction training after cocaine self-administration induces glutamatergic plasticity to inhibit cocaine seeking. J Neurosci. 2010 Jun 9;30(23): 7984-7992.

Functional Impact of a Single-Nucleotide Polymorphism in the OPRD1 Promoter Region

The delta-opioid receptor mediates the rewarding effects of many substances of abuse. Dr. Zhang and colleagues reported an increased frequency of the minor G-allele of single-nucleotide polymorphism (SNP) rs569356 (the only variant identified so far in the promoter region of the delta-opioid receptor gene (OPRD1)) in European American subjects with opioid dependence compared with European American controls. Functional genetic variation in promoter regions may alter the affinity of transcription factors and other modulatory proteins that bind to the DNA sequence and thus influence the specificity and kinetics of the transcription process. In this study, Dr. Zhang and colleagues examined the functional significance of this variant through luciferase reporter and electrophoretic mobility shift assays (EMSA). The minor G-allele was associated with significantly greater expression levels of firefly luciferase than the major A-allele of SNP rs569356 ($P=0.003$). EMSA also showed specific gel shift bands, suggesting that SNP rs569356 is situated in the binding site of potential transcription factors. These results suggest that the minor G-allele of SNP rs569356 may enhance transcription factor binding and increase OPRD1 expression. Zhang H, Gelernter J, Gruen JR, Kranzler HR, Herman AI, Simen AA. Functional Impact of a Single-Nucleotide Polymorphism in the OPRD1 Promoter Region. J Hum Genet. 2010 May; 55(5): 278-284.

A Novel MicroRNA Regulates Cocaine Intake Through CREB Signalling

Non-coding RNAs are emerging as important regulators of biological processes; however their role in regulation of addictive processes remains poorly characterized. Dr. Kenny and co-workers have identified a 21 nucleotide

microRNA , miR-212, that is found at higher levels in the dorsal striatal brain region of animals that self-administer cocaine. In rats with extended access to cocaine, reduction of miR-212 levels in the striatum leads to increased cocaine intake, while overexpression of miR-212 leads to decreased cocaine intake. Further molecular experiments revealed that miR-212 achieves it effects via simultaneous reduction in expression of several messenger RNAs which encode regulatory proteins that impinge upon the Raf1 protein kinase signaling pathway (including the SPRED1 repressor of Raf1). Overall these gene expression changes lead to increased levels of Raf1 protein kinase activity, increased expression of the CREB regulatory protein TORC , and ultimately increased activity of the transcription factor CREB. The identification of a novel miR-212 pathway that regulates cocaine intake provides a new and unexpected target for the development of potential therapeutic agents to treat cocaine addiction. Hollander JA, Im HI, Amelio AL, Kocerha J, Bali P, Lu Q, Willoughby D, Wahlestedt C, Conkright MD, Kenny PJ. Striatal microRNA controls cocaine intake through CREB signalling. Nature. 2010; Jul 8; 466(7303): 197-202.

Cortical DNA Methylation Maintains Remote Memory

Contextual fear conditioning, in which rodents receive a foot shock in a particular environmental milieu, leads to memories of the environmental milieu that last for several months. During this time period "the memory transitions from 'recent' to 'remote'". It is believed that during memory consolidation the control of the memory shifts from the hippocampal brain region to dependence upon the anterior cingulated (ACC) or cortical brain region. Previously DNA methylation of specific genes in the hippocampus had been shown to be important for memory formation; however the molecular basis of memory maintenance remains mysterious. Dr. Miller and co-workers found that a single associative learning experience led to DNA methylation of the memory-associated gene calcineurin in the cortex. This DNA methylation lasted at least 30 days after the initial associative learning event. Interestingly, inhibitors of the DNA methyltransferase enzyme that methylates DNA disrupted the memory. Overall these experiments suggest that maintenance of long lasting memory requires DNA methylation in the prefrontal cortex. Future investigations in this area may shed light on the role of DNA methylation in memory-related addictive processes and suggest ways in which this epigenetic pathway could be manipulated therapeutically. Miller CA, Gavin CF, White JA, Parrish RR, Honasoge A, Yancey CR, Rivera IM, Rubio MD, Rumbaugh G, Sweatt JD. Cortical DNA methylation maintains remote memory. Nat Neurosci. 2010; Jun 13(6): 664-666.

Additional Loci Associated with the Genetics of Smoking Behavior

Nicotine dependence is determined by an interplay of neurobiological, environmental, developmental and genetic factors. Environmental influences are important in the initiation of smoking, but the heritability of smoking persistence, smoking quantity and nicotine dependence is strongly influenced by genetic factors. Genetic variants within a cluster of nicotinic acetylcholine receptor genes on chromosome 15q25 are associated with nicotine dependence, as well as smoking-related diseases such as lung cancer, peripheral artery disease, and chronic obstructive pulmonary disease. Due to many replication studies, there is high confidence in the15q25 genetic variants, but they account for a small portion of the genetic variance for nicotine dependence. To search for additional variants associated with smoking behavior, Dr. Kari Stefansson and colleagues performed meta-analyses of genome-wide association studies focusing on cigarettes smoked per day (CPD) and smoking initiation. There were 30,431 ever smokers and 16,050 never-smokers for smoking initiation and 31,266 subjects. For each subject, 2,500,000 imputed and genotyped SNPs were combined and analyzed. In addition to the 15q25 locus, two new loci (8p11, and 19q13) were found to be

genome-wide significant for CPD, and passed further quality control metrics. No significant loci were observed for smoking initiation. The SNPs on chromosome 8p11 are in close proximity to another cluster of nicotinic acetylcholine receptor subunit genes, CHRNB3 and CHRNA6. The SNPs on chromosome 19q13 are located in a genomic region harboring CYP2A6, which plays a major role in the oxidation of nicotine. Other SNPs on 19q13 are in the RAB4B gene and the CYP2B6 gene. Overall, this work provides additional genetic loci with strong associations to nicotine dependence and CPD. The dissection of the causal variants and pathways to nicotine dependence and smoking related diseases is underway. Thorgeirsson T, et al. Sequence variants at CHRNB3-CHRNA6 and CYP2A6 affect smoking behavior. Nat Genet. 2010; May 42(5): 448-453.

Argonaute 2 in Dopamine 2 Receptor Expressing Neurons Regulates Cocaine Addiction

Cocaine regulates gene expression and the expression of proteins within a region of the brain called the striatum. The changes in gene expression occur through the release of the neurotransmitter, dopamine from the nerve terminals of VTA neurons that form synapses with neurons in the striatum Dopamine acts on the dopamine receptor 2 (DRD2) located on striatal neurons to produce changes in electrical excitability and changes in the expression of mRNAs (messenger RNA). mRNA is translated into proteins that carry out the functions of the cell. It has recently been discovered that microRNAs (miRNAs), a non coding RNA, binds to mRNAs to regulate the amount of the translation of protein from mRNA. Levels of translation are regulated by the RISC (the RNA-induced silencing complex). This complex consists of DICER that generates the miRNA and Argonaut that binds the miRNA and regulates mRNA decay or suppression of translation. Dr. Anne Schafer together with Noble Laureate, Paul Greengard examined the role that Ago2 plays in regulating miRNA expression induced by cocaine in DRD2 expressing neurons to identify which miRNA among the 300 miRNAs play a role in regulating gene expression altered by cocaine. Schafer and her colleagues show that abolishing the function of the Ago2 protein selectively in DRD2 neurons of the striatum significantly reduces the motivation of mice to self-administer cocaine without affecting the number, morphology, or distribution of neurons in the striatum or their dopaminergic innervation. This is associated with a reduction of 94/376 miRNAs expressed in DRD2 striatal neurons with 15 showing a 3 to 17 fold reduction in expression. 23 of the 63 miRNA induced by cocaine are Ago2 dependent. Among these 23 miRNAs are miRNAs that regulate CREB, FosB, Mef2, BDNF, and Cdk5r1, all genes that have been implicated in mediating addiction to cocaine. These results show that Ago2 through its regulation of miRNAs plays a significant role in cocaine addiction. Future experiments will determine the role that the 23 miRNAs play in mediating changes in stable gene expression following cocaine self-administration. Schaefer A, Im HI, Veno MT, Fowler CD, Min A, Intrator A, Kjems J, Kenny P, O'Carroll D, Greengard P. Journal of Experimental Medicine, July 19, 2010 Cite by DOI: 10.1084/jem.20100451.

Cortical Laminar Development Is Coordinated at Bottom through Gap Junctions

During cortical embryonic development, the nuclei of the dividing neural precursor cells in the ventricular zone and subventricular zone translocate back and forth between the ventricular surface and basal surface. This phenomenon is known as interkinetic nuclear translocation. During this process the nuclei of the dividing neural precursors move away from the ventricular surface basally to divide, then move back to the surface to either migrate radially with the rest of the committed cell bodies to the cortical surface or prepare for another round of translocation basally for another division. The timing and coordination of nuclear translocation for these precursors are very important, since normal

cortical layers can only emerge by precisely timed cell migration from ventricular zones into the right cortical layers at the right time. How this precisely timed nuclear translocation is coordinated has not been well known. A group of NIDA funded researchers at Yale University, led by Dr. Pasko Rakic, report that the neural precursor cells generate spontaneous transient Ca2+ waves in the ventricular zones. The Ca2+ wave signals the precursor cells' timing and location of interkinetic movement through gap junctions on the cell membrane. Blocking the gap junctions using a chemical MFA, or through gap junction subunit gene knockdown, delays or blocks the nuclear migration. This delay also changes the nuclear length/width ratio, with consequences in neural cell differentiation and migration, and may lead to abnormal corticogenesis and dysfunction of the cerebral cortex in adult organisms. Liu X, Hashimoto-Torii K, Torii M, Ding C, Rakic P. Gap Junctions/Hemichannels Modulate Interkinetic Nuclear Migration in the Forebrain Precursors. Journal of Neuroscience 2010: 30: 4197-4209.

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Research Findings - Basic Behavioral Research

Prenatal Oxycodone Impairs Spatial Learning and/or Memory in Rats

Recent changes in demographic patterns of drug abuse have resulted in increased non-medical use of prescription opiates. Prescription drugs are now abused by younger users and more females than males, with potential risk for in-utero exposure. A research team led by Dr. Schrott and colleagues has developed a rat model that simulates prescription opiate-dependence in women who become pregnant and continue to abuse these drugs. In this procedure, adult female Sprague-Dawley rats are treated for 30 days via oral gavage with ascending doses of oxycodone HCl, up to a final dose of 15mg/kg/day, and this final dose is then maintained during breeding and gestation. Controls are treated with water. In a recent study, adult male offspring of dams treated with this regimen were tested on a radial arm maze (during three phases: shaping, acquisition, and retention), a Morris water maze (with a short and a long intertrial interval), and a spatial T-maze (to test hippocampus-dependent spatial memory). The findings reveal that this oxycodone pattern of exposure caused deficits in all three tasks used to assess spatial learning or memory. More specifically, the researchers observed radial arm maze deficits characterized by a greater number of reference memory errors, especially in the beginning of testing. By contrast, in the T-maze, oxycodone-exposed rats learned the task as well as prenatal water controls but they had a modest deficit in task retention when assessed 5 days after acquisition training. For the Morris water maze, the intertrial interval affected the pattern of learning. Thus, while there was no deficit during training under a short intertrial interval, with longer intervals oxycodone-exposed rats showed poorer acquisition. The spatial learning deficit of increased latency to find, and distance traveled to, the platform in the water maze was corroborated by analyzing the animals' behavioral search strategy. During water maze training, drug-exposed animals showed a decreased use of spatial strategies and an increase in non-spatial strategies, especially wall-hugging, compared to prenatal water control rats on day 2 of acquisition. In summary, these results indicate that prenatal oxycodone exposure may impair learning and memory assessed on spatial tasks. Davis CP, Franklin LT, Johnson GS, Schrott LM. Prenatal Oxycodone Exposure Impairs Spatial Learning and/or Memory in Rats. Behav Brain Res. 2010; 212(1): 27-34.

A New Tool To Assess Statewide Capacity For Integrative Treatment of SUD With Other Psychiatric Disorders

Dr. R. Andrew Chambers, a psychiatrist at the Indiana School of Medicine, has a NIDA K08 award to study the etiology and neurobiological basis of drug addiction and comorbid psychiatric disorders in animal models. As part of this

career development award, he also sees patients with dual diagnosis disorders, and he has been very active in promoting the need for integrated mental health and addiction services, as well as overcoming barriers of inadequate physician training and professional expertise in this area. In this paper, Dr. Chambers and his colleagues report on the design and implementation of a new Dual Diagnosis Physician-infrastructure Assessment Tool (DDPAT) to quantify statewide dimensions of this workforce problem. The DDPAT complements other survey instruments that are more comprehensive in assessing health systems but that don't directly assess physician workforce size, training background, or clinical roles with respect to dual diagnosis care. In the first phase of this project, they surveyed Indiana's six state psychiatric facilities, all 30 community health centers (CMHCs), and all 13 stand-alone addiction treatment centers with a simple 10 item questionnaire. They received responses from 100% of these facilities. In the second phase, they report a 75% response rate on a 10 item questionnaire from all physicians affiliated with these facilities. They found that 69% of all treatment centers, and 97% of the CMHCs reported dual diagnosis capability. However, only 29% of physicians treated both mental illness and addictions, and only 8% had certification in an addiction specialty. The addiction treatment centers had the highest percentage of addiction-certified physicians (21%), but only a minority of these centers reported dual diagnosis capability. Overall, their findings suggest a disconnection between how centers report their dual diagnosis capability and the levels of physician expertise and involvement in dual diagnosis treatment. They also found an overall shortage of psychiatrists in these facilities, and note that the workforce is aging. Their study indicates that the DDPAT is a useful and simple assessment tool to characterize a statewide physician workforce with respect to dual diagnosis capabilities and profiles of treatment centers. Given the extent to which dual diagnosis presentations are mainstream in behavioral health care, the authors hope that their findings will motivate changes in physician workforce development in Indiana and prompt the use of similar assessments in other states. Chambers RA, Connor MC, Boggs CJ, Parker GF. The Dual Diagnosis Physician-infrastructure Assessment Tool: examining physician attributes and dual diagnosis capacity. Psychiatr Serv. 2010;61(2): 184-188.

Activation of κ-Opioid Receptor In the Ventral Tegmental Area Attenuates Drug-Seeking Behavior In Rats

Previous research by Dr. Wenlin Sun and others indicates that glutamate-mediated activation of dopamine (DA) neurons in the VTA, and subsequent increases in DA receptor activation in the prefrontal cortex (PFC), are critically involved in cocaine-induced reinstatement of extinguished cocaine seeking in an animal model of relapse. These observations suggest that decreasing activity of VTA DA neurons projecting to the PFC may attenuate relapse. Recent studies using electrophysiological recording from brain slice preparations have shown that there are distinct subpopulations of DA neurons in the VTA. In particular, a subset of VTA neurons that express κ-opioid receptors (κORs) project to the PFC and amygdala, and not to other VTA targets, and these DA neurons are inhibited by κOR agonists. Therefore, Dr. Sun predicted that activation of κORs would inhibit cocaine-induced reinstatement. To test this hypothesis, the investigators infused the selective κOR agonist U50 588 bilaterally into the VTA in animals trained to self administer cocaine. During the maintenance phase of self-administration, the agonist had no effect on the rats' behavior. However, after self-administration was extinguished and then reinstated with a priming dose of cocaine, U50 588 in the VTA dose dependently attenuated cocaine-seeking (responses on the lever previously associated with cocaine delivery). This effect was selective for cocaine in that U50 588 did not suppress reinstatement in a separate group of rats trained to respond for food. This study used a novel approach - κOR agonist administration - to selectively inhibit the activity of a subset of VTA DA

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neurons. Because these DA neurons project to both PFC and amygdala, further research will be needed to determine whether decreases of DA in the PFC, the amygdala, or both accounted for the attenuation of cocaine seeking. However, other evidence converges on the PFC as the critical target for interfering with the motivation to seek drug. The κOR agonist was used in this study as a tool to test the hypothesis that this VTA-PFC/amygdala DA circuit is critically involved in relapse, but the results also suggest that κOR agonists might be considered for therapeutic approaches to relapse prevention. Sun W, Xue Y, Huang Z, Steketee JD. Regulation of cocaine-reinstated drug-seeking behavior by kappa-opioid receptors in the ventral tegmental area of rats. Psychopharmacology (Berl). 2010 Mar 16. [Epub ahead of print]

Electrical Stimulation of the Lateral Habenula Inhibits Cocaine Seeking in Rats

Deep-brain-stimulation (DBS) has had considerable success in the treatment of neurological disorders and has shown promising results in treating psychiatric disorders. DBS of nucleus accumbens has also been shown to block reinstatement of cocaine seeking in an animal model. The lateral habenula (LHb) innervates the ventral tegmental area (VTA) and prefrontal cortex with glutamatergic projections, and it known to be critical for modulation of negative reinforcement, punishment and aversive responses. In this study, supported by a NIDA CEBRA award, Dr. Yadid and his colleagues explored the use of LHb DBS to reduce cocaine self-administration, extinction, and reinstatement in rats. An electrode was implanted into the LHb and rats were trained to self-administer cocaine for 21 days until they achieved at least three days of stable performance. After that, they received DBS in either the presence or absence of cocaine. DBS reduced cocaine seeking behavior during both self-administration and extinction training. DBS also attenuated the rats' lever presses following reinstatement with a small priming dose of cocaine. They also carried out a number of control experiments to assess whether LHb DBS affected physical performance, which it did not. In tests of depressive-like behaviors, that is, anhedonia (two bottle choice test) and despair (swim test), LHb DBS was without effect. Interestingly, in contrast to the LHb DBS effect, lesions of LHb had no effect on drug self-administration or reinstatement and delayed rather than enhanced extinction. They also measured protein levels of the glutamatergic receptor subunits NR1 and GluR1, the synaptic scaffolding protein PSD95, and β subunits of the GABAA receptors in the VTA. Cocaine self-administration elevated the glutamatergic receptor subunits and PSD95, but not GABAAβ protein levels. Following DBS treatment, levels of the elevated proteins returned to control values. The results suggest that the effect of LHb DBS on cocaine reinforcement may be via attenuation of cocaine-induced increases in glutaminergic input to the VTA. Friedman A, Lax E, Dikshtein Y, Abraham L, Flaumenhaft Y, Sudai E, Ben-Tzion M, Ami-Ad L, Yaka R, Yadid G. Electrical stimulation of the lateral habenula produces enduring inhibitory effect on cocaine seeking behavior. Neuropharmacology. 2010 Jun 22. [Epub ahead of print].

Tricyclics May Act at the Toll-like Receptors to Enhance Opioid Analgesia

Opioids have Toll-like receptor (TLR) activity and this action tends to produce pain. This raises the question whether other pharmacotherapies for pain may have TLR activity, contributing to or opposing their clinical effects. In the current research, NIDA grantees Dr. Mark Hutchinson (University of Adelaide) and Drs. Steven Maier and Linda Watkins (University of Colorado) and colleagues examined the actions of tricyclics on TLR4 signaling. In silico simulations revealed that several tricyclics docked to the same binding pocket on the TLR accessory protein as do opioids. Eight tricyclics were tested in rats and mice. While tricyclics had no effect on basal pain responsivity, they

potentiated morphine analgesia in rank-order with their potency as TLR4 inhibitors. This potentiation was absent in TLR4 knock-out mice. These studies provide converging lines of evidence that several tricyclics or their active metabolites may exert their biological actions, in part, via modulation of TLR4 signaling and suggest that inhibition of TLR4 signaling may potentially contribute to the efficacy of tricyclics in treating chronic pain and enhancing the analgesic efficacy of opioids. Hutchinson MR, Loram LC, Zhang Y, Shridhar M, Rezvani N, Berkelhammer D, Phipps S, Foster PS, Landgraf K, Falke JJ, Rice KC, Maier SF, Yin H, Watkins LR. Evidence that tricyclic small molecules may possess toll-like receptor and myeloid differentiation protein 2 activity. Neuroscience 2010: (168): 551-563.

Opioid-Adrenergic Analgesic Synergy Involves Spinal and Peripheral Heterodimers

Agonists acting at alpha 2-adrenergic and delta opioid receptors inhibit spinal pain transmission. When co-administered, agonists activating these receptors interact in a synergistic manner. Action at heterodimers has been proposed as a molecular basis for this synergy. To examine this question, NIDA grantees Dr. George Wilcox (University of Minnesota), Dr. Laura Stone (McGill University) and colleagues used immunohistochemistry to investigate the spatial relationship between alpha 2-adrenergic and opioid receptors in the rat spinal cord to determine whether co-expression could be demonstrated between these receptors. They observed extensive co-localization between alpha 2A-adrenergic and delta-opioid receptors on substance P-immunoreactive varicosities in the superficial dorsal horn of the spinal cord and in peripheral nerve terminals in the skin. These elements were co-localized in subcellular structures of 0.5 micrometers or less in diameter in isolated nerve terminals. Furthermore, co-incubation of isolated synaptosomes with alpha 2 and delta agonists resulted in synergistic inhibition of K+-stimulated neuropeptide release. These findings suggest that co-expression of alpha 2-adrenergic and delta opioid receptors on primary afferent nociceptive fibers may represent an anatomical substrate for analgesic synergy. Riedl MS, Schnell SA, Overland AC, Chabot-Doré A-J, 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. Journal of Comparative Neurology, 2009: (513): 385-398.

Central Activation of the Peroxisome Proliferator-Activated Receptor Gamma Can Induce A Chronic Pain State: Possible Target for the Treatment of Chronic Inflammatory Pain

Systemic administration of thiazolidinediones reduces peripheral inflammation in vivo, presumably by acting at peroxisome proliferator-activated receptor gamma (PPAR gamma) in peripheral tissues. NIDA-grantee Dr. Bradley Taylor (University of Kentucky) and colleagues postulated that brain PPAR gamma modulates peripheral edema and the processing of inflammatory pain signals in the dorsal horn of the spinal cord. In the rat plantar carrageenan behavioral model of inflammatory pain, Dr. Taylor examined paw edema, behavioral heat hyperalgesia, and dorsal horn expression of the immediate-early gene c-fos after intracerebroventricular (ICV) administration of PPAR gamma agonists or vehicle. PPAR gamma agonists dose-dependently reduced paw thickness, paw volume and behavioral withdrawal responses to noxious heat. Further, the number of carrageenan-induced Fos-like immunoreactive profiles was less in PPAR gamma agonist treated rats as compared to vehicle controls. Intraperitoneal and intrathecal administrations of PPAR gamma agonists did not produce a similar effect. Further, co-administration of ICV administration of PPAR gamma antagonists reversed these actions. Thus, pharmacological activation of PPAR gamma in the brain rapidly inhibits local edema and the spinal transmission of noxious inflammatory signals and may be a target for

the development of novel pharmacological pain treatments. Morgenweck J, Abdel-aleem OS, McNamara KC, Donahue RR, Badr MZ, Taylor BK. Activation of peroxisome proliferator-activated receptor gamma in brain inhibits inflammatory pain, dorsal horn expression of Fos, and local edema. Neuropharmacology, 2010: (58): 337-345.

Neuroadaptations in the Transition to Compulsive Drug Intake Suggest Glutamatergic Targets for Treatment

Dr. Friedbert Weiss has been investigating neurochemical substrates of reinforcing drug effects, with particular emphasis on the neurotransmitter, glutamate (GLU). Pharmacologic manipulation of metabotropic GLU receptors can reverse behavioral effects of acute or chronic cocaine administration, including the rewarding effects of this psychostimulant, and attenuate cue-induced relapse in an animal model. Two GLU receptors of interest in recent studies include mGluR2/3, which negatively modulates GLU transmission, and mGluR5, which increases GLU release when activated. The PI sought to determine if neuroadaptations in these receptor substrates, occurring over the course of repeated cocaine self-administration, might be important for the compulsive, uncontrollable pattern of intake that emerges over a 6h/day drug schedule of drug access. Male Wistar rats provided with one versus 6h/day of drug availability showed the usual pattern of intake over 22 days: Steady intake by the short access group (ShA, exposed to 1h/day cocaine) and gradually increasing intake by the long access group (LgA, self-administering for 6h/day). LgA rats were also willing to "work harder" to obtain the drug as evidenced by significantly higher break points on a progressive ratio schedule. Next groups were tested for break point changes consequent to treatment with either an mGluR2/3 agonist (LY) or an mGluR5 antagonist (MTEP) to dampen GLU transmission. LY dose-dependently lowered the breakpoint for cocaine in LgA rats, with decreases in ShA animals only at the highest dose. By contrast MTEP had no effect on LgA in this test, while dose-dependently lowering break points in the ShA group. These findings suggest that the two classes of GLU receptors may show differential neuroadaptations over the course of chronic cocaine self-administration. The researchers also measured mGluR with immunoblotting and binding of [35S]GTP-γS to assess receptor expression levels and functional activity (via G-protein coupling), respectively. Following escalation, only LgA rats showed a significant reduction in mGluR5 protein levels in the nucleus accumbens (NAS). While LY (the mGluR2/3 agonist) concentration-dependently stimulated [35S]GTP-γS binding in all tissues, signficiantly greater agonist-induced binding was measured in the medial prefrontal cortex mPFC) and ventral tegmental area (VTA) of LgA rats. As these regions are important cell body areas (VTA) and terminal projection regions (NAS, mPFC) of a mesocorticolimbic dopamine system that is critical for reinforcing properties of drugs, GLU receptor neuroadaptations in this system may play an important role in the emergence of addictive behavior. In summary, both pharmacologic manipulations attenuated the reinforcing effects of cocaine and indicate that mGluR2/3 and mGluR5 may be enhanced versus down-regulated, respectively, in the transition to uncontrollable drug intake. The authors caution that GLU compounds specific for these receptor targets may be plagued with non-specific effects, thus limiting the translation to human use. Therefore, additional research on putative pharmacotherapies acting on GLU receptor substrates will be needed. Hao Y, Martin-Fardon R, Weiss F. Behavioral and Functional Evidence of Metabotropic Glutamate Receptor 2/3 and Metabotropic Glutamate Receptor 5 Dysregulation in Cocaine-Escalated Rats: Factor in the Transition to Dependence. Biol Psychiat. 2010 Aug; 68(3): 240-248.

Unique and Persistent Nicotine-Induced Changes in Gene Expression May Underlie Adolescent Vulnerability

Researchers at George Washington University have previously shown that chronic nicotine (nic) exposure during adolescence differentially regulates subtypes of nic receptors, in comparison to adult rats. In a new study, these NIDA funded investigators studied tissue from the ventral tegmental area (VTA) region for dopamine cell bodies after two weeks of passive infusion with nic or saline. Adult and periadolescent animals were sacrificed for whole genome microarray analysis immediately after these two weeks or after four weeks of abstinence. To validate expression data for selected genes, quantitative real-time PCR was also used. In comparison to saline-infused controls, clusters of genes were identified that represented "transient responders" (significantly changed at two weeks), "late responders" (change in expression after abstinence only) and "persistent responders" (up- or down-regulated at both time points). Some clusters revealed genes that were uniquely changed in expression during adolescent nic exposure or during adult nic exposure. Other clusters showed overlap between the two age groups. Interestingly, twice as many genes from the adolescent nic treated group were persistently regulated (remaining up- or down-regulated after four weeks of abstinence), and the number of late regulated genes (change only at the four week abstinence point) was four fold for the adolescent exposed group. These findings suggest unique genomic responses to nic exposure that may persist into adulthood and underlie teen vulnerability for rapid emergence of dependence. To investigate biological significance of unique gene changes, the researchers applied a Ingenuity Pathways Analysis. This analysis allowed for the identification of functions, networks and canonical pathways, revealing over-representation of unique adolescent genes in the synaptic long-term potentiation (LTP), circadian rhythm signaling and CDK5 signaling canonical pathways. These observations are important because they reveal nic-induced changes in adolescent gene expression within systems that regulate neuroplasticity (LTP) and neural development. In conclusion, this study further supports earlier findings to sugest that the effects of chronic nic exposure depends upon age of drug use, and that nic may induce downstream effects that persist long after exposure is halted. Doura MB, Luu TV, Lee NH, Perry DC. Persistent gene expression changes in ventral tegmental area of adolescent but not adult rats in response to chronic nicotine. Neurosci 2010, doi: 10.1016/j.neuroscience.2010.06.071 In Press, Uncorrected Proof, Available online 13 July 2010.

Measuring Behavioral Arousal to Stress and Drug Cues in Alcohol- and Cocaine-Addicted Individuals

Previous research reveals that negative emotional arousal, in response to stress or drug-associated cues, plays a role in the development and continuation of substance use disorders. Until recently, emotional arousal has been measured by self-report or electrophysiological proxy. Recent studies from Dr. Tara Chaplin and Dr. Rijita Sinha, have been using a new Behavioral Arousal Scale (BAS) to measure behavioral and bodily arousal in response to stress and drug-related cues. Individuals with alcohol dependence and cocaine dependence were compared to healthy controls in a study of ninety seven addicts between the ages of 21 and 50: Fifty-two alcohol dependent (AD), 45 cocaine-dependent (COC). Drug-using individuals were compared with 68 healthy controls (HC). All participants were exposed to individually-tailored stressful, drug-cue, and neutral (relaxing) imagery. Results from the BAS revealed acceptable inter-rater reliability and internal consistency. Also, measures correlated with self-report of subjective negative emotion and craving. In addition, BAS scores were higher in response to stress imagery than for neutral conditions in all three groups. Inter-group comparisons revealed that: COC participants showed higher BAS response to stress than AD or HC participants; and both COC and AD participants showed greater BAS response to drug cue imagery than HC participants. In conclusion, behavioral arousal is a domain in which stress and drug related arousal is expressed and

assessment of this domain could provide unique information about vulnerability to craving and relapse in addicted subjects. Objective assessments made with use of the BAS might also be useful for formulating and assessing personalized treatment approaches for addiction. Chaplin TM, Hong K, Fox HC, Siedlarz KM, Bergquiat K, Sinha R. Behavioral Arousal in response to Stress and Drug Cue in Alcohol and Cocaine addicted Individuals Versus Healthy Controls. Hum Psychopharmacol. 2010 Jul;25(5): 368-376.

Gender Differences in Caregiver Emotion Socialization of Low-Income Toddlers

Previous research reveals that low-income children are at elevated risk for emotion-related problems. Very little research has examined gender and emotion socialization in low-income families, however. Dr. Tara Chaplin and her mentor, Dr. Rajita Sinha, recently published a chapter on gender and emotion socialization in New Directions for Child and Adolescent Development, proposing two models for understanding the relationship between emotion socialization and the development of psychopathology, particularly in low-income children. These models are based on new data from a study designed to examine emotion socialization responses by low-income female caregivers to their toddlers' sadness/anxiety and anger displays. Sixty-five 2 1/2 year olds (33 boys and 32 girls) participated in this laboratory-based study. Children were exposed to a frustrating, toy wait task with their primary caregivers present. Sadness and anxiety were coded from facial, vocal and postural cues in the children. Caregiver responses to child emotion were coded based on verbalizations, behaviors and/or emotion expressions and were classified as no response, support/reward, override (dismissing or distracting the child), punishment and caregiver distress. Results of the coding show that girls showed slightly less sadness/anxiety and slightly greater anger than boys. For those children expressing one or more emotion in the task, caregiver responses indicated more supportive reactions to boys than to girls. However they responded to anger with punishment about twice as often for girls than boys, and with caregiver distress about six times more often for girls than boys. These descriptive data suggest that low-income (primarily African American) female caregivers respond in ways that encourage boys' anger and discourage or punish girls' anger. There were few consistent differences in caregiver responses to sadness/anxiety. The authors conclude that implications of caregiver response in children's social-emotional development might be explained by (1) an Emotion Competence Model, in which parental responses that support child emotions lead to greater emotional competence, or by (2) the Differential Emotions Model, that theorizes encouragement/reward of particular emotions leads children to express patterns of emotion that may, in conjunction with other risk factors, lead them toward particular forms of psychopathology. Chaplin TM, Casey J, Sinha R, Mayes LC. Gender Differences in Caregiver Emotion Socialization of Low-Income Toddlers. New Dir Child Adolec Dev. 2010 128; 11-27.

Access to a Running Wheel Reduces Both Extinction and Reinstatement Responding in Female Rats

Access to exercise in a running wheel acts as a positive reinforcer for rats and Dr. Marilyn Carroll and colleagues at the University of Minnesota have previously shown that it can reduce both acquisition and maintenance of cocaine self-administration when concurrently available. The present study examined the effect of wheel running access on extinction and reinstatement of cocaine seeking in female rats. After the rats were trained to run in a wheel during 6-h sessions, they were then catheterized and placed in an operant conditioning chamber where they did not have access to the wheel but were allowed to self-administer iv cocaine. Following maintenance of cocaine self-administration, the rats were divided into four groups and were tested on

extinction and cocaine-primed reinstatement of cocaine seeking while they had varying access to a wheel in an adjoining compartment. The four groups were based on the following wheel access conditions: (1) access during both extinction and reinstatement (WER), (2) access only during extinction (WE), (3) access only during reinstatement (WR), and (4) access during neither extinction nor reinstatement (WL). Results indicated that during extinction, both groups that had access to running (WE and WER) responded less than the groups that did not have access (WR and WL). Similarly, both groups that had access to running during reinstatement (WR and WER) had lower cocaine-primed reinstatement than the groups without access (WE and WL). The finding that group WE did not have suppressed reinstatement indicated that their suppressed responding during extinction did not carry forward into reinstatement, i.e., it was not enduring. However, a probe session of wheel exposure in the WE rats did induce suppression of cocaine-primed reinstatement. These data show that wheel running immediately and effectively reduces cocaine-seeking behavior, but concurrent access to running is necessary for the suppressive effect. Results indicated that the attenuating effects of wheel running on cocaine seeking was not due to competition for time, but rather suggest that the reinforcing value of wheel running competed with the reinforcing value of cocaine. These data suggest that exercise may be a useful and self-sustaining intervention to reduce cocaine-seeking behavior. Zlebnik NE, Anker JJ, Gliddon LA, Carroll ME. Reduction of extinction and reinstatement of cocaine seeking by wheel running in female rats. Psychopharmacology. 2010; 209(1): 113-125.

Differential Sensitivity to Reinstatement in Adolescent and Adult Male Rats

Animal studies have shown that in general, the reinforcing effects of stimulant drugs is greater in adolescents than adults during acquisition and maintenance of drug self-administration. No studies, however, have compared adults and adolescents in other phases of drug abuse, including extinction (when the drug is discontinued) and during models of relapse when responding is reinstated with either a priming dose of the drug, a stressor, or cues previously associated with drug delivery. Male adolescent and adult rats were recently compared in these paradigms by Dr. Marilyn Carroll and her colleague Justin Anker at the University of Minnesota. On postnatal days 23 (adolescents) and 90 (adults), rats were implanted with intravenous (i.v.) catheters and trained to lever press for i.v. infusions of cocaine (0.4 mg/kg) during two daily 2-h sessions. The rats then self-administered i.v. cocaine for ten additional sessions. Subsequently, visual and auditory stimuli that previously signaled drug delivery were turned off and rats underwent extinction, during which time drug and cues were not available for 20 sessions. Next, in reinstatement testing (a procedure used to model human relapse) rats were tested for cocaine-, cue-, and yohimbine (stress)-induced cocaine seeking using a within-subject multicomponent procedure. Results indicated that during maintenance and extinction, adolescents self-administered more cocaine than adults. During reinstatement, adolescents exhibited greater drug seeking (responding on the lever which previously delivered i.v. cocaine) than adults following cocaine priming injections and yohimbine administration (to activate a stress response). However, adults responded more than adolescents following presentation of drug-associated cues. These results demonstrate that vulnerability to relapse in adolescents and adults differ across measures of drug-seeking behavior, and that adolescents may be especially vulnerable to relapse precipitated by drugs and stress. The authors speculate that these findings may be linked to development of key brain areas involved in reward-, inhibitory-, and memory-related processes during adolescence. Anker JJ, Carroll ME. Reinstatement of cocaine seeking induced by drugs, cues, and stress in adolescent and adult rats. Psychopharmacology, 2010; 208(2): 211-222.

Adolescent Rats Repeatedly Treated with δ9-THC Display Cognitive Deficits Upon Subsequent Drug Challenge in Adulthood

Early-onset marijuana use has been associated with short- and long-term deficits in cognitive processing. In human users, self-selection bias prevents determination of the extent to which these effects result only from drug use, rather than pre-existing conditions. Dr. Jenny Wiley at the Research Triangle Institute (formerly, a NIDA grantee at the Virginia Commonwealth University) examined long-term effects of δ9-tetrahydrocannabinol (δ9-THC, the major psychoactive constituent of marijuana), administered to male rats during adolescence, on a delayed nonmatch-to-position task (DNMP) in adulthood. DNMP is an operant procedure that is commonly used to examine the effects of drugs on short-term memory in rats. This procedure consists of a series of trials in which initially one of two levers is extended into an operant chamber. Five presses on the lever results in presentation of food and withdrawal of the lever. Following varying delays, both levers are introduced together and the next food reinforcement is contingent upon pressing the lever that was previously extended. In the present experiment, rats were injected daily with 10 mg/kg δ9-THC during or after adolescence [postnatal days (PN) 21-50 or PN50-79), respectively] or with vehicle. On PN91, training in DNMP was initiated in the three groups. Pharmacological challenge began on approximately PN300. Rats were challenged sequentially with δ9-THC and anandamide (an endogenous cannabinoid receptor ligand) in order to determine differential inter-group sensitivity to the disruptive effects of these cannabinoids on accuracy in the procedure. For comparison purposes, scopolamine was tested as a positive control and amphetamine as a negative control. The researchers found that vehicle-treated rats required more sessions to reach criterion performance than the two δ9-THC groups, but that once criterion was achieved, there were no differences in accuracy among the three groups. When tested under the δ9-THC challenge (drug administered before testing), however, differences emerged. Whereas doses of δ9-THC up to 30 mg/kg did not impair accuracy in the vehicle-treated rats, both groups that received daily administration of δ9-THC exhibited decreases in accuracy when tested under 10 mg/kg, with 3 mg/kg decreasing accuracy only in rats treated during adolescence. While anandamide did not decrease accuracy in any group, rats treated with δ9-THC during adolescence initiated fewer trials at the 30 mg/kg dose of anandamide than did rats in the other groups. To the extent tested, these differences were pharmacologically selective for cannabinoids, as scopolamine decreased accuracy at the same dose in all groups and amphetamine did not affect accuracy in any of the groups at doses that did not impair overall responding. These results suggest that in rats repeated administration of a modest dose of δ9-THC during adolescence (PN21-50) or shortly thereafter (PN50-79) produces a long-term increase in latent sensitivity to cannabinoid-induced impairment of performance in a complex operant task. These results suggest that in humans, regular administration of δ9-THC during adolescence may also have long-term effects on cognitive performance that remain latent until revealed later under δ9-THC challenge. Wiley JL. Burston JJ. Chronic Æ9-tetrahydrocannabinol during adolescence in male rats increases sensitivity to subsequent cannabinoid effects in delayed nonmatch-to-position in rats. Pharmacol Biochem Behavior 2010; 94(4): 516-523.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - Behavioral and Brain Development Research

Longitudinal Characterization of White Matter Maturation during Adolescence

Late adolescence has a number of developmental transitions, though brain maturational changes during this period are subtle and difficult to quantitatively evaluate with standard structural brain images. To date, primarily cross-sectional studies have characterized typical developmental changes during adolescence, but these processes need further description within a longitudinal framework. To assess the developmental trajectory of brain white matter, Dr. Bava and colleagues examined 22 healthy adolescents with diffusion tensor images (DTI) collected at a mean age of 17.8 years and 16-months later. Fractional anisotropy and mean, radial, and axial diffusivity were compared across the two time points. At follow-up, adolescents showed a significant change (>or=153 contiguous voxels each at $p<0.01$) in diffusion properties, including in bilateral superior longitudinal fasciculi, superior corona radiata, anterior thalamic radiations, and posterior limb of the internal capsule. Overall, correlations with cognitive performances suggested behavioral improvement corresponding with white matter changes. These longitudinal DTI findings support continued microstructural change in white matter during late adolescence, and suggest ongoing refinement of projection and association fibers into early adulthood. Bava S, Thayer R, Jacobus J, Ward M, Jernigan TL, Tapert SF. Longitudinal characterization of white matter maturation during adolescence. Brain Research 2010 Apr 23;1327: 38-46.

Neurocognitive Correlates of White Matter Quality in Adolescent Substance Users

Progressive myelination during adolescence implicates an increased vulnerability to neurotoxic substances and enduring neurocognitive consequences. This study conducted by Dr. Bava and colleagues examined the cognitive manifestations of altered white matter microstructure in chronic marijuana and alcohol-using (MJ+ALC) adolescents. Thirty-six MJ+ALC adolescents (ages 16-19) and 36 demographically similar controls were evaluated with diffusion tensor imaging and neurocognitive tests. Regions of group difference in fractional anisotropy (FA) and mean diffusivity (MD) were analyzed in relation to cognitive performance. In users, lower FA in temporal areas related to poorer performance on attention, working memory, and speeded processing tasks. Among regions where users had higher FA than controls, occipital FA was positively associated with working memory and complex visuomotor sequencing, whereas FA in anterior regions was negatively associated with verbal memory performance. Findings suggest differential influences of white matter development on cognition in MJ+ALC using

Publications

Staff Highlights

Grantee Honors

adolescents than in non-using peers. Neuroadaptation may reflect additive and subtractive responses to substance use that are complicated by competing maturational processes. Bava S, Jacobus J, Mahmood O, Yang TT, Tapert SF. Neurocognitive correlates of white matter quality in adolescent substance users. Brain Cogn. 2010 Apr;72(3): 347-354.

A Pilot Randomized Study of Smokeless Tobacco Use among Smokers not Interested in Quitting: Changes in Smoking Behavior and Readiness to Quit

Several prior studies suggest that smokeless tobacco use results in less carcinogenic risk than does cigarette smoking. Whether smokers will use smokeless tobacco is unclear, as is the impact of such use on long-term smoking behavior and cessation. It is equally plausible that smokeless tobacco use among smokers could either (a) increase total tobacco exposure and undermine motivation to quit or (b) decrease overall tobacco exposure, motivate smokers to quit, and enhance cessation. Either outcome is of major public health significance. Dr. Carpenter and colleagues conducted a small (N = 31), short-term (2 week) pilot study in which smokers uninterested in quitting were randomized to (a) receive Ariva or Stonewall (both spitless and smokeless tobacco lozenges) or (b) continue smoking conventional cigarettes. Ariva/Stonewall use led to a significant reduction (40%, 95% CI: 24%-55%) in cigarettes per day, no significant increases in total tobacco use (cigarettes + Ariva/Stonewall; $p > .05$), and significant increases in two measures of readiness to quit, either in the next month ($p < .001$) or within the next 6 months ($p = .04$), as well as significant increases in self-efficacy to quit smoking ($p < .001$). No such changes were found among smokers maintained on conventional cigarettes. These results suggest no deleterious effect on short-term smoking and quitting behavior among smokers who use smokeless tobacco. More broadly, this study suggests a strong need for a large prospective randomized clinical trial to more accurately assess the long-term viability of smokeless tobacco use as a method for cessation induction among unmotivated smokers. Carpenter MJ, Gray KM. A pilot randomized study of smokeless tobacco use among smokers not interested in quitting: changes in smoking behavior and readiness to quit. Nicotine Tob Res. 2010 Feb;12(2): 136-143.

EEG Spectral Phenotypes: Heritability and Association with Marijuana and Alcohol Dependence in an American Indian Community Study

Native Americans have some of the highest rates of marijuana and alcohol use and abuse, yet neurobiological measures associated with dependence on these substances in this population remain largely undescribed. The present investigation, conducted by Dr. Ehlers and colleagues, evaluated the heritability of spectral characteristics of the electroencephalogram (EEG) and their correlation with marijuana and alcohol dependence in an American Indian community. Participants (n=626) were evaluated for marijuana (MJ) and alcohol (ALC) dependence, as well as other psychiatric disorders. EEGs were collected from six cortical sites and spectral power determined in five frequency bands (delta 1.0-4.0 Hz, theta 4.0-7.5 Hz, alpha 7.5-12.0 Hz, low beta 12.0-20.0 Hz and high beta/gamma 20-50 Hz). Stepwise linear regression was used to detect correlations between MJ and ALC dependence and the spectral characteristics of the EEG using a model that took into account: age, gender, Native American Heritage (NAH) and a lifetime diagnosis of antisocial personality and/or conduct disorder (ASPD/CD). Increases in spectral power in the delta frequency range, were significantly correlated with gender ($p<0.001$) and marijuana dependence ($p<0.003$). Gender, age, NAH and ASPD/CD were all significantly ($p<0.001$) correlated with theta, alpha and beta band power,

whereas alcohol dependence ($p<0.01$), gender ($p<0.001$), and ASPD/CD ($p<0.001$) were all correlated with high beta/gamma band power. These data suggest that the traits of EEG delta and high beta/gamma activity are correlated with MJ dependence and alcohol dependence, respectively, in this community sample of Native Americans. Ehlers CL, Phillips E, Gizer IR, Gilder DA, Wilhelmsen KC. EEG spectral phenotypes: heritability and association with marijuana and alcohol dependence in an American Indian community study. Drug Alcohol Depend. 2010 Jan 15;106(2-3): 101-110.

Cannabis Use and Memory Brain Function in Adolescent Boys: A Cross-Sectional Multicenter Functional Magnetic Resonance Imaging Study

Early-onset cannabis use has been associated with later use/abuse, mental health problems (psychosis, depression), and abnormal development of cognition and brain function. During adolescence, ongoing neurodevelopmental maturation and experience shape the neural circuitry underlying complex cognitive functions such as memory and executive control. Prefrontal and temporal regions are critically involved in these functions. Maturational processes leave these brain areas prone to the potentially harmful effects of cannabis use. Dr. Jager and colleagues performed a two-site (United States and the Netherlands; pooled data) functional magnetic resonance imaging (MRI) study with a cross-sectional design, investigating the effects of adolescent cannabis use on working memory (WM) and associative memory (AM) brain function in 21 abstinent but frequent cannabis-using boys (13-19) years of age and compared them with 24 nonusing peers. Brain activity during WM was assessed before and after rule-based learning (automatization). AM was assessed using a pictorial hippocampal-dependent memory task. Cannabis users performed normally on both memory tasks. During WM assessment, cannabis users showed excessive activity in prefrontal regions when a task was novel, whereas automatization of the task reduced activity to the same level in users and controls. No effect of cannabis use on AM-related brain function was found. In adolescent cannabis users, the WM system was overactive during a novel task, suggesting functional compensation. Inefficient WM recruitment was not related to a failure in automatization but became evident when processing continuously changing information. The results seem to confirm the vulnerability of still developing frontal lobe functioning for early-onset cannabis use. Jager G, Block RI, Luijten M, Ramsey NF. Cannabis use and memory brain function in adolescent boys: A cross-sectional multicenter functional magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 2010;49(6): 561-572.

Abnormal Cerebellar Morphometry in Abstinent Adolescent Marijuana Users

Functional neuroimaging data from adults have, in general, revealed frontocerebellar dysfunction associated with acute and chronic marijuana (MJ) use. The goal of this study, conducted by Dr. Medina and colleagues, was to characterize cerebellar volume in adolescent chronic MJ users following 1 month of monitored abstinence. Participants were MJ users ($n=16$) and controls ($n=16$) aged 16-18 years. Extensive exclusionary criteria included history of psychiatric or neurologic disorders. Drug use history, neuropsychological data, and structural brain scans were collected after 28 days of monitored abstinence. Trained research staff defined cerebellar volumes (including three cerebellar vermis lobes and both cerebellar hemispheres) on high-resolution T1-weighted magnetic resonance images. Adolescent MJ users demonstrated significantly larger inferior posterior (lobules VIII-X) vermis volume than controls, above and beyond effects of lifetime alcohol and other drug use, gender, and intracranial volume. Larger vermis volumes were associated with poorer executive functioning. Following 1 month

of abstinence, adolescent MJ users had significantly larger posterior cerebellar vermis volumes than non-using controls. These greater volumes are suggested to be pathological based on linkage to poorer executive functioning. Longitudinal studies are needed to examine typical cerebellar development during adolescence and the influence of marijuana use. Medina KL, Nagel BJ, Tapert SF. Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Res. 2010 May 30;182(2): 152-159.

Test of Association between GABRA2 (SNP rs279871) and Adolescent Conduct/Alcohol Use Disorders Utilizing a Sample of Clinic Referred Youth with Serious Substance and Conduct Problems, Controls and Available First Degree Relatives

Recent findings have linked the GABRA2 gene with antisocial personality disorder and alcohol dependence (AD) in adults and conduct disorder (CD), but not AD symptoms, in children and adolescents. Dr. Sakai and colleagues sought to replicate previous findings and test for an association between a single nucleotide polymorphism (SNP) in the GABRA2 gene (rs279871) and CD among adolescents. Adolescent patients (n=371), 13-18 years old, were recruited from a university substance abuse treatment program. Patient siblings (n=245), parents of patients (n=355), adolescent controls (n=185), siblings of controls (n=163) and parents of controls (n=263) were included in these analyses (total sample n=1582). Case-control (using only Caucasian and Hispanic probands) and family-based association tests were completed to test for association between rs279871 and several a priori CD and AD phenotypes. For case-control association tests, rs279871 was significantly associated with CD (p=0.02) but not AD phenotypes; the result did not survive strict correction for multiple testing. All family-based association tests were non-significant (CD p=0.48; CD symptom count age corrected within sex p=0.91; AD p=0.84; alcohol use disorder p=0.52). Consistent with previous findings, the results do not support the association between GABRA2 SNP rs279871 and AD in adolescents. The results also do not support an association between rs279871 and CD; the study limitations are reviewed. Sakai JT, Stallings MC, Crowley TJ, Gelhorn HL, McQueen MB, Ehringer MA. Test of association between GABRA2 (SNP rs279871) and adolescent conduct/alcohol use disorders utilizing a sample of clinic referred youth with serious substance and conduct problems, controls and available first degree relatives. Drug Alcohol Depend. 2010 Jan 15;106(2-3): 199-203.

Prenatal Cocaine Exposure, Environmental Stress, and Cortisol Stress Reactivity in 11-year-olds

Researchers from the multi-site (Detroit, Miami, Memphis, and Providence) Maternal Lifestyle study examined the association between prenatal cocaine exposure and postnatal environmental adversity on salivary cortisol stress reactivity in school-aged children. Subjects included 743 11-year-old children (n = 320 cocaine-exposed; 423 comparison) followed since birth in a longitudinal prospective multisite study. Saliva samples were collected to measure cortisol at baseline and after a standardized procedure to induce psychological stress. Children were divided into those who showed an increase in cortisol from baseline to post stress and those who showed a decrease or blunted cortisol response. Covariates measured included site, birth weight, maternal pre and postnatal use of alcohol, tobacco or marijuana, social class, changes in caretakers, maternal depression and psychological symptoms, domestic and community violence, child abuse, and quality of the home. With adjustment for confounding variables, cortisol reactivity to stress was more likely to be blunted in children with prenatal cocaine exposure. Children exposed to cocaine and who experienced domestic violence showed the strongest effects. The combination of prenatal cocaine exposure and an

adverse postnatal environment could down regulate the hypothalamic-pituitary-adrenal axis resulting in the blunted cortisol response to stress possibly increasing risk for later psychopathology and adult disease. Lester BM, Lagasse LL, Shankaran S, Bada HS, Bauer CR, Lin RD, Abhik AR. Prenatal cocaine exposure related to cortisol stress reactivity in 11-year-old children. J Pediatr. 2010 Aug;157(2): 288-295.e1.

Sleep Problems in Children with Prenatal Substance Exposure

This study examined associations between sleep problems and prenatal exposure to cocaine, opiates, marijuana, alcohol, and nicotine in children aged 1 month to 12 years in the Maternal Lifestyle multi-site study. There were 808 participants, 374 exposed to cocaine and/or opiates, and 434 comparison subjects. Sleep problems in early, middle, and/or late childhood were assessed as composites of maternal report items. Prenatal nicotine exposure was the only unique predictor of sleep problems with adjustment for covariates, including socioeconomic status, marital status, physical abuse, prenatal medical care, and postnatal cigarette smoke exposure. Prenatal exposure to nicotine was positively associated with children's sleep problems persisting throughout the first 12 years of life. Targeting of this group of children for educational and behavioral efforts to prevent and treat sleep problems is merited given that good sleep may serve as a protective factor for other developmental outcomes. Stone KC, LaGasse LL, Lester BM, Shankaran S, Bada HS, Bauer CR, Hammond JA. Sleep problems in children with prenatal substance exposure: the maternal lifestyle study. Arch Pediatr Adolesc Med. 2010 May;164(5): 452-456.

Prenatal Cocaine Exposure, BMI and Blood Pressure at Age 9

Prenatal cocaine exposure has been linked to intrauterine growth retardation and poor birth outcomes; little is known about the effects on longer-term medical outcomes, such as overweight status and hypertension in childhood. The objective of this study was to examine the association between prenatal cocaine exposure and BMI and blood pressure at 9 years of age among children followed prospectively in the multisite longitudinal MLS study evaluating the impact of maternal lifestyle during pregnancy on childhood outcome. This analysis includes 880 children (277 cocaine exposed and 603 with no cocaine exposure) with blood pressure, height, and weight measurements at 9 years of age. Regression analyses were conducted to explore the relationship between prenatal cocaine exposure and BMI and blood pressure at 9 years of age after controlling for demographics, other drug exposure, birth weight, maternal weight, infant postnatal weight gain, and childhood television viewing, exercise, and dietary habits at 9 years. At 9 years of age, 15% of the children were prehypertensive and 19% were hypertensive; 16% were at risk for overweight status and 21% were overweight. A small percentage of women were exposed to high levels of prenatal cocaine throughout pregnancy. A higher BMI was noted in children born to these women. Path analysis used to further explore these relationships suggested that high cocaine exposure has an indirect effect on systolic and diastolic blood pressures that is mediated through its effect on BMI. High levels of in-utero cocaine exposure are a marker for elevated BMI and blood pressure among children born full term. Shankaran S, Bann CM, Bauer CR, Lester BM, Bada HS, Das A, Higgins RD, Poole WK, LaGasse LL, Hammond J, Woldt E. Prenatal cocaine exposure and BMI and blood pressure at 9 years of age. J Hypertens. 2010 Jun;28(6): 1166-1175.

Prenatal Methamphetamine Exposure and Neonatal Neurobehavioral

Outcomes in the USA and New Zealand Methamphetamine (MA) use among

pregnant women is a world-wide problem, but little is known of its impact on exposed infants. The prospective, controlled longitudinal Infant Development, Environment and Lifestyle (IDEAL) study of prenatal MA exposure from birth to 36 months was conducted in the US and NZ. The US cohort has 183 exposed and 196 comparison infants; the NZ cohort has 85 exposed and 95 comparison infants. Exposure was determined by self-report and meconium assay with alcohol, marijuana, and tobacco exposures present in both groups. The NICU Neurobehavior Scale (NNNS) was administered within 5 days of life. NNNS summary scores were analyzed for exposure including heavy exposure and frequency of use by trimester and dose-response relationship with the amphetamine analyte. MA exposure was associated with poorer quality of movement, more total stress/abstinence, physiological stress, and CNS stress with more nonoptimal reflexes in NZ but not in the USA. Heavy MA exposure was associated with lower arousal and excitability. First trimester MA use predicted more stress and third trimester use more lethargy and hypotonicity. Dose-response effects were observed between amphetamine concentration in meconium and CNS stress. Across cultures, prenatal MA exposure was associated with a similar neurobehavioral pattern of under arousal, low tone, poorer quality of movement and increased stress. LaGasse LL, Wouldes T, Newman E, Smith LM, Shah RZ, Derauf C, Huestis MA, Arria AM, Della Grotta S, Wilcox T, Lester BM. Prenatal methamphetamine exposure and neonatal neurobehavioral outcomes in the USA and New Zealand. Neurotoxicol. Teratol 2010, doi:10.1016/j.ntt.2010.06.009.

Prenatal Drug Exposure: Infant and Toddler Outcomes

This paper provides a current overview of the scientific literature on the impact of maternal drug use, specifically opioid and cocaine, during pregnancy on the acute and long-term outcomes of infants and toddlers from birth through age 3 years. Emphasis with regard to opioids is placed on heroin and opioid substitutes used to treat opioid addiction, including methadone, which has long been regarded as the standard of care in pregnancy, and buprenorphine, which is increasingly being investigated and prescribed as an alternative to methadone. Controlled studies comparing methadone at high and low doses, as well as those comparing methadone with buprenorphine, are highlighted and the diagnosis and management of neonatal abstinence syndrome is discussed. Over the past two decades, attention of the scientific and lay communities has also been focused on the potential adverse effects of cocaine and crack cocaine, especially during the height of the cocaine epidemic in the United States. Herein, the findings are summarized from prospective studies comparing cocaine-exposed with non-cocaine-exposed infants and toddlers with respect to anthropometric growth, infant neurobehavior, visual and auditory function, and cognitive, motor, and language development. The potentially stigmatizing label of the so-called "crack baby" preceded the evidence now accumulating from well-designed prospective investigations that have revealed less severe sequelae in the majority of prenatally exposed infants than originally anticipated. In contrast to opioids, which may produce neonatal abstinence syndrome and infant neurobehavioral deficits, prenatal cocaine exposure appears to be associated with what has been described as statistically significant but subtle decrements in neurobehavioral, cognitive, and language function, especially when viewed in the context of other exposures and the caregiving environment which may mediate or moderate the effects. Whether these early findings may herald more significant learning and behavioral problems during school-age and adolescence when the child is inevitably confronted with increasing social and academic challenges is the subject of ongoing longitudinal research. Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. J Addict Dis. 2010 Apr;29(2): 245-258.

ERP and Response Inhibition in ADHD with and without Prenatal

Alcohol Exposure

The attention and cognitive problems seen in individuals with a history of prenatal alcohol exposure often resemble those associated with attention deficit hyperactivity disorder (ADHD), but few studies have directly assessed the unique influence of each on neurobehavioral outcomes. Dr. Avison and his colleagues at Wayne State School of Medicine in Detroit recorded event-related potentials (ERPs) during a Go/No-go response inhibition task in young adults with prospectively obtained histories of prenatal alcohol exposure and childhood ADHD. Regardless of prenatal alcohol exposure, participants with childhood ADHD were less accurate at inhibiting responses. However, only the ADHD group without prenatal alcohol exposure showed a markedly diminished P3 difference between No-go and Go, which may reflect a more effortful strategy related to inhibitory control at the neural processing level. This finding supports a growing body of evidence suggesting that the manifestation of idiopathic ADHD symptoms may stem from a neurophysiologic process that is different from the ADHD symptomatology associated with prenatal alcohol exposure. Individuals who have been prenatally exposed to alcohol and present with ADHD symptomatology may represent a unique endophenotype of the disorder, which may require different treatment approaches from those found to be effective with idiopathic ADHD. Burden MJ, Jacobson JL, Westerlund A, Lundahl LH, Morrison A, Dodge NC, Klorman R, Nelson CA, Avison MJ, Jacobson SW. An event-related potential study of response inhibition in ADHD with and without prenatal alcohol exposure. Alcohol Clin Exp Res 2010 Apr; 34: 617-627.

Nicotine and Metabolites in Meconium as Evidence of Maternal Cigarette Smoking during Pregnancy and Neonatal Growth Deficits

Many women continue tobacco use during pregnancy despite known adverse consequences on neonatal growth and development. Testing meconium, the first neonatal feces, for tobacco biomarkers offers objective evidence of prenatal tobacco exposure. However, relationships between the amount, frequency, and timing of cigarette smoking during gestation and tobacco biomarker meconium concentrations and neonatal outcomes are unclear. In this study by Dr. Marilyn Huestis (NIDA IRP) and her extramural colleague Dr. Rina Eiden, eighty-seven pregnant women provided detailed self-reports of daily tobacco consumption throughout pregnancy. Nicotine, cotinine, and trans-3'-hydroxycotinine were quantified in neonatal meconium by liquid chromatography-tandem mass spectrometry. Among nonsmokers, all meconium specimens were negative, whereas nearly all meconium specimens were positive if the mother self-reported tobacco use into the third trimester. Tobacco biomarker concentrations were significantly albeit weakly correlated with mean cigarettes per day in the third trimester. Reduced birth weight, gestational age, or head circumference were observed if meconium contained one or more tobacco biomarkers, but deficits did not correlate with biomarker concentrations. While previously thought to reflect second and third trimester drug exposure, meconium appears to reliably identify only third trimester drug use. While a 10 ng/g nicotine, cotinine, or trans-3'-hydroxycotinine cutoff in meconium was previously proposed to differentiate tobacco-exposed from nonexposed or passively exposed neonates, improved maternal self-reporting techniques in this cohort suggest that a lower cutoff, equivalent to the analytic limits of quantification, is more appropriate. Gray TR, Eiden RD, Leonard KE, Connors G, Shisler S, Huestis MA. Nicotine and metabolites in meconium as evidence of maternal cigarette smoking during pregnancy and predictors of neonatal growth deficits. Nicotine Tob Res. 2010 Jun;12(6): 658-664. Epub 2010 Apr 28.

New Meconium Biomarkers of Prenatal Methamphetamine

Exposure Increase Identification of Affected Neonates

Prenatal methamphetamine (MAMP) exposure is poorly reflected in neonatal meconium. Often, maternal self-reported MAMP use is not corroborated by positive results in amphetamines immunoassays of meconium, and even if initial test results are positive, they frequently are not confirmed for MAMP or amphetamine (AMP) by chromatographic analysis. The presence of the MAMP metabolites p-hydroxymethamphetamine (pOHMAMP), p-hydroxyamphetamine (pOHAMP), and norephedrine (NOREPH) in meconium may improve the identification of MAMP- and AMP-exposed neonates. In this study by Dr. Marilyn Huestis (NIDA IRP) and her extramural colleagues from the IDEAL prenatal methamphetamine study, immunoassay-positive and -negative meconium samples were subjected to liquid chromatography- tandem mass spectrometric reanalysis for these recently identified metabolites. pOHAMP and NOREPH were detected only when MAMP and/or AMP were present and thus do not appear to be promising biomarkers of prenatal MAMP exposure. pOHMAMP, in contrast, identified 6 additional neonates whose mothers reported MAMP exposure, yet had a meconium sample screened as negative; pOHMAMP was more likely to be present if maternal MAMP use continued into the third trimester. Although the pOHMAMP results for meconium samples corroborated the maternal self-reports, the confirmation rate for positive meconium screening results did not improve with the inclusion of these new biomarkers. pOHMAMP identified additional MAMP- exposed neonates; therefore, MAMP, AMP, and pOHMAMP should be included in meconium chromatographic analyses. Maximizing the identification of MAMP-exposed children requires improvement in immunoassay screening tests to reduce false-negative and false-positive results. Additional research will help clarify which AMP-related compounds, if any, contribute to unconfirmed positive results in screening tests. Furthermore, nonamphetamine compounds endogenous to the complex meconium matrix also may cross-react, making chromatographic confirmation of screening results essential. Gray TR, Kelly T, LaGasse LL, Smith LM, Derauf C, Grant P, Shah R, Arria A, Haning W, Della Grotta S, Strauss A, Lester BM, Huestis MA. New meconium biomarkers of prenatal methamphetamine exposure increase identification of affected neonates. Clin Chem 2010 May 56(5): 856-860, Epub 2010 Feb 25.

Improvement in Intelligence from 6 to 10 years in Children of Teenage Mothers

This study by Dr. Marie Cornelius and colleagues is part of a study of the long-term outcomes of cigarette smoking in teenage mothers. This study investigates change in IQ scores among 290 children born to teenage mothers and identifies social, economic, and environmental variables that may be associated with change in intelligence test performance. The children of 290 teenage mothers (72% African-American and 28% European American) were assessed with the Stanford-Binet Intelligence Scale-4th Edition at ages 6 and 10. The mean composite score at age 6 was 84.8 and 91.2 at age 10, an improvement of 6.4 points. Significant cross-sectional predictors at both ages 6 and 10 of higher Stanford-Binet Intelligence Scale scores were maternal cognitive ability, school grade, white ethnicity, and caregiver education. Having more children in the household significantly predicted lower Stanford-Binet Intelligence Scale scores at age 6. Higher satisfaction with maternal social support predicted higher Stanford-Binet Intelligence Scale scores at age 10. Change in IQ scores was not related to maternal socioeconomic status, social support, home environment, ethnicity, or family interactions. Custodial stability was associated with an improvement in IQ scores, whereas increase in caregiver depression was related to decline in IQ scores. These findings suggest that improvement in IQ scores of offspring of teenage mothers may be related to stability of maternal custody. More research is needed to determine the impact of the maturation of adolescent mothers' parenting and the role of early education on improvement in cognitive abilities. Cornelius MD,

Goldschmidt L, De Genna NM, Richardson GA, Leech SL, Day R. Improvement in intelligence test scores from 6 to 10 years in children of teenage mothers. J Dev Behav Pediatr. 2010 Jun;31(5): 405-413.

Substance Use in HIV-Infected Women During Pregnancy: Self-Report Versus Meconium Analysis

Dr. Kathy Tassiopoulos and her colleagues from the Pediatric HIV/AIDS Cohort Study evaluated prenatal substance use in a cohort of 480 HIV-infected women and their uninfected children. Substance use was reported by 29%; the most common substances reported were tobacco (18%), alcohol (10%), and marijuana (7.2%). Fewer than 4% of women reported cocaine or opiate use. Substance use was more common in the first trimester (25%) than the second (17%) and third (15%) and was associated with race/ethnicity, education, birthplace, age and marital status. For 264 mother/infant pairs with meconium results, sensitivity of self-report was 86% for tobacco, 80% for marijuana and 67% for cocaine. Higher discordance between self-report and urine/blood toxicology was observed for cocaine, marijuana and opiates in a non-random subset of mothers/infants with these tests. Findings suggest reasonably complete self-reporting of substance use as confirmed by meconium analysis. Illicit substance use was low and substantially less than that reported in earlier studies of HIV-infected women, but alcohol and tobacco exposure was prevalent. Tassiopoulos K, Read JS, Brogly S, Rich K, Lester B, Spector SA, Yogev R, Seage GR 3rd. Substance use in HIV-infected women during pregnancy: self-report versus meconium analysis. AIDS Behav. 2010 Jun 8. [Epub ahead of print].

Relationships Between Markers of Vascular Dysfunction and Neurodevelopmental Outcomes in Perinatally HIV-infected Youth

This study from the Pediatric HIV/AIDS Cohort Study (PHACS) examined the relationship between markers of vascular dysfunction and neurodevelopmental status in pediatric HIV disease. A cross-sectional design within a prospective, 15-site cohort study was conducted in the United States. Nine vascular biomarkers were examined in 89 HIV-infected children: soluble P-selectin/sCD62P, fibrinogen, adiponectin, monocyte chemoattractant protein-1/CCL-2, interleukin-6, C-reactive protein, soluble vascular cell adhesion molecule-1/sCD106, sE-selectin/sCD62E, and soluble intercellular adhesion molecule-1/sCD54. The Wechsler Intelligence Scale for Children-Fourth edition (WISC-IV) was administered yielding indices for verbal comprehension, perceptual reasoning, working memory and processing speed, and overall composite Full-Scale IQ score. Linear regression models were used to evaluate neurodevelopmental status (measured by WISC-IV scores) as a function of each biomarker while adjusting for demographics, disease severity, and receipt of HAART. Biomarker levels were evaluated in quartiles to evaluate trends in WISC-IV responses. Among the 89 HIV-infected children (median age = 12 years), 56% were girls, 71% black, 16% Hispanic, and 43% had yearly household income below US $20,000. Log (soluble P-selectin) was significantly correlated with all WISC-IV scores; adjusted slopes showed 6-11-point average decrease in scores for each one log unit increase in soluble P-selectin. Final linear regression models for log (fibrinogen) adjusted for sociodemographic and disease characteristics also indicated a negative correlation with all WISC-IV scores (13-30-point decrease for each one log unit increase in fibrinogen); these decreases were significant in the verbal comprehension, perceptual reasoning, and Full-Scale IQ scores. Proinflammatory microvascular and immunologic mechanisms may be involved in neurodevelopmental impairment in children with perinatally acquired HIV disease. Kapetanovic S, Leister E, Nichols S, Miller T, Tassiopoulos K, Hazra R, Gelbard H, Malee KM, Kammerer B, Mendez AJ, Williams PL, Pediatric HIV/AIDS Cohort Study Team. Relationships between markers of vascular dysfunction and

neurodevelopmental outcomes in perinatally HIV-infected youth. AIDS. 2010 Jun 19;24(10): 1481-1491.

Substance Use and Psychosocial Factors in High-Risk Youth Living with HIV

The purpose of this study, conducted in the Adolescent Trials Network for HIV/AIDS Interventions (ATN) was to test relationships between psychosocial factors and alcohol and illicit drug use among high-risk youth living with HIV (YLH). One hundred eighty-six high-risk youth with HIV (defined as those with a substance use problem, sexual risk problem, or medication adherence problem) were enrolled across five cities (ages 16-24). Alcohol and illicit drug use were measured with the alcohol, smoking, and substance involvement screening test and a timeline follow-back interview. Questionnaires assessed constructs from the adapted Transtheoretical Model (TTM) including a continuous measure of motivational readiness in response to criticisms of the stage component. Path analysis was utilized to fit cross-sectional data collected via computer assisted personal interviewing (baseline data from intervention study). Separate models were fit for each commonly used substance. In the previous month, 47% used alcohol, 37% used cannabis, and 9% used other illicit drugs. Path models fit the data well and accounted for 30% of the variance in alcohol use and 47% in cannabis use. Higher self-efficacy predicted lower alcohol and cannabis use, but motivational readiness was only directly related to cannabis use. A reduction in pros of substance use was indirectly related to use. Social support and psychological distress were associated with TTM constructs. Interventions focusing on improving motivation and self-efficacy for healthy behaviors may reduce substance use in YLH. Naar-King S, Kolmodin K, Parsons JT, Murphy D, ATN 004 Protocol Team, Adolescent Trials Network for HIV/AIDS Interventions. Psychosocial factors and substance use in high-risk youth living with HIV: a multi-site study. AIDS Care. 2010 Apr;22(4): 475-482.

Youth Living with HIV and Problem Substance Use: Elevated Distress is Associated with Nonadherence and Sexual Risk

The purpose of this Adolescent Trials Network for HIV/AIDS Interventions (ATN) study was to examine health risk behaviors in distressed youth living with HIV (YLH) with problem substance use. The study assessed distress, antiretroviral (ARV) adherence, and unprotected sex in a racially and geographically diverse sample of 122 YLH. A total of 87% of distressed YLH reported significantly more past-month ARV nonadherence (odds ratio [OR] = 7.15) and were more likely to have unprotected sex under the influence (OR = 5.14) than nondistressed youth. Distressed YLH with problem substance use may benefit from interventions to improve adherence and to decrease sexual risk, especially while under the influence of drugs. Nugent NR, Brown LK, Belzer M, Harper GW, Nachman S, Naar-King S, Adolescent Trials Network for HIV/AIDS Interventions. Youth living with HIV and problem substance use: elevated distress is associated with nonadherence and sexual risk. J Int Assoc Physicians AIDS Care (Chic Ill). 2010 Mar-Apr;9(2): 113-115.

Transition of Adolescents with HIV to Adult Care in the ATN

The transition process from pediatric to adult health care for adolescents with chronic diseases is always challenging and can be even more so for adolescents with HIV disease. The purpose of this study was to describe characteristics and current practices surrounding the transition of adolescents from the clinics of the Adolescent Trials Network for HIV/AIDS Interventions (ATN) to adult medical care. This report focuses on the processes of transition, perceived barriers and facilitators, and anecdotal reports of successes and failures.

Practice models used to assist adolescents during transition to adult medical care are described. Interviews were conducted with 19 key informants from 14 Adolescent Trials Network clinics. Findings revealed no consistent definition of "successful" transition, little consensus among the sites regarding specific elements of a transition program, and a lack of mechanisms to assess outcomes. Sites that viewed transition as a process rather than an event consistently described more structured program elements. Gilliam PP, Ellen JM, Leonard L, Kinsman S, Jevitt CM, Straub DM. Transition of adolescents with HIV to adult care: Characteristics and current practices of the Adolescent Trials Network for HIV/AIDS Interventions. J Assoc Nurses AIDS Care. 2010 Jun 9. [Epub ahead of print].

Identification of HIV-Infected 12- to 24-Year-Old Men and Women in 15 US Cities Through Venue-Based Testing

Racial and ethnic minority women and men who have sex with men (WSM and MSM) compose the majority of new HIV cases among adolescents and young adults. The purpose of this study was to test whether "venue-based testing" could identify human immunodeficiency virus (HIV) infection in US youth, 12 to 24 years of age, who were otherwise not aware of their infection. Venues were selected in communities surrounding the 15 Adolescent Trials Network for HIV/AIDS Interventions (ATN) clinical sites to take part in the study over a 3-month period. At each venue, ATN sites recruited 20 to 30 English- or Spanish-speaking at-risk youth (12 to 24 years of age), resulting in a total of 1217 study participants, including 611 MSM and 606 WSM. Intervention Venue-based HIV testing had two components: An anonymous audio computer-assisted self-administered interview and an anonymous HIV antibody assay. The prevalence of HIV infection in MSM and WSM was 15.3% and 0.3%, respectively. Sixty percent of the MSM and 100% of the WSM claimed to not know of their infection. Venue-based testing may be an important strategy to identify HIV-infected younger MSM; however, other strategies are needed for WSM. Barnes W, D'Angelo L, Yamazaki M, Belzer M, Schroeder S, Palmer-Castor J, Futterman D, Kapogiannis B, Muenz L, Harris DR, Ellen JM; for the Adolescent Trials Network for HIV/AIDS Interventions. Identification of HIV-Infected 12- to 24-year-old men and women in 15 US cities through venue-based testing. Arch Pediatr Adolesc Med. 2010 Mar;164(3): 273-276.

Motivational Intervention Targeting Substance Use, Sexual Risk Behavior and Medication Adherence in Youth Living with HIV

Interventions targeting multiple risk behaviors are needed for youth living with HIV (YLH). A randomized clinical trial compared Healthy Choices, a four session motivational intervention targeting two of the three risk behaviors (HIV medication adherence, sexual risk behavior and substance use) to multidisciplinary specialty care alone. This article presents intermediary outcomes available at 3-month follow-up, variables proposed to be precursors to behavior change (motivation, self-efficacy, and depression). YLH (N=186) with at least one of the three problem behaviors were recruited from four sites in the Adolescent Trials Network for HIV/AIDS Interventions and one non-Adolescent Trials Network site, and were assessed at baseline and 3 months. Of the 94 youth randomly assigned to the treatment condition, 84% received at least one session, 67% received at least two sessions, 56% received at least three sessions, and 49% completed all four sessions. In intent-to-treat analysis, only depression was significantly improved in the treatment group as compared with controls. However, in per-protocol analysis, youth receiving at least two sessions of the intervention also showed significant improvements in motivational readiness to change as compared with youth in the control condition. Results suggest the potential benefits of clinic-based motivational interventions for YLH who access these interventions. Delivering interventions in the community using an outreach model may improve access. Analysis of

subsequent time points will determine effects on actual behavior change. Naar-King S, Parsons JT, Murphy D, Kolmodin K, Harris DR and the Adolescent Trials Network 004 Protocol Team. A multisite randomized trial of a motivational intervention targeting multiple risks in youth living with HIV: initial effects on motivation, self-efficacy, and depression. J Adolesc Health. 2010 May;46(5): 422-428.

Demographic Profiles of Newly Acquired HIV Infections among Adolescents and Young Adults in the U.S.

Understanding the demographic and risk profiles of youth with recent HIV infection offers insight for imputing the dynamics of the epidemic and targeting prevention efforts. Three hundred forty-two HIV-positive youth were tested as part of the Adolescent Trials Network for HIV/AIDS Interventions (ATN) using a Sensitive/Less Sensitive strategy; 33% were classified as recently infected; with the majority male (58%), 51% African American and 26% Hispanic. There was no difference in the percent of recent vs. established cases for injection drug use (2.7% vs. 4.8%), sex while under the influence of non-injection drugs and/or alcohol (24.1% vs. 22.2%), or exchange of sex for drugs/money or given drugs/money for sex (8.9% vs. 7.8%). Among recently infected male youth 84% of all blacks, 88% of all whites, and 94% of Hispanics engaged in men-having-sex-with-men (MSM) behaviors. Of 112 recent infection cases 29% were on ARVs vs. 20% of those with established infections. Sill AM, Constantine NT, Wilson CM, Peralta L, Adolescent Trials Network for HIV/AIDS Interventions. Demographic profiles of newly acquired HIV infections among adolescents and young adults in the U.S. J Adolesc Health. 2010 Jan;46(1): 93-96.

Multiple Risk Behaviors among Youth Living with HIV

The purpose of this study was to describe multiple risk behaviors (substance use, sexual risk, and medication adherence) in a multi-site sample of youth living with human immunodeficiency virus (HIV) in five U.S. cites. Youth (N=352) were recruited from four Adolescent Trials Network (ATN) sites (Philadelphia, Fort Lauderdale, Baltimore, and Los Angeles) and one non-ATN site in Detroit and screened for multiple problem behaviors for an intervention study. A substance abuse problem was determined with the CRAFFT, a six-item adolescent screener. Single items were used to screen for current sexual risk and for an HIV medication adherence problem. Of the youth, 239 (68%) had at least one of the three risk behavior problems based on the screener. A total of 186 (52.8%) completed longer, in-depth questionnaires for each problem behavior. Of the 352 youth screened, 60% had problem level substance use and 42% had a sexual risk problem. Of the 165 (47%) who were prescribed medications, 91 (55%) reported an adherence problem. A total of 112 (32%) reported no problem behavior, 123 (35%) reported 1 problem behavior, 95 (27%) reported 2 problem behaviors, and 20 (6%) reported 3 problem behaviors. Males were more likely to have a substance use problem. Younger youth living with HIV and those perinatally infected were more likely to have an adherence problem. Among the 186 (52.8%) completing longer measures, those with a substance abuse problem had higher substance use on a timeline follow-back procedure than those without. Participants who screened positive for a sexual risk problem reported more unprotected sex on an in-depth interview than those without. Those who screened positive for an adherence problem had higher viral loads than those without an adherence problem. Results suggest high rates of problem behaviors among youth living with HIV, particularly in older youth. Younger and perinatally infected youth may require specialized adherence interventions. Associations between the screener and more in-depth assessment measures suggest potential clinical utility of screening youth for high-risk behaviors. Tanney MR, Naar-King S, Murphy DA, Parsons JT, Janisse H, ATN 004 Protocol Team. Multiple risk behaviors among

youth living with human immunodeficiency virus in five U.S. cities. J Adolesc Health. 2010 Jan;46(1): 11-16.

Risks for Nonadherence to ART among Perinatally HIV Infected Youth in the U.S.

Adherence to antiretroviral regimens continues to be a significant problem in HIV-infected individuals facing a lifetime of therapy. Youth who were infected through perinatal transmission enter into adolescence often with a history of multiple medication regimens. Thus, adherence can be a particularly important issue in these young people, as medication options can often be limited. This cross-sectional, observational study was conducted as part of the Adolescent Trials Network for HIV/AIDS Interventions (ATN) to determine the prevalence of personal barriers to adherence and to identify associations among the following barriers in subjects 12 to 24 years old: mental health barriers, self-efficacy and outcome expectancy, and structural barriers. Among the 368 study participants, 274 (74.5%) were adherent and 94 (25.5%) were nonadherent to highly active antiretroviral therapy (HAART). No significant differences were found between adherent and nonadherent subjects according to mental health disorders. Adherence was associated with some but not all structural barriers. Both self-efficacy and outcome expectancy were significantly higher in adherent versus nonadherent subjects. In subjects with low self-efficacy and outcome expectancy, adherence differed according to the presence or absence of either mental health or structural barriers, similar to findings in behaviorally-infected adolescents. Interventions that address the breadth and clustering of adherence barriers in adolescents are needed to have the maximum chance for positive effects. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIV/AIDS Interventions. Prevalence and interactions of patient-related risks for nonadherence to antiretroviral therapy among perinatally infected youth in the United States. AIDS Patient Care STDS. 2010 Feb;24(2): 97-104.

Health Literacy and ART Adherence among HIV-Infected Adolescents

This study from the Adolescent Trials Network for HIV/AIDS Interventions (ATN) investigates HIV positive adolescents' health literacy and whether factors associated with health literacy in HIV-positive adults are associated with health literacy among HIV-positive adolescents. Adolescents in this study were behaviorally and perinatally HIV-infected youth (n=186) from five U.S. cities. Participants had a mean age of 20.5, and 49.5% were male. Contrary to findings for adult HIV-positive patients, among adolescents health literacy was not significantly associated with: Medication adherence adjusting for age and education level; viral load; or self-efficacy to adhere to medication regimens. The only significant association was of health literacy with medical care received. Murphy DA, Lam P, Naar-King S, Robert HD, Parsons JT, Muenz LR, Adolescent Medicine Trials Network for HIV/AIDS Interventions. Health literacy and antiretroviral adherence among HIV-infected adolescents. Patient Educ Couns. 2010 Apr;79(1): 25-29.

Predictors of Condom Use in a Multisite Study of High-Risk Youth Living with HIV

Risky sexual behavior among youth living with HIV (YLH) must be addressed in order to prevent the spread of the disease. This Adolescent Trials Network for HIV/AIDS Interventions (ATN) study investigated factors associated with condom use in a multi-site sample of YLH (ages 16-24). Baseline assessments were conducted with 186 YLH using a computer assisted personal interview (CAPI). Path analysis suggested that condom use was directly predicted by

motivational readiness and self-efficacy for safer sex. Substance use was not a significant predictor of condom use. Interventions that promote self-efficacy and motivational readiness through a variety of mechanisms may be useful in understanding and conceptualizing sexual risk behavior in YLH. However, further predictors must be studied to account for more variance. Outlaw AY, Naar-King S, Janisse H, Parsons JT and the Adolescent Trials Network for HIV/AIDS Interventions. Predictors of condom use in a multisite study of high-risk youth living with HIV. AIDS Educ Prev. 2010 Feb;22(1): 1-14.

Development of Sexual and Ethnic Identity For Gay-Bisexual-Questioning Latino and African American Male Adolescents

Identity development is a critical task of adolescence and occurs across multiple areas of self-identification. Although research on the identity development process among individuals who are ethnic and sexual minorities has been conducted for individuals who have one minority status or the other, few studies have examined these processes in people who are both ethnic and sexual minorities. In this qualitative study conducted as part of intervention development work in the Adolescent Trials Network for HIV/AIDS Interventions (ATN) , the authors examined the dual identity development processes related to ethnic and sexual identity among gay-bisexual-questioning (GBQ) Latino and African American male adolescents. Results indicated that the processes associated with the development of sexual orientation and ethnic identity occur concurrently. However, the actual processes involved with the development of each identity not only differed, but seemed to be independent of each other because neither process was referenced in the development of the other. Overall, the process of ethnic identity development involved the process of becoming aware of one's ethnic and cultural heritage, whereas sexual identity development involved finding one's own personally relevant sexual orientation label and connecting to that community. The implications of these findings for the development of interventions to assist in the healthy development of GBQ adolescents are discussed. Jamil OB, Harper GW, Fernandez MI, Adolescent Trials Network for HIV/AIDS Interventions. Sexual and ethnic identity development among gay-bisexual-questioning (GBQ) male ethnic minority adolescents. Cultur Divers Ethnic Minor Psychol. 2009 Jul;15(3): 203-214.

Impaired Generation of Hepatitis B Virus-Specific Memory B Cells in HIV-Infected Individuals Following Vaccination

Hepatitis B-specific memory B cell (HSMBC) frequencies were measured following hepatitis B vaccination in 15 HIV uninfected and 12 HIV infected adolescents in the Adolescent Trials Network for HIV/AIDS Interventions (ATN). HSMBC were detected at significantly lower frequencies in HIV infected than in HIV uninfected individuals. The detection of HBsAb >10mIU/ml at study week 28 was strongly associated with the detection of HSMBC and a direct correlation between HBsAb titers and HSMBC frequencies was observed. In HIV uninfected individuals, antibody titers >1000mIU/ml were associated with higher HSMC frequencies. Lower HSMBC frequencies, reduced memory B cell (MBC) proliferation, and altered B cell phenotypes were measured in viremic HIV infected individuals compared with aviremic HIV infected or HIV uninfected individuals. Mehta N, Cunningham CK, Flynn P, Pepe J, Obaro S, Kapogiannis BG, Bethel J, Luzuriaga K, Adolescent Trials Network for HIV/AIDS Interventions. Impaired generation of hepatitis B virus-specific memory B cells in HIV infected individuals following vaccination. Vaccine. 2010 May 7;28(21): 3672-3678.

Hepatitis B Vaccination in Urban Adolescents

Multiple studies have shown excellent response rates after hepatitis B

immunization in youth; however, one previous study conducted in urban youth demonstrated poor responses. Urban youth, ages 12 to 17 years, at participating Adolescent Medicine Trials Network for HIV/AIDS Interventions Clinical/Research sites were randomized to receive either 2 doses of Recombivax HB (10 microg hepatitis B surface antigen) or Twinrix (20 microg hepatitis B surface antigen and 720 EL.U hepatitis A antigen) at 0 and 24 weeks. Safety data were collected and antibody measures performed at 0, 28, and 76 weeks. A total of 123 subjects were enrolled and 102 had week 28 serum samples available for antibody measure. A positive response (serum antibody > or =10 mIU/mL) to hepatitis B antigen was documented in 41 of 47 Recombivax HB recipients and in 52 of 55 Twinrix recipients. In an adjusted analysis, those identified as Hispanic ethnicity (N = 86) were more likely to have a positive response whereas those who identified as not heterosexual (N = 9) were less likely to respond. The majority of youth in the Twinrix arm were hepatitis A antibody positive at baseline (26/51; 51%); however, 24 of 25 hepatitis A antibody negative youth responded to the hepatitis A component. Both vaccines were safe. Response rate to 2 doses of Recombivax HB in urban youth is lower than previous studies suggest. The factors associated with diminished response are not known. Cunningham CK, Rudy BJ, Xu J, Bethel J, Kapogiannis BG, Ahmad S, Wilson CM, Flynn PM; Adolescent Medicine Trials Network for HIV/AIDS Interventions. Randomized trial to determine safety and immunogenicity of two strategies for hepatitis B vaccination in healthy urban adolescents in the United States. Pediatr Infect Dis J. 2010 Jun;29(6): 530-534.

Mobilizing Communities around HIV Prevention for Youth to Bring About Structural Changes

Increasingly, HIV prevention efforts must focus on altering features of the social and physical environment to reduce risks associated with HIV acquisition and transmission. Community coalitions provide a vehicle for bringing about sustainable structural changes. This article shares lessons and key strategies regarding how three community coalitions located in Miami and Tampa, Florida, and San Juan, Puerto Rico engaged their respective communities as part of the Adolescent Trials for HIV/AIDS Interventions in bringing about structural changes affecting policies, practices and programs related to HIV prevention for 12-24-year-olds. Outcomes of this work include increased access to HIV testing and counseling in the juvenile correctional system (Miami), increased monitoring of sexual abuse between young women and older men within public housing, and support services to deter age discordant relationships (Tampa) and increased access to community-based HIV testing (San Juan). Chutuape KS, Willard N, Sanchez K, Straub DM, Ochoa TN, Howell K, Rivera C, Ramos I, Ellen JM; Adolescent Medicine Trials Network for HIV/AIDS Interventions. Mobilizing communities around HIV prevention for youth: how three coalitions applied key strategies to bring about structural changes. AIDS Educ Prev. 2010 Feb;22(1): 15-27.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - Clinical Neuroscience Research

Genetic Variants are Associated with Methadone Doses Required for Effective Treatment of Heroin Dependence

M.J. Kreek and associates at The Rockefeller University determined whether dose differences of methadone in maintained heroin addicts are related to gene variants of ABCB1 (MDR1) gene which encodes the transporter P-glycoprotein of which methadone is a substrate. There is a heterogeneous distribution of genotype allele frequencies between those requiring a higher (>150 mg/day) and lower dose groups for one SNP. Further, individuals with a 3-locus haplotype were 5-fold more likely to need a higher dose; those heterogeneous for this had a 3-fold chance of stabilizing at a lower dose. These data suggest gene variants may be clinically relevant with regard to methadone doses needed for maintenance. Levran O, O'Hara K, Peles E, Li D, Barral S, Ray B, Borg L, Ott J, Adelson M, Kreek MJ. ABCBI (MDR1) genetic variants are associated with methadone doses required for effective treatment of heroin dependence. Hum Mol Genet. 2008; 17(14): 2219-2227.

Genome-wide Association Study Identifies Genes that May Contribute to Risk for Developing Heroin Addiction

M.J. Kreek and associates at The Rockefeller University used an Affymetrix 100k chip to conduct a genome-wide association study in former severe heroin addicts and controls—separately assessing Caucasians and African Americans. Significant associations were found for the vulnerability to develop heroin addiction but they differ between the ethnic groups. In Caucasians, a variant was found in the unannotated region of 1q23.3. In African Americans, another SNP was found in the cytosolic dual specificity phosphatase 27 gene DUSP27. Analysis of the most significant variants in Caucasians yield three loci in the synaptic membrane exocytosis regulating protein 2 gene RIMS2 while those in African-Americans are in cardiomyopathy associated gene CMYA3. Nielsen DA, Fei J, Yuferov V, Ho A, He C, Ott J, Kreek MJ. Genome-wide association study identifies genes that may contribute to risk for developing heroin addiction. Psychiat Genet. 2010 June. [Epub ahead of print].

Individual Differences in Heritability of Risk-Taking

A.P. Anokhin at Washington University studied male and female monozygotic and dizygotic twins to assess the heritability of risk-taking using the BART (an accepted measure of risk-taking). Subjects were assessed twice during early adolescence (ages 12 and 14). Heritability was modest at the early age but later increased to 55% in males but became non-significant in females. It appears, therefore, that this particular test of risk-taking may assess an endophenotype and may only be valid in males. Anokhin AP, Golosheykin S,

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Grant J, Heath AC. Heritability of risk-taking in adolescence: a longitudinal twin study. Twin Res Hum Genet. 2009 Aug; 12(4): 366-371.

Harsh Corporal Punishment (HCP) is Associated with Decreased Measure of Blood Flow in Dopamine-Rich Regions

M.H. Teicher and associates at Harvard and McLean Hospital recruited college students who reported spanking and such as children to assess neurobiological structures that could have been affected by the punishment. The assessment was accomplished by a specially-developed analysis of T2 relaxometry in steady-state fMRI which is inversely correlated with regional cerebral blood volume. Subjects who had experienced HCP had significantly greater relaxation time in the right caudate and right putamen which to some extent also correlated inversely with measures of short term visual and global memory. While there was no correlation to drug use in these regions, there were correlations between frequency of drug use and relaxation time in bilateral DLPFC and ACC. These data indicate that a relationship between corporal punishment which is less severe than outright physical punishment can influence neurophysiological development which in part increases risk for drug abuse. Sheu Y-S, Polcari A, Anderson CM, Teicher MH. Harsh corporal punishment is associated with increased T2 relaxation time in dopamine-rich regions. NeuroImage. 2010. [doi:10.1016/j.neuroimage.2010.06.043 [Epub ahead of print].

Successful Reversal Learning Recruits Frontocortical Regions Distinct from those of General Response Inhibition

The ability to flexibly respond to changes in the environment is critical for adaptive behavior, and is germane to decisions to refrain from responding to drug cues in drug abuse recovery. Reversal learning (RL) procedures test adaptive response updating when contingencies are altered. David Jentsch and colleagues at UCLA used functional magnetic resonance imaging to examine brain areas that support specific RL components by comparing neural responses to RL and initial learning (acquisition) to isolate reversal-related brain activation independent of cognitive control processes invoked during initial feedback-based learning. Lateral orbitofrontal cortex (OFC) was more activated during reversal than acquisition, suggesting its relevance for reformation of established stimulus-response associations. In addition, the dorsal anterior cingulate (dACC) and right inferior frontal gyrus (rIFG) correlated with change in post-reversal accuracy. These regions and lateral OFC represent distinct neural components that support behavioral flexibility important for adaptive learning. That chronic drug abuse disrupts frontocortical neurocircuitry presents a partial explanation for the difficulty in maintaining abstinence. Ghahremani DG, Monterosso J, Jentsch JD, Bilder RM, Poldrack RA. Neural components underlying behavioral flexibility in human reversal learning. Cereb Cortex. 2010 Aug; 20(8): 1843-1852.

fMRI Study Reveals Brain Circuitry Recruited When We May Need to Say "When"

A. Aron and colleagues at UCSD used trans-cranial magnetic stimulation (TMS) to determine the specific neurocognitive process that underlies the ability to respond with restraint which is an important aspect of cognitive control. The study measured the difference between how much responses slowed (response delay effect) when people respond to "go" stimulus and when they might suddenly need to stop the initiated response compared to when they do not need to stop. They hypothesized that this response delay effect could relate to one or more neurocognitive mechanism(s): partial response suppression (i.e., "active braking"), prolonged decision time, and slower response facilitation.

Publications

Staff Highlights

Grantee Honors

Using TMS, they found that the response delay effect is at least partly explained by active braking, possibly involving a mechanism that is similar to that used to stop responses completely. These results further our understanding of how people respond with restraint by pointing to proactive recruitment of a neurocognitive mechanism heretofore associated with outright stopping. Jahfari S, Stinear CM, Claffey M, Verbruggen F, Aron AR. Responding with restraint: what are the neurocognitive mechanisms? J Cogn Neurosci. 2010 Jul; 22(7): 1479-1492.

Anti-Morphine Antibody: A Novel Target of Medication on the Development of Morphine Tolerance?

J. Mao and colleagues at Massachusetts General Hospital evaluated tolerance to the antinociceptive effect of morphine after a prolonged exposure. After seven consecutive days, development of anti-morphine antibody was evident in rats rendered tolerant to antinociception. The anti-morphine antibody surpressed morphine-induced outward inhibiting current when it was superfused onto animal's spinal cord. Co-administration of morphine with a monoclonal antibody (2.4G(2)) against Fc receptors for seven days significantly attenuated the production of anti-morphine antibody, as well as the behavioral manifestation of morphine tolerance in some rats. These results indicate that anti-morphine antibody produced by chronic morphine exposure may contribute to the development of morphine tolerance possibly through counteracting the inhibitory morphine effect on spinal cord dorsal horn neurons. Kim H, Oh S, Sung B, Tian Y, Yang L, Wang S, Mao J. Anti-morphine antibody contributes to the development of morphine tolerance in rats. Neurosci Lett. 2010 Aug 23;480(3): 196-200.

Sex Differences in Pain and Misuse of Prescription Analgesics among Persons with HIV

J.C. Tsao and colleagues examined sex differences in pain and the use and misuse of prescription analgesics in a representative sample of HIV+ persons in the United States, using a data system that permits a prospective, longitudinal design and structural equation modeling. Women reported more pain than men over a 6-month period regardless of mode of HIV transmission or prior drug use history. Men acknowledged more misuse of prescription analgesics over a 1-year period compared with women, after taking into account pain, use of analgesics specifically for pain, and drug use history. Problem drug use history exerted significant direct and indirect effects on pain, opioid misuse, and pain-specific analgesic use across sex. The findings are consistent with prior evidence indicating female pain predominance as well as the under-treatment of pain among women with HIV. The studies inform the need to improve the assessment and long-term management of pain in HIV+ persons. Tsao JC, Stein JA, Dobalian A. Sex differences in pain and misuse of prescription analgesics among persons with HIV. Pain Med. 2010 Jun;11(6): 815-824.

Overlapping Cognitive Resources Play a Role in Both Pain Processing and Executive Working Memory

T.D. Wager and colleagues evaluated whether pain processing and cognitive function engaged an overlapping set of domain-general, capacity-limited mental resources. A novel paradigm was used in the study to measure concurrent pain and executive working memory in that both task difficulty and the intensity of nociceptive stimulus could be individually calibrated for each participant. Participants reported less pain during the working memory task compared to a visual-matching control condition. Conversely, increasing levels of heat incrementally reduced task performance. Path analyses showed that variations in pain mediated this effect, and that even within a given heat level,

trial-by-trial fluctuations in pain predicted decrements in performance. These findings suggested that overlapping cognitive resources play a role in both pain processing and executive working memory. It was proposed that the paradigm could further be used to understand more precisely which components of executive function or other cognitive resources contribute to the experience of pain. Buhle J, Wager TD. Performance-dependent inhibition of pain by an executive working memory task. Pain. 2010 Apr;149(1): 19-26.

Gender Differences in Risk Factors for Aberrant Prescription Opioid Use

A.D. Wasan and colleagues conducted a longitudinal predictive study to examine gender differences in the clinical correlates of risk for opioid misuse among chronic non-cancer pain patients prescribed opioids for pain. Understanding gender differences in substance abuse risk among chronic non-cancer pain patients is important for clinical assessment and treatment. The observational study used a series of patient report outcomes. After 5 months, the subjects were administered a structured prescription drug use interview and submitted a urine sample for toxicology assessment. Their treating physicians also completed a substance misuse behavior checklist. The 5-month follow-up assessment revealed that women tended to score higher on items relating to psychological distress, whereas the male patients tended to report having more legal and behavioral problems. The study suggests that risk factors associated with prescription opioid misuse may differ between men and women. Women are at greater risk to misuse opioids because of emotional issues and affective distress, whereas men tend to misuse opioids because of legal and problematic behavioral issues. Jamison RN, Butler SF, Budman SH, Edwards RR, Wasan AD. Gender differences in risk factors for aberrant prescription opioid use. J Pain. 2010 Apr;11(4): 312-320.

Brain fMRI as Signature of Clinical Trigeminal Neuropathic Pain

D. Borsook, A.D. Wasan and colleagues at McLean Hosptial evaluated the use of brain functional magnetic resonance imaging (fMRI) methods as a signature for clinical pain and pain management. A double-blind 1:1 randomized trial was conducted to evaluate the effects of lamotrigine vs. placebo on patient reported outcome of pain. Lamotrigine decreased pain intensity and achieved an average 63% reduced analgesic effect (from 5.6 to 3.5 on a VAS scale), while it had no effect on other sensory stimuli. Under that condition, the contrast analysis of fMRI results for heat stimuli applied to the affected face for lamotrigine vs. placebo showed an overall decrease in the signal that measures brain blood oxygen dependent level. The pilot study suggested a potential inhibitory effect of the drug on predominantly cortical regions (frontal, parietal, and temporal) that are detectable using fMRI. Scrivani S, Wallin D, Moulton EA, Cole S, Wasan AD, Lockerman L, Bajwa Z, Upadhyay J, Becerra L, Borsook D. An fMRI evaluation of lamotrigine for the treatment of trigeminal neuropathic pain: pilot study. Pain Med. 2010 Jun;11(6): 920-941.

Virtual Reality Hypnosis as an Adjunct Analgesic for Pain Associated with Recovery from Physical Trauma

S.R. Sharar and colleagues assessed the adjunct analgesic effect of virtual reality hypnosis--posthypnotic suggestions administered in combination with standard analgesic care. The posthypnotic suggestions were pain reduction/forgetting about the pain, emotional calm, improved sleep, recalling positive experiences, and looking forward to a better future. Patients under virtual reality hypnosis reported less pain intensity and less pain unpleasantness in comparison to those who experienced virtual reality distraction without hypnosis and standard care alone. Since pain following

traumatic injuries often prolongs injury recovery and provides additional challenge in patient management, the study suggests that virtual reality hypnosis could hold promise as an adjunctive analgesic approach. Patterson DR, Jensen MP, Wiechman SA, Sharar SR. Virtual reality hypnosis for pain associated with recovery from physical trauma. Int J Clin Exp Hypn. 2010 Jul;58(3): 288-300.

Genetic x Environmental Mediation in the Association between Conduct Problems and Maltreatment

J.K. Hewitt and colleagues estimated the contribution of gene x environment to the association between maltreatment and conduct problems. Bivariate behavior genetic analyses were conducted on approximately 1,650 twin and sibling pairs drawn from a large longitudinal study of adolescent health. The correlation between maltreatment and conduct problems was found to be small - much of the association between maltreatment and conduct problems was due to a nonpassive gene-environment correlation. Results were more consistent with the hypothesis that parents respond to children's genetically-influenced conduct problems by maltreating them rather than the maltreatment causing conduct problems. Schulz-Heik RJ, Rhee SH, Silvern LE, Haberstick BC, Hopfer C, Lessem JM, Hewitt JK. The association between conduct problems and maltreatment: testing genetic and environmental mediation. Behav Genet. 2010 May;40(3): 338-348.

Monetary Incentives Promote Smoking Abstinence in Adults with ADHD

S.H. Kollins and colleagues explored the effect of monetary incentives to promote abstinence from extended smoking withdrawal. Participants were paid according to an escalating schedule for maintaining abstinence measured as self-report of no smoking and an objective measure of expired air carbon monoxide. About 64% (14/22) of smokers with ADHD and 50% (11/22) of smokers without ADHD maintained complete abstinence for the 2-week duration of the study. About 22% (5/22) and 9% (2/22) of smokers with ADHD and without ADHD, respectively, continued abstinence for up to 10 days following the removal of the contingencies. Though abstinence rates were higher for the smokers with ADHD, the group differences were not statistically significant. Results suggest that monetary incentives may be a useful approach for promoting abstinence in adult smokers with ADHD, perhaps owing to altered reinforcement processes in these individuals. Kollins SH, McClernon FJ, Van Voorhees EE. Monetary incentives promote smoking abstinence in adults with attention deficit hyperactivity disorder (ADHD). Exp Clin Psychopharmacol. 2010 Jun;18(3): 221-228.

Hippocampal and Striatal Gray Matter Volume Associated with a Smoking Cessation Treatment Outcome

F.J. McClernon and colleagues studied associations between the volumes of regional gray matter as measured by voxel-based morphometry and a smoking cessation treatment outcome as measured by point prevalence abstinence at 4 weeks. About 44% (8/18) of smokers achieved abstinence 4 weeks after cessation treatment. After controlling for all covariates, quitters (compared to relapsers) had significantly higher gray matter volume in the left putamen and right occipital lobe and significantly lower gray matter volume in bilateral hippocampus and right cuneus. The results suggest that maintaining smoking abstinence is associated with higher pre-quit brain volume in regions that subserve habit learning and visual processing, and lower brain volume in regions that subserve long-term memory processes and visual information processing. Froeliger B, Kozink RV, Rose JE, Behm FM, Salley AN, McClernon

FJ. Hippocampal and striatal gray matter volume are associated with a smoking cessation treatment outcome: results of an exploratory voxel-based morphometric analysis. Psychopharmacology (Berl). 2010 Jul;210(4): 577-583.

Mental Rotation of Hands in HIV Infection: Neuropsychological Evidence of Dysfunction in Fronto-Striato-Parietal Networks

I. Grant and colleagues reported a significant interaction between HIV serostatus and performance on mental rotation tasks, the ability to manipulate three-dimensional objects in space that evaluates neurally complex aspect of spatial cognition. Individuals with HIV committed a greater number of errors than demographically similar seronegative persons on mental rotation tasks, but not on a two-dimensional rotation task. Rotation errors were associated with worse performance on measures of executive functions and working memory, but not with measures of visuoperception. These findings suggest that the observed deficit in the mental rotation may arise from a disrupted fronto-striato-parietal network. Weber E, Woods SP, Cameron MV, Gibson SA, Grant I; HIV Neurobehavioral Research Center Group. Mental rotation of hands in HIV infection: neuropsychological evidence of dysfunction in fronto-striato-parietal networks. J Neuropsychiatry Clin Neurosci. 2010 Winter;22(1): 115-122.

Association of Met/Met Genotype, Executive Dysfunction and their Liabilities for Risky Sexual Behavior

I. Grant and colleagues investigated genetic contributes to executive dysfunction and sexual risk behavior. Catechol-O-methyltransferease (COMT) metabolizes prefrontal cortex dopamine (DA), a neurotransmitter involved in executive behavior. The Val158Met genotype has been linked to executive dysfunction, which might increase sexual risk behaviors favoring HIV transmission. Executive dysfunction, but not COMT, was associated with number of sexual partners. However, there was an interaction between COMT polymorphisms and executive dysfunction; the number of sexual partners and sexual acts was more significant for Met/Met genotypes, intermediate for Val/Met and not significant for Val/Val. The results suggest that in the context of HIV and methamphetamine dependence, dopaminergic overactivity in prefrontal cortex conferred by the Met/Met genotype was liable for executive dysfunction and potentially associated risky sexual behavior. Bousman CA, Cherner M, Atkinson JH, Heaton RK, Grant I, Everall IP, HNRC Group. COMT Val158Met polymorphism, executive dysfunction, and sexual risk behavior in the context of HIV infection and methamphetamine dependence. Interdiscip Perspect Infect Dis. [doi:10.1155/2010/678648].

Longer Term Improvement in Neurocognitive Functioning and Affective Distress among Methamphetamine Users Who Achieve Stable Abstinence

I. Grant and colleagues evaluated the effect of long-term sobriety on neuropsychological and affective evaluations in methamphetamine-dependent individuals. At baseline, methamphetamine-dependent participants performed significantly worse than the healthy subjects on global neuropsychological functioning and were significantly more distressed. About 30% (25/83) of methamphetamine-dependent participants remained abstinent, with identified normalization of function at the one-year follow-up. Both the long-term abstainers and healthy subjects had comparable global neuropsychological performance and affective distress levels, whereas dependants who continued to use methamphetamine had worse performance than the comparison participants. In addition, the abstinent participants demonstrated significantly and disproportionately greater improvement in processing speed and slightly

greater improvement in motor abilities than the other participants. These results suggest partial recovery of neuropsychological functioning and improvement in affective distress upon sustained abstinence from methamphetamine that may extend beyond a year or more. Iudicello JE, Woods SP, Vigil O, Cobb Scott J, Cherner M, Heaton RK, Hampton Atkinson J, Grant I. Longer term improvement in neurocognitive functioning and affective distress among methamphetamine users who achieve stable abstinence. J Clin Exp Neuropsychol. 2010 Aug;32(7): 704-718.

White Matter Integrity is Associated with Treatment Outcome Measures in Cocaine Dependence

M. Potenza and colleagues at Yale School of Medicine assessed the correlation of white matter integrity with treatment outcome measures in cocaine dependence. Diffusion tensor imaging (DTI) was used to assess the white matter (WM) of 16 treatment-seeking cocaine-dependent patients before 8 weeks of therapy. Longest self-reported abstinence from cocaine and percent of cocaine-negative urine samples during treatment positively correlated with fractional anisotropy values and negatively correlated with lambda(1), lambda(T), and mean diffusivity values across extensive brain regions including the corpus callosum, frontal, parietal, temporal, and occipital lobes, and cerebellum. The findings of an association between better WM integrity at treatment onset and longer abstinence suggest that strategies for improving WM integrity warrant consideration in developing new interventions for cocaine dependence. Xu J, DeVito EE, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. White matter integrity is associated with treatment outcome measures in cocaine dependence. Neuropsychopharmacology. 2010 Jun;35(7): 1541-1549.

Striatal Dopamine D2 Receptor Availability Predicts Enduring Thalamic and Medial Prefrontal Responses to Reward

R. Goldstein and colleagues at Brookhaven National Laboratories used PET brain imaging to investigate whether a reduction in dopamine (DA) D2 receptor availability along with the reduced ventral frontal metabolism underlies compromised sensitivity to nondrug reward, a core characteristic of drug addiction. Cocaine abusers who had received PET scans for DA D2 binding shortly after initiating abstinence peformed a monetary reward task using fMRI 3 years later. Initial low DA D2 receptor availability in the dorsal striatum was found to be associated with later decreased thalamic response to monetary reward, whereas low availability in ventral striatum was associated with increased medial prefrontal (Brodmann Area 6/8/32) response to monetary reward. These preliminary results suggest that resting striatal DA D2 receptor availability predicts variability in functional responses to a nondrug reinforcer (money) in prefrontal cortex, implicated in behavioral monitoring, and in thalamus, implicated in conditioned responses and expectation, in cocaine-addicted individuals. Asensio S, Romero MJ, Romero FJ, Wong C, Alia-Klein N, Tomasi D, Wang G, Telang F, Volkow ND, Goldstein RZ. Striatal dopamine D2 receptor availability predicts the thalamic and medial prefrontal responses to reward in cocaine abusers three years later. Synapse. 2010;64(5): 397-402.

Approaching the Bad and Avoiding the Good: Lateral Prefrontal Cortical Asymmetry Distinguishes Between Action and Valence

M. Lieberman and E. Berkman of UCLA used fMRI to determine whether action motivation or stimulus valence is a better descriptor of prefrontal asymmetry. Previous neuroscience investigations have established a left-right prefrontal asymmetry between approaching pleasant and avoiding unpleasant stimuli, but these investigations typically do not untangle the roles of action motivation

(approach vs. avoidance) and stimulus valence (pleasant vs. unpleasant) in this asymmetry. Results from this study using fMRI suggest that prefrontal asymmetry is associated with action motivation and not with stimulus valence. Specifically, there was increased left (vs. right) activation in dorsolateral, but not orbitofrontal, prefrontal cortex during approach (vs. avoidance) actions regardless of the stimulus valence, but no such effect was observed for pleasant compared to unpleasant stimuli. Together, these results support the notion that prefrontal asymmetry is associated with action motivation regardless of stimulus valence and, as such, might be linked with goal pursuit processes more broadly. Berkman ET, Lieberman MD. Approaching the bad and avoiding the good: lateral prefrontal cortical asymmetry distinguishes between action and valence. J Cogn Neurosci. 2010 Sep;22(9): 1970-1979.

Individuals with Psychopathic Traits Have Hypersensitive Mesolimbic Dopamine Reward Systems Activity

J. Buckholtz and colleagues at Vanderbilt University combined Positron Emission Tomography and fMRI to examine links between dopamine release, reward sensitivity and personality traits associated with psychopathy. Psychopathy is a personality disorder that is strongly linked to criminal behavior and substance abuse. Impulsive-antisocial psychopathic traits selectively predicted nucleus accumbens dopamine release using [F-18]fallypride and reward anticipation-related neural activity with fMRI in response to pharmacological and monetary reinforcers, respectively. These findings suggest that neurochemical and neurophysiological hyper-reactivity of the dopaminergic reward system may comprise a neural substrate for impulsive-antisocial behavior and substance abuse in psychopathy. Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Benning SD, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Cole D, Kessler RM, Zald DH. Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. Nat Neurosci. 2010;13(4): 419-421.

Effects of Acute Psychosocial Stress on Cigarette Craving and Smoking

E. Childs and H. de Wit at the University of Chicago studied the effects of acute psychosocial stress on cigarette craving, the subjective effects of smoking, and smoking behavior. Stress is thought to influence use of drugs, including cigarette smoking, but the mechanisms by which it does so are not clear. Stress significantly increased cigarette craving but did not increase smoking. When individual differences in nicotine dependence were taken into account, stress influenced CO boost and pleasure from smoking the first cigarette. The results support previous evidence that acute psychosocial stress increases smoking desire. Childs E, de Wit H. Effects of acute psychosocial stress on cigarette craving and smoking. Nicotine Tob Res. 2010 Apr;12(4): 449-453.

Cardiovascular, Hormonal, and Emotional Responses Related to Inhibitory Control in Relation to Sex and Menstrual Cycle Phase

E. Childs and colleagues at the University of Chicago studied how men and women vary in acute stress responses, using the Stop Signal Reaction Time Task as the stressor. Men exhibited greater cortisol responses to stress than women in either the follicular or luteal menstrual phase. Luteal women exhibited the greatest subjective and allopregnanolone responses to stress, whereas follicular women exhibited blunted noradrenaline responses. Partial correlations controlling for group differences revealed that individuals who were most sensitive to the subjective effects of stress exhibited the largest salivary cortisol, noradrenaline, and allopregnanolone responses and the smallest progesterone responses to stress. Childs E, Dlugos A, De Wit H. Cardiovascular,

hormonal, and emotional responses to the TSST in relation to sex and menstrual cycle phase. Psychophysiology. 2010 May;47(3): 550-559.

Dopaminergic Prediction Error Responsivity Contributes to Adolescent Reward Seeking

J. Cohen and colleagues at UCLA used fMRI to investigate which aspect of reward processing is responsible for the reward hypersensitivity previously reported in human adolescents. They used a task design that allowed decision value and prediction error signals to be separated. Neural prediction error signals in the striatum peaked in adolescence, whereas neural decision value signals varied depending on how value was modeled. This suggests that heightened dopaminergic prediction error responsivity contributes to adolescent reward seeking. Cohen JR, Asarnow RF, Sabb FW, Bilder RM, Bookheimer SY, Knowlton BJ, Poldrack RA. A unique adolescent response to reward prediction errors. Nat Neurosci. 2010 Jun;13(6): 669-671.

Beta2* Nicotinic Acetylcholine Receptors Modulate Pain Sensitivity in Acutely Abstinent Tobacco Smokers

K. Cosgrove and colleagues at Yale School of Medicine examined the relationship between beta(2)*-nAChR availability and nociception during acute withdrawal in human tobacco smokers using ligand SPECT brain imaging. Nicotine and tobacco smoking administration have demonstrated antinociceptive effects that are mediated by the nicotinic acetylcholine receptor containing the beta2* subunit (beta(2)*-nAChR). Following 7-13 days of tobacco smoking abstinence, increased pain sensitivity, was significantly associated with higher beta(2)*-nAChR availability in the thalamus, parietal, frontal, anterior cingulate, temporal, and occipital cortices. The percent change in pain sensitivity from the first to second cold pressor task was significantly correlated with beta(2)*-nAChR availability in the thalamus, cerebellum, striatum, parietal, anterior cingulate, temporal, and occipital cortices. Similar associations were not observed with pain tolerance. This suggests that beta(2)*-nAChRs play a role in pain sensitivity but not pain tolerance during tobacco smoking withdrawal. Lower beta(2)*- nAChR availability during acute abstinence may be protective for relapse. Cosgrove KP, Esterlis I, McKee S, Bois F, Alagille D, Tamagnan GD, Seibyl JP, Krishnan-Sarin S, Staley JK. Beta2* nicotinic acetylcholine receptors modulate pain sensitivity in acutely abstinent tobacco smokers. Nicotine & Tobacco Res. 2010;12(5): 535-539.

Lesions in the Posterior Ventromedial Prefrontal Cortex Increase the Influence of Recent Events in Decision-Making

A. Bechara and colleagues at University of Southern California assessed brain substrates implicated in two decision making dimensions in a sample of prefrontal cortex patients: (a) the tendency to differently weigh recent compared to past experience; and (b) the tendency to differently weigh gains compared to losses. The results indicated that decisions become influenced by more recent, as opposed to older, events when the damage reaches the posterior sectors of the ventromedial prefrontal cortex (VMPC). Furthermore, the degree of this recency deficit was related to the size of the lesion. These results suggest that the posterior area of the prefrontal cortex directly modulates the capacity to use time-delayed information. Hochman G, Yechiam E, Bechara A. Recency gets larger as lesions move from anterior to posterior locations within the ventromedial prefrontal cortex. Behavioural Brain Res. 2010;213(1): 27-34.

Decreased Cerebral Cortical Serotonin Transporter Binding in Ecstasy Users

S. Kish and colleagues at University of Toronto used PET ligand imaging structural MRI to obtain more precise data regarding changes in serotonin re-uptake sites in recreational users of the drug ecstasy (3,4-methylenedioxymethamphetamine). In particular, the possibility that structural brain differences might account for serotonin transporter binding changes has not been explored. Using PET, results showed that serotonin transporter binding in ecstasy users was significantly decreased throughout all cerebral cortices (range -19 to -46%) and hippocampus (-21%) and related to the extent of drug use (years, maximum dose), but was normal in basal ganglia and midbrain. The serotonin transporter binding loss was not related to structural changes or partial volume effect, use of other stimulant drugs, blood testosterone or estradiol levels, major serotonin transporter gene promoter polymorphisms, gender, psychiatric status, or self-reported hyperthermia or tolerance. The ecstasy group reported subnormal mood and demonstrated generally modest deficits on some tests of attention, executive function and memory, with the latter associated with serotonin transporter decrease. The findings suggest that the typical, low dose (one to two tablets/session) chronic ecstasy-polydrug users might display a highly selective mild to marked loss of serotonin transporter in cerebral cortex/hippocampus, which is not gender-specific or completely accounted for by structural brain changes, recent use of other drugs (as assessed by hair analyses) or other potential confounds that the investigators could address. Kish SJ, Lerch J, Furukawa Y, Tong J, McCluskey T, Wilkins D, Houle S, Meyer J, Mundo E, Wilson AA, Rusjan PM, Saint-Cyr JA, Guttman M, Collins DL, Shapiro C, Warsh JJ, Boileau I. Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C] DASB and structural brain imaging study. Brain. 2010 Jun;133(6): 1779-1797.

Brain CB1 Cannabinoid Receptors in Healthy Subjects and Schizophrenics

D. Wong and colleagues at Johns Hopkins School of Medicine used ligand PET imaging to demonstrate whether schizophrenics exhibit alterations in cannabinoid CB1 receptors using the novel radiotracer, [(11)C]OMAR (JHU75528). CB1 binding (expressed as the distribution volume; V(T)) was highest in the globus pallidus and the cortex in both controls and patients with schizophrenia. Controls showed a correlation with the known distribution of CB1 and decline of [(11)C]OMAR binding with age, most significantly in the globus pallidus. Mean binding in patients with schizophrenia was observed across all regions studied, and this increase was statistically significant in the pons. The results suggest that [(11)C] OMAR can image alterations in human CB1 receptors in normal aging and schizophrenia. In addition, results in subjects with schizophrenia seem to suggest an association of elevated binding specific brain regions and symptoms of the disease. Wong DF, Kuwabara H, Horti AG, Raymont V, Brasic J, Guevara M, Ye W, Dannals RF, Ravert HT, Nandi A, Rahmim A, Ming JE, Grachev I, Roy C, Cascella N. Quantification of cerebral cannabinoid receptors subtype 1 (CB1) in healthy subjects and schizophrenia by the novel PET radioligand [11C]OMAR. NeuroImage. 2010 Oct;52(4): 1505-1513.

Social Cognitive Conflict Resolution: Contributions of Domain-General and Domain-Specific Neural Systems

K. Ochsner and colleagues at Columbia University used fMRI to examine cognitive control mechanisms that allow individuals to resolve conflicts between competing social cues. Healthy subjects were scanned while they drew inferences about the social targets' emotional states based on congruent or incongruent nonverbal and contextual social cues. Conflicts between social cues recruited the anterior cingulate and lateral prefrontal cortex, brain areas

associated with domain-general control processes. These data provide evidence about both domain-general and domain-specific mechanisms involved in resolving social cognitive conflicts. Zaki J, Hennigan K, Weber J, Ochsner KN. Social cognitive conflict resolution: contributions of domain-general and domain-specific neural systems. J Neurosci. 2010 Jun;30(25): 8481-8488.

The Interrelationship of Dopamine D2-like Receptor Availability in Striatal and Extrastriatal Brain Regions in Healthy Humans: A Principal Component Analysis of [18F]Fallypride Binding

D. Zald and colleagues at Vanderbilt University used PET ligand imaging to examine individual differences in the levels of dopamine D2-like receptor in one brain region compared to D2 binding in other brain regions. The relationship between D2-like binding potential (D2BP) was examined across striatal and extrastriatal regions in a sample of healthy participants using PET imaging. Individual differences in D2-like D2BP were explained by three distinguishable components. A single component explained almost all of the variance within the striatum, indicating that individual differences in receptor availability vary in a homogenous manner across the caudate, putamen, and ventral striatum. Cortical D2BP was only modestly related to striatal BPND and mostly loaded on a distinct component. After controlling for the general level of cortical D2BP, an inverse relationship emerged between receptor availability in the striatum and the ventral temporal and ventromedial frontal cortices, suggesting possible cross-regulation of D2-like receptors in these regions. The analysis additionally revealed evidence of: (1) a distinct component involving the midbrain and limbic areas; (2) a dissociation between D2BP in the medial and lateral temporal regions; and (3) a dissociation between D2BP in the medial/midline and lateral thalamus. Given that individual differences in D2-like receptor availability reflect several distinct patterns, this study has significant implications for neuropsychiatric models that posit global or regionally specific relationships between dopaminergic tone and behavior. Zald DH, Woodward ND, Cowan RL, Riccardi P, Ansari MS, Baldwin RM, Cowan RL, Smith CE, Hakyemez H, Li R, Kessler RM. The interrelationship of dopamine D2-like receptor availability in striatal and extrastriatal brain regions in healthy humans: A principal component analysis of [18F]fallypride binding. NeuroImage. 2010;51(1): 53-62.

Altered Neural Cholinergic Receptor Systems in Cocaine-Addicted Subjects

B. Adinoff and colleagues at Southwestern Medical Center used SPECT brain imaging to study alterations in cholinergic receptor systems in limbic regions of abstinent cocaine-addicted subjects. Subjects were administered the muscarinic and nicotinic cholinergic agonist physostigmine, the muscarinic antagonist scopolamine, and saline. Both cholinergic probes induced rCBF changes as measured by SPECT in relatively distinct, cholinergic-rich, limbic brain regions. After physostigmine, cocaine-addicted subjects showed altered rCBF, relative to controls, in limbic regions, including the left hippocampus, left amygdala, and right insula. Group differences in the right dorsolateral prefrontal cortex, posterior cingulate, and middle temporal gyrus were also evident. Scopolamine also revealed group differences in the left hippocampus and right insula as well as the posterior cingulate and middle temporal gyrus. The results suggest that cholinergic systems may offer a pharmacologic target for cocaine addiction treatment. Adinoff B, Devous MD, Williams MJ, Best SE, Harris TS, Minhajuddin A, Zielinski T, Cullum M. Altered neural cholinergic receptor systems in cocaine-addicted subjects. Neuropsychopharmacology. 2010 Jun;35(7): 1485-1499.

Component Neural Systems for the Creation of Emotional

Memories During Free Viewing of a Complex, Real-World Event

LaBar and colleagues at Duke University used fMRI To investigate the neural systems that contribute to the formation of complex, self-relevant emotional memories. Dedicated fans of rival college basketball teams watched a competitive game while undergoing fMRI scanning. During a subsequent recognition memory task, participants were shown video clips depicting plays of the game, stemming either from previously-viewed game segments (targets) or from non-viewed portions of the same game (foils). After an old-new judgment, participants provided emotional valence and intensity ratings of the clips. The fMRI signal acquired during free viewing of the game was decomposed into spatially independent components. Brain systems that were correlated with emotional intensity ratings included regions implicated in memory and emotional functions, such as the hippocampus and amygdala, as well as a midline fronto-cingulo-parietal network implicated in social cognition and self-relevant processing, including temporal lobe regions. These findings contribute to our understanding of how emotional factors impact distributed neural systems to successfully encode dynamic, personally-relevant event sequences. These findings provide a foundation for understanding the strong emotional memories related to drug use. Botzung A, Labar KS, Kragel P, Miles A, Rubin DC. Component neural systems for the creation of emotional memories during free viewing of a complex, real-world event. Front Hum Neurosci 2010;4: 34.

Cognitive Mechanisms Underlying Risky Decision-Making in Chronic Cannabis Users

Porrino and colleagues at Wake Forest University in collaboration with J. Busmeyer and colleagues at Indiana University used a computational model to determine the cognitive processes underlying poor performance of cannabis users on a test of decision-making, the Iowa Gambling Task (IGT). Two computational models of IGT performance were compared; the Expectancy Valence Learning model (EVL) and the Prospect Valence Learning model (PVL). The results indicated that cannabis abusers tended to be under-influenced by loss magnitude, treating each loss as a constant and minor negative outcome regardless of the size of the loss. In addition, they were more influenced by gains, and made decisions that were less consistent with their expectancies relative to non-using controls. Fridberg DJ, Queller S, Ahn W, Kim W, Bishara AJ, Busemeyer JR, Porrino L, Stout JC. Cognitive mechanisms underlying risky decision-making in chronic cannabis users. J Math Psychol. 2010;54(1): 28-38.

Effect of Methamphetamine Dependence on Everyday Functional Ability

B. Henry and colleagues at the University of California, San Diego examined the effect of the Methamphetamine (METH) on the ability to carry out everyday activities. Chronic METH exposure has been associated with neurotoxic effects, profound neuropsychological deficits, and impaired quality of life. The effect of METH dependence on everyday functioning was assessed using a performance-based measure designed to evaluate real-life skills. METH-dependent participants exhibited significant impairment on several functions, including comprehension, finance, transportation, communication, and medication management compared to drug-free comparison subjects. METH dependence may be associated with decreased everyday functioning ability potentially mediated by frontal cortex dysfunction or the emergence of psychopathology related to chronic drug use. Henry BL, Minassian A, Perry W. Effect of methamphetamine dependence on everyday functional ability. Addict Behav. 2010;35(6): 593-598.

Impaired Insight in Cocaine Addiction: Laboratory Evidence and Effects on Cocaine-Seeking Behavior

R. Goldstein and colleagues at Brookhaven National Laboratories sought to empirically demonstrate whether drug abusers exhibit impaired insight into behavior. Such an insight deficit has been suggested, but never directly tested, in drug addiction. Sixteen cocaine addicted individuals testing positive for cocaine in urine, 26 cocaine addicted individuals testing negative for cocaine in urine, and 23 healthy controls completed a probabilistic choice task that assessed objective preference for viewing four types of pictures (pleasant, unpleasant, neutral and cocaine). Results showed that the urine positive cocaine subjects exhibited impaired insight into their own choice behavior compared with healthy controls; this same study group also selected the most cocaine pictures (and fewest pleasant pictures) for viewing. Importantly, however, it was the urine negative cocaine subjects whose behavior was most influenced by insight, such that impaired insight in this subgroup only was associated with higher cocaine-related choice on the task and more severe actual cocaine use. These findings suggest that interventions to enhance insight may decrease drug-seeking behavior, especially in urine negative cocaine subjects, potentially improving their longer-term clinical outcomes. Moeller SJ, Maloney T, Parvaz MA, Alia-Klein N, Woicik PA, Telang F, Wang GJ, Volkow ND, Goldstein RZ. Impaired insight in cocaine addiction: laboratory evidence and effects on cocaine-seeking behaviour. Brain. 2010;133(5): 1484-1493.

BOLD Responses to Negative Reward Prediction Errors in Human Habenula

R. Salas and PR Montague and colleagues at Baylor School of Medicine used fMRI to determine which brain regions carry information about negative reward prediction errors in humans. Positive reward prediction error (an event that is better than expected) is a key element in reinforced learning that is signaled by dopamine cells, but little is known about brain systems that encode negative reward prediction errors (worse than expected events). Animal studies have indicated that the habenula, an integrative region in the dorsal midbrain, encodes negative reward-related events such as negative reward prediction error signals. In this study, a new method is described to functionally locate and study the habenula in humans using fMRI, based on the expected reward-dependent response phenomenology of habenula and striatum. Conclusive evidence is provided for activation in human habenula to negative reward prediction errors. These data suggest that dysfunctions of habenula may contribute to insensitivity to negative consequences of substance abuse. Salas R, Baldwin P, de Biasi M, Montague PR. BOLD Responses to negative reward prediction errors in human habenula. Front Hum Neurosci. 2010;4: 36.

Overlapping Neural Systems Mediating Extinction, Reversal and Regulation of Fear

M. Delgado and D. Schiller at Rutgers University used fMRI to determine what brain systems regulate the extinction of learned fear. Learned fear is a process allowing quick detection of associations between cues in the environment and prediction of imminent threat. Adaptive function in a changing environment, however, requires organisms to quickly update this learning and have the ability to hinder fear responses when predictions are no longer correct. This study focused on three strategies that can modify conditioned fear, namely extinction, reversal and regulation of fear, and reviews their underlying neural mechanisms. By directly comparing neuroimaging data from separate studies using the three strategies that can modify conditioned fear overlapping brain structures that comprise a general circuitry in the human brain are highlighted.

This circuitry potentially enables the flexible control of fear, regardless of the particular task demands. This study raises the question of whether similar circuitry is engaged during extinction and/or regulation of drug-related learned responses. Schiller D, Delgado MR. Overlapping neural systems mediating extinction, reversal and regulation of fear. Trends Cog Sci. 2010;14(6): 268-276.

Striatal and Extrastriatal Dopamine Release Measured with PET and [F-18] Fallypride

A. Abi-Dargham and colleagues at Columbia University used PET ligand brain imaging to determine how dopamine release can differ across brain regions. [F-18] fallypride is a PET radioligand that allows measurement of the effects of amphetamine on D2/D3 ligand binding in striatum and extrastriatal brain regions such as the cerebral cortex. In healthy volunteer subjects, it was found that there was a robust release of dopamine following amphetamine administration in the ventral striatum, globus pallidus, and posterior putamen, with other striatal subregions exhibiting slightly higher variability. Dopamine release was not reliably detected in cortical regions. The results demonstrate that [F-18] fallypride is a suitable ligand for measuring amphetamine effect in striatum and limbic regions, but it is not suitable for measuring the effect in cortical regions and may not provide the most powerful way to measure the effect in striatum. Slifstein M, Kegeles LS, Xu X, Thompson JL, Urban N, Castrillon J, Hackett E, Bae S, Laruelle M, Abi-Dargham A. Striatal and extrastriatal dopamine release measured with PET and [F-18] fallypride. Synapse. 2010;64(5): 350-362.

Disrupted Functional Connectivity in Dopaminergic Midbrain in Cocaine Abusers

D. Tomasi and colleagues at Brookhaven National Laboratories used functional connectivity analysis of BOLD MRI signals to determine how chronic cocaine use affects system-wide brain function. Cocaine addicted subjects performed a sustained attention task during BOLD MRI scans. Cocaine abusers compared to controls, had lower positive functional connectivity of the midbrain region that contains dopamine neurons with other brain regions including the thalamus, cerebellum, and rostral cingulate, and this was associated with decreased activation in thalamus and cerebellum and enhanced deactivation in rostral cingulate. These findings suggest that decreased functional connectivity of the midbrain interferes with the activation and deactivation signals associated with sustained attention in cocaine addicts. Tomasi D, Volkow ND, Wang R, Carrillo JH, Maloney T, Alia-Klein N, Woicik PA, Telang F, Goldstein RZ. Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers. PLoS ONE. 2010;5(5): e10815.

Methylphenidate Attenuates Limbic Brain Inhibition after Cocaine-Cues Exposure in Cocaine Abusers

R. Goldstein and colleagues at Brookhaven National Laboratories used glucose metabolism PET brain imaging to determine the effects of increased tonic dopamine levels (using oral methylphenidate) on brain activation induced by cocaine-cues in cocaine abusers. Methylphenidate administration did not increase self-reported drug craving during a cocaine-cues video any more than placebo; craving increased 68% during the placebo session and 64% after methylphenidate. In contrast, brain activation during viewing of the cocaine video differed between the placebo and methylphenidate sessions. During the placebo session, cocaine-cues decreased glucose metabolism in left limbic regions (insula, orbitofrontal, accumbens) and right parahippocampus, whereas during the methylphenidate session the only reliable changes were decreases

in auditory and visual regions, which also occurred with placebo. Decreases in metabolism in these regions were not associated with craving. Significant correlations with craving were found in anterior orbitofrontal cortex ($p<0.005$), amygdala, striatum and middle insula. These results suggest that methylphenidate's attenuation of brain reactivity to cocaine-cues is distinct from that involved in craving. Volkow ND, Wang G, Tomasi D, Telang F, Fowler JS, Pradhan K, Jayne M, Logan J, Goldstein RZ, Alia-Klein N, Wong C. Methylphenidate attenuates limbic brain inhibition after cocaine-cues exposure in cocaine abusers. PLoS ONE. 2010;5(7): e11509.

Ventromedial Prefrontal Cortex Damage Impairs Judgment of Harmful Intent

A. Bechara and colleagues at the University of Southern California investigated the effects of damage to the orbitofrontal cortex on human's ability to infer intentions. People will often forgive harm if it is unintentional or accidental and will condemn failed attempts to harm. Prior work demonstrated that patients with damage to the ventromedial prefrontal cortex (VMPC) deliver abnormal judgments in response to moral dilemmas and that these patients are especially impaired in triggering emotional responses to inferred or abstract events (e.g., intentions), as opposed to real or actual outcomes. In this study, it was confirmed that VMPC patients judged attempted harms, including attempted murder, as more morally permissible relative to controls. These results highlight the critical role of the VMPC in processing harmful intent for moral judgment. Young L, Bechara A, Tranel D, Damasio H, Hauser M, Damasio A. Damage to ventromedial prefrontal cortex impairs judgment of harmful intent. Neuron. 2010;65(6): 845-851.

Prefrontal-Striatal Pathway Underlies Cognitive Regulation of Craving

K. Ochnsner and colleagues at Columbia University used fMRI to examine neural activity in cigarette smokers related to cognitive strategies to regulate craving. Cognitive down-regulation of craving was associated with (i) activity in regions previously associated with regulating emotion in particular and cognitive control in general, including dorsomedial, dorsolateral, and ventrolateral prefrontal cortices, and (ii) decreased activity in regions previously associated with craving, including the ventral striatum, subgenual cingulate, amygdala, and ventral tegmental area. Decreases in craving correlated with decreases in ventral striatum activity and increases in dorsolateral prefrontal cortex activity, with ventral striatal activity fully mediating the relationship between lateral prefrontal cortex and reported craving. These results provide insight into the mechanisms that enable cognitive strategies to effectively regulate craving, suggesting that it involves neural dynamics parallel to those involved in regulating other emotions. In so doing, this study provides a methodological tool and conceptual foundation for studying this ability across substance using populations and developing more effective treatments for substance use disorders. Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN. Prefrontal-striatal pathway underlies cognitive regulation of craving. Proc Natl Acad Sci U S A 2010 Aug; Available from: http://www.ncbi.nlm.nih.gov/pubmed/20679212

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - Epidemiology and Etiology Research

Co-twin-control Analysis of SUD Risk Associated With Early-onset Cannabis Use

Researchers assessed whether, after controlling for genetic and shared environmental influences, early cannabis use remains a significant predictor of other drug use, abuse, and dependence, and whether the risk for early-users is greater than that for later cannabis users. Data from a 1992 telephone diagnostic interview of 8169 male twins (M=42.0 years at interview) who served in the U.S. military during the Vietnam-era were used to identify a subsample of 293 monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for early cannabis use (before age 18). Using cotwin-control analyses, outcomes assessed were: lifetime illegal drug use (stimulant/cocaine, sedative, opiate, and hallucinogen/PCP), lifetime DSM-III-R illegal drug abuse/dependence, and lifetime DSM-III-R alcohol dependence. After controlling for covariates, early cannabis users were at greater risk than their later/never-using cotwins for 8 of 9 substance-related comparisons, including: using other illegal drugs (ORs: 2.71-4.09), having illegal drug abuse/dependence (ORs: 2.02-2.13), and developing alcohol dependence (OR=2.36). When analyses were limited to pairs in which the cotwin used cannabis later, early and later-users only differed significantly on sedative, opiate, and hallucinogen use. After familial influences on early cannabis use were controlled for, cannabis use-regardless of the age of initiation-still conferred increased risk of other illegal drug use, drug abuse/dependence, and alcohol dependence. The authors conclude that, in contrast to previous research, there is limited evidence for increased risk associated with early-onset use in this sample of Vietnam-era veterans. Grant J, Lynskey M, Scherrer J, Agrawal A, Heath A, Bucholz K. A Cotwin-Control Analysis Of Drug Use And Abuse/Dependence Risk Associated With Early-Onset Cannabis Use. Addict Behav. 2010; 35 (1): 35-41.

Family Income Supplements in Adolescence Reduced Psychiatric and Substance Use Disorders in Adulthood

This paper follows up a natural experiment in which some families received income supplements and the prevalence of adolescent behavioral symptoms decreased significantly. The adolescents in the prior study are now young adult, and this follow up study examined the effects of income supplements in adolescence and adulthood on the prevalence of adult psychiatric disorders. The study used a quasi-experimental, longitudinal design. The sample consists of a representative sample who were aged 9, 11, or 13 years in 1993 (349 [25%] of whom are American Indian) who were assessed for psychiatric and substance use disorders through age 21 years (1993-2006). Of the 1420 who participated in 1993, 1185 were interviewed as adults. From 1996, when a

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casino opened on the Indian reservation, every American Indian but no non-Indians received an annual income supplement that increased from $500 to around $9000. Main outcome measures were prevalence of adult psychiatric disorders and substance use disorders based on the Diagnostic and Statistical Manual of Mental Disorders in 3 age cohorts, adjusted for age, sex, length of time in the family home, and number of Indian parents. Results indicated that as adults, significantly fewer Indians than non-Indians had a psychiatric disorder, particularly alcohol and cannabis abuse, dependence, or both. The youngest age-cohort of Indian youth had the longest exposure to the family income. Interactions between race/ethnicity and age cohort were significant. Fewer of the youngest Indian age-cohort had any psychiatric disorder than the Indian middle cohort or oldest cohort or the youngest non-Indian cohort. The income supplement received in adulthood had no impact on adult psychopathology. The authors conclude that lower prevalence of psychopathology in American Indian youth following a family income supplement, compared with the non-exposed, non-Indian population, persisted into adulthood. As the authors note in their discussion, this does not obviate a possible role for genetic factors in the genesis of these disorders, but it strongly suggests that environmental factors can play a key role. Costello E, Erkanli A, Copeland W, Angold A. Association Of Family Income Supplements In Adolescence With Development Of Psychiatric And Substance Use Disorders In Adulthood Among An American Indian Population. JAMA. 2010; 303 (19): 1954-1960.

Methadone Maintenance Therapy Promotes Initiation of Antiretroviral Therapy among Injection Drug Users

Despite proven benefits of antiretroviral therapy (ART), many HIV-infected IDUs do not access treatment even in settings with free health care. Researchers examined whether methadone maintenance therapy (MMT) increased initiation and adherence to ART among an IDU population with free health care. They examined prospectively a cohort of opioid-using antiretroviral-naive HIV-infected IDU and investigated factors associated with initiation of ART as well as subsequent adherence. Factors associated independently with time to first initiation of ART were modelled using Cox proportional hazards regression. Between May 1996 and April 2008, 231 antiretroviral-naive HIV-infected opioid-using IDU were enrolled, among whom 152 (65.8%) initiated ART, for an incidence density of 30.5 [95% confidence interval (CI): 25.9-35.6] per 100 person-years. After adjustment for time-updated clinical characteristics and other potential confounders, use of MMT was associated independently with more rapid uptake of ART [relative hazard = 1.62 (95% CI: 1.15-2.28); P = 0.006]. Those prescribed methadone also had higher rates of ART adherence after first antiretroviral initiation [odds ratio = 1.49 (95% CI: 1.07-2.08); P = 0.019]. These results demonstrate that MMT contributes to more rapid initiation and subsequent adherence to ART among opioid-using HIV-infected IDU. Addressing international barriers to the use and availability of methadone may increase dramatically uptake of HIV treatment among this population. Uhlmann S, Milloy M, Kerr T, Zhang R, Guillemi S, Marsh D, Hogg R, Montaner J, Wood E. Methadone Maintenance Therapy Promotes Initiation Of Antiretroviral Therapy Among Injection Drug Users. Addiction. 2010; 105 (5): 907-913.

Temporal Trends in Highly Active Antiretroviral Therapy Initiation among Injection Drug Users in Baltimore, Maryland, 1996-2008

Researchers characterized temporal trends in highly active antiretroviral therapy (HAART) initiation from 1996 to 2008 among treatment-eligible persons in a community-based cohort of current and former IDUs in Baltimore, Maryland. The study, AIDS Linked to the IntraVenous Experience (ALIVE))

cohort has been observing HIV-positive IDUs since 1988. HAART eligibility was defined as the first visit after 1 January 1996 at which the patient's CD4 (+) cell count was <350 cells/muL. Temporal trends and predictors of HAART initiation were examined using chi (2) tests for trend and lognormal survival models. Data showed that the median age of 582 HAART-eligible IDUs was 41 years; 75% of the subjects were male, 97% were African American, and 60% were active IDUs. Of these 582 individuals, 345 initiated HAART over 1803 person-years (19.2 subjects per 100 person-years; 95% confidence interval, 17.2-21.3 subjects per 100 person-years); there was no statistically significant temporal trend in HAART initiation. Independent predictors of delayed initiation included heavy injection drug use; having a prior AIDS diagnosis, having a lower CD4 (+) cell count, having a usual source of care, and having health insurance were predictors of more-rapid initiation. The delay between eligibility and initiation decreased among those who became eligible most recently (2003-2007), compared with those in earlier periods (1996-2002); however, a substantial number of patients who became eligible in recent years either initiated HAART after a substantial delay or did not initiate HAART at all. This study failed to observe substantial improvement in HAART initiation among current and former IDUs over a 12-year period; heavy use of injection drugs remains the major barrier to HAART initiation and to consistent HIV care. The fact that many IDUs initiate HAART after a significant delay or do not initiate it at all raises concern that disparities in HIV care for IDUs remain at a time of simplified antiretroviral regimens and increasing adoption of earlier treatment. Mehta SH, Kirk GD, Astemborski J, Galai N. Temporal Trends In Highly Active Antiretroviral Therapy Initiation Among Injection Drug Users In Baltimore, Maryland, 1996-2008. Clin Infect Dis. 2010; 50 (12): 1664-1671.

Flashblood: Blood Sharing among Female Injecting Drug Users in Tanzania

This cross-sectional study examined the association between the blood-sharing practice of ''flashblood'' use and demographic factors, HIV status, and variables associated with risky sex and drug behaviors among female IDUs in Dar es Salaam, Tanzania. Flashblood is a syringe-full of blood passed from someone who has just injected heroin to someone else who injects it in lieu of heroin. One hundred and sixty-nine female IDUs were recruited using purposive sampling for hard-to-reach populations. The t-test and chi(2) test were used to analyze associations between flashblood use, demographic and personal characteristics and risky sex and drug use variables. The association between flashblood use and residential neighborhood was also mapped. Flashblood users were found more likely to: be married (P = 0.05), have lived in the current housing situation for a shorter time (P < 0.000), have been forced as a child to have sex by a family member (P = 0.007), inject heroin more in the last 30 days (P = 0.005), smoke marijuana at an earlier age (P = 0.04), use contaminated rinse-water (P < 0.03), pool money for drugs (P < 0.03) and share drugs (P = 0.000). Non-flashblood users were more likely to live with their parents (P = 0.003). Neighborhood flashblood use was highest near downtown and in the next two adjoining suburbs and lowest in the most distant suburbs. These data indicate that more vulnerable women who are also heavy users of drugs and live in shorter-term housing are injecting flashblood. The practice of flashblood now appears to be spreading from the inner city to the suburbs of Dar es Salaam. McCurdy SA, Ross MW, Williams ML, Kilonzo GP, Leshabari MT. Flashblood: Blood Sharing Among Female Injecting Drug Users In Tanzania. Addiction. 2010; 105: 1062-1070.

HIV Infection during Limited Versus Combined HIV Prevention Programs for IDUs in New York City: The Importance of Transmission Behaviors

As no single HIV prevention program has eliminated HIV transmission, there is

growing interest in the effectiveness of "combined" prevention programming. In this study, researchers sought to compare HIV infection among persons injecting in the initial programs environment (IPE) in New York City (i.e., self-initiated risk reduction, methadone, education/outreach, and HIV testing) to HIV infection among persons injecting in a combined programs environment (CPE) (i.e., the above programs plus large-scale syringe exchange) to identify potential behavioral mechanisms through which combined programs are effective. Subjects were recruited for the study from the Beth Israel drug detoxification program, where a risk behavior questionnaire was administered and HIV testing was conducted. Subjects (n=261) who injected only between 1984 and 1994 (IPE) were compared to those (n=1153) who injected only between 1995 and 2008 (CPE). HIV infection was found to be significantly lower among CPE subjects compared to IPE subjects: prevalence 6% versus 21%, estimated incidence 0.3/100 person-years versus 4/100 person-years (both $p<0.001$). The percentage of subjects at risk of acquiring HIV through receptive syringe sharing was similar across CPE and IPE subjects (30% versus 33%). The percentage of subjects at risk of transmitting HIV through injection-related behaviors (i.e., who were both HIV seropositive and reported passing used needles/syringes to others) was much lower among the CPE subjects than among the IPE subjects (1% versus 10%, $p<0.001$). These analyses indicate that combined prevention programs can greatly reduce HIV transmission risks. Additional efforts to reduce distributive sharing by HIV seropositive injecting drug users (IDUs) may be needed, given that this is a critical behavior in HIV transmission in high seroprevalence settings. Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman D, Torian L, Beatice S, Semaan S, Friedman S. HIV Infection During Limited Versus Combined HIV Prevention Programs For IDUs In New York City: The Importance Of Transmission Behaviors. Drug Alcohol Depend. 2010;109 (1-3): 154-160.

A Longitudinal Study of Sexual Risk Behavior among the Adolescent Children of HIV-positive and HIV-negative Drug-abusing Fathers

This is a longitudinal study of the precursors of sexual risk behavior among a cohort of adolescent children of HIV-positive and HIV-negative drug-abusing or drug-dependent fathers. Individual structured interviews were administered to 296 drug-abusing or drug-dependent fathers, 43% of whom were HIV positive, and an adolescent child of each father (mean age = 16.3 years; SD = 2.8). Adolescents were re-interviewed approximately one year later, at Time 2. Structural equation modeling showed multiple direct and indirect pathways from psychosocial factors to adolescent sexual risk behavior (sexually active, number of sexual partners and frequency of condom use). Greater paternal drug addiction and infection with HIV/AIDS, and the youth's perception of environmental hostility (discrimination and victimization), were both related to increased adolescent maladjustment and substance use. Greater paternal drug addiction and infection with HIV/AIDS also were associated with a weaker father-child mutual attachment, which was linked with increased adolescent maladjustment and substance use. Greater perceived environmental hostility (discrimination and victimization), a weak father-child relationship, and greater adolescent maladjustment and substance use had direct pathways to adolescent sexual risk behavior. Findings suggest complex interrelationships among paternal, environmental, social, personal, and substance use factors as longitudinal predictors of sexual risk behavior in children whose fathers abuse or are dependent upon drugs. The importance of perceived environmental hostility, the father-child relationship, and adolescent maladjustment and substance use may have implications for public policy as well as prevention and treatment programs. Brook D, Brook J, Rubenstone E, Zhang C, Finch S. A Longitudinal Study Of Sexual Risk Behavior Among The Adolescent Children Of HIV-Positive And HIV-Negative Drug-Abusing Fathers. J Adolesc Health. 2010; 46(3): 224-231.

Discrimination, Psychosocial Stress, and Health Among Latin American Immigrants in Oregon

Chronic psychosocial stress related to discrimination has been shown to be associated with biological measures such as elevated systolic blood pressure (SBP), increased body fat, and higher fasting glucose levels. Few studies have examined these relationships in immigrant populations. The present study recruited a sample of 132 Oregon Latino immigrant adults to investigate the relationships between perceived discrimination and several health measures (blood pressure, body mass index [BMI], and fasting glucose). Results indicate that perceived discrimination stress predicted elevated SBP among men but not among women. Perceived discrimination was significantly higher among obese women than among women of normal BMI. The same pattern was not observed for men. Further, a strong trend relationship was detected: the higher women's reported discrimination stress, the higher their fasting glucose levels. Again, this pattern was not observed for men. These results suggest that chronic psychosocial stress plays an important role in disease risk among Latin American immigrants, and that male and female immigrants may have distinctive physiological responses. If confirmed, these findings may have important clinical and public health implications for chronic disease prevention among Latinos. McClure H, Snodgrass J, Martinez C, Eddy J, Jiménez R, Isiordia L. Discrimination, Psychosocial Stress, And Health Among Latin American Immigrants In Oregon. Am J Hum Biol. 2010; 22(3): 421-423.

Sharing and Selling of Prescription Medications in a College Student Sample

The aims of this study were to: 1) estimate the prevalence of prescription medication diversion among college students; 2) to compare classes of medications with respect to the likelihood of diversion; 3) document the most common methods of diversion; and, 4) examine the characteristics of students who diverted medications. To pursue these aims, investigators conducted a cross-sectional analysis of personal interview data collected between August 2006 and August 2007 as part of an ongoing longitudinal study. The cohort of students, who were between the ages of 17 and 19 years at study onset, attended a large public university in the mid-Atlantic region. Information was gathered regarding a wide variety of variables, including demographics, diversion of medically prescribed drugs, illicit drug use, and childhood conduct problems. Results showed that among 483 students prescribed a medication, 35.8% diverted a medication at least once in their lifetime. The most commonly diverted medication classes were prescription attention-deficit/hyperactivity disorder medication (61.7% diversion rate) and prescription analgesics (35.1% diversion rate). Sharing was the most common method of diversion, with 33.6% of students sharing their medication(s) and 9.3% selling in their lifetime. Comparative analyses revealed that prescription medication diverters had used more illicit drugs in the past year and had more childhood conduct problems than non-diverters. The authors conclude that these findings may have important clinical implications for improved physician-patient communication and vigilance regarding prescribing analgesic and stimulant medications for young adults. Garnier L, Arria A, Caldeira K, Vincent K, O 'Grady K, Wish E. Sharing And Selling Of Prescription Medications In A College Student Sample. J Clin Psychiatry. 2010; 71 (3): 262-269.

Anxiety as Predictor of First Use of Substances and Progression to SUD Among Boys

This study examined associations of generalized and social anxiety with age at first use of tobacco, alcohol, and marijuana and the interval from first use to first problem use of each substance. Participants were 503 males who

comprised the youngest cohort (first assessed in the first grade) of the Pittsburgh Youth Study, a longitudinal community-based study of boys. Annual assessments of generalized and social anxiety, delinquency, and substance use from first grade through high school were included. The authors found that both types of anxiety predicted earlier first use of alcohol and tobacco, and generalized anxiety predicted earlier first use of marijuana. Both types of anxiety predicted the progression from first use to problems related to marijuana. The effect of generalized anxiety tended to be significant above and beyond the effect of delinquency, while the effect of social anxiety on risk for first use of substances was not. Overall, the findings suggest that associations between anxiety and substance use and related problems depend on the class of substance and the type of anxiety. Marmorstein N, White H, Loeber R, Stouthamer-Loeber M. Anxiety As A Predictor Of Age At First Use Of Substances And Progression To Substance Use Problems Among Boys. J Abnorm Child Psychol. 2010; 38(2): 211-224.

Nonmedical Use of Promethazine Hydrochloride among Heroin Injectors in Vietnam: Unrecognized Risks and Unintended Consequences

Surveillance studies have noted intravenous injection of promethazine hydrochloride (PHC) among populations that use heroin in South and Southeast Asia. However, little is known about onset and initiation of PHC use and its relationship to habitual heroin use. As part of a longitudinal study of heroin initiation, a sample of 179 new heroin users, aged 15-27 years, were interviewed between October 2005 and December 2006 in Hanoi, Vietnam. Cox proportional hazard regression analysis was used to characterize age at promethazine initiation and its association with relevant covariates. 76% reported lifetime use of PHC. Mean age of PHC initiation was 21.3 years, on average 6 months following onset of heroin injection. In multivariate analysis, lifetime use of diazepam [HR = 1.69 (1.17, 2.44); p-value = .01] and injecting heroin for more than 1.58 years [HR = 1.46 (1.04, 2.06); p-value = .03] were associated with PHC initiation. Intravenous injection of PHC is a relatively common practice among young injection heroin users in Hanoi, Vietnam who use it on a situational basis to substitute for heroin (when heroin is not available or when heroin is too costly) or to augment the effects of an inadequate heroin dosing (delaying onset of heroin withdraw). Existing drug prevention strategies in Vietnam are focused primarily on heroin and most new heroin users initiate PHC use without prior knowledge of its high risk for serious vein damage. Future research is needed on the PHC use among heroin users, including long-term medical consequences of PHC exposure. Clatts M, Giang L, Goldsamt L, Col—n-L—pez V. Nonmedical Use Of Promethazine Hydrochloride Among Heroin Injectors In Vietnam: Unrecognized Risks And Unintended Consequences. Subst Use Misuse. 2010; 45(4): 515-527.

Prevalence and Incidence of HCV Infection among Vietnam Heroin Users with Recent Onset of Injection

HCV infection continues to spread at an alarming rate among IDU populations. The available evidence suggests that HCV is acquired relatively quickly following onset of injection. However, there are few prospective studies of HCV acquisition, particularly among IDU populations in resource-poor settings. A sample of young male heroin injectors with recent onset of injection (<4 years) was recruited in Hanoi, Vietnam for a prospective assessment of the early course of injection (n = 179). Both behavioral and biological assessments (including detailed retrospective assessment of injection initiation) were conducted at baseline and repeated at 6-month intervals for a period of 16 months. Variables associated with HCV infection (p value < 0.05) in bivariate analyses were considered for inclusion in logistic regression models to identify risk factors independently associated with HCV infection. HCV incidence was

calculated by using the incidence density approach and was expressed in terms of person-years of observation. The baseline of prevalence of HCV was 46%. HCV significantly increased in relation to time since first injection, from 30% in subjects with

Offer of Financial Incentives for Unprotected Sex in the Context of Sex Work

Commercial sex workers (CSW) are often portrayed as vectors of disease transmission. However, the role clients play in sexual risk taking and related decision making has not yet been thoroughly characterized. In this study, participants were from the Vancouver Injection Drug Users Study, a longitudinal cohort. Analyses were restricted to those who reported selling sex between June 2001 and December 2005. Using multivariate generalized estimating equation, researchers evaluated the prevalence of and factors associated with being offered money for sex without a condom. A total of 232 CSW were included in the analyses, with 73.7% reporting being offered more money for condom non-use, and 30.6% accepting. Variables independently associated with being offered money for sex without a condom included daily speedball use [adjusted odds ratio (AOR) = 1.21, 95% confidence interval (CI): 0.23-0.62], daily crack smoking (AOR = 1.51, 95% CI: 1.04-2.19), daily heroin injection (AOR = 1.76, 95% CI: 1.27-2.43) and drug use with clients (AOR = 3.22, 95% CI: 2.37-4.37). HIV seropositivity was not significant (AOR = 0.98, 95% CI: 0.67-1.44). These findings highlight the role clients play in contributing to unprotected sex through economic influence and exploitation of CSW drug use. HIV serostatus has no bearing on whether more money is offered for sex without a condom. Novel interventions are needed to engage both CSW and clients in risk reduction and consistency in safe sex practices. Johnston C, Callon C, Li K, Wood E, Kerr T. Offer Of Financial Incentives For Unprotected Sex In The Context Of Sex Work. Drug Alcohol Rev. 2010; 29(2): 144-149.

Community-Associated Methicillin-Resistant Staphylococcus aureus is Prevalent in Wounds of Community-Based Injection Drug Users

Injection drug users (IDUs) have an elevated risk for carriage of Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA). Cutaneous injection-related infections are common in IDUs but detailed studies are few. Based on a subsample of 218 individuals from a community-recruited cohort of IDUs at a supervised injection facility, researchers investigated the microbiology and related antibiotic susceptibility profiles of isolates from 59 wounds. Twenty-seven percent of subjects had at least one wound and 25 (43%) were culture positive for S. aureus alone [14 MRSA and 11 (19%) methicillin-susceptible (MSSA) isolates]. Sixteen of 18 MRSA isolates were classified as community associated (CA) by the presence of genes encoding for PVL. MRSA and MSSA occurred in mixed infection with other organisms on three and six occasions, respectively. All CA-MRSA isolates were susceptible to tetracycline, vancomycin and linezolid but only 13% were susceptible to clindamycin compared to 63% of MSSA isolates. The frequency of CA-MRSA is a cause for public health concern in wound infection in the IDU setting. Lloyd-Smith E, Hull M, Tyndall M, Zhang R, Wood E, Montaner J, Kerr T, Romney M. Community-Associated Methicillin-Resistant Staphylococcus Aureus Is Prevalent In Wounds Of Community-Based Injection Drug Users. Epidemiol Infect. 2010; 138(5): 713-720.

Non-Injection Drug Use Patterns and History of Injection among Street Youth

Efforts to prevent youth from initiating injection drug use require a better understanding of drug use patterns that may predispose to injecting. Here researchers identify such patterns and describe the circumstances of first injection among street youth. From October 2005 to November 2007, data were collected for the At Risk Youth Study. A prospective cohort of 560 street-recruited youth aged 14-26 in Vancouver, Canada. Non-injection drug use behaviors were compared between those with and without a history of injection through multiple logistic regression. The circumstances of first injection were also examined in gender-stratified analyses. Youth who had previously injected were more likely to have engaged in non-injection use of heroin or of crystal methamphetamine. Daily users of marijuana were less likely to have injected. Among prior injectors, the median age of first injection was lower among females. Females were also more likely to have had a sexual partner present at first injection and to have become a regular injector within one week of initiation. These data show that preventing transition to injection among street youth will likely require special attention to predisposing drug use patterns and knowledge of how gender differences can influence the circumstances of first injection. Hadland S, Kerr T, Marshall B, Small W, Lai C, Montaner J, Wood E. Non-Injection Drug Use Patterns and History of Injection Among Street Youth. Eur Addict Res. 2010; 16(2): 91-98.

Late Presentation for HIV Care in the United States and Canada

Initiatives to improve early detection and access to HIV services have increased over time. Researchers assessed the immune status of patients at initial presentation for HIV care from 1997 to 2007 in 13 US and Canadian clinical cohorts. They analyzed data from 44,491 HIV-infected patients enrolled in the North American-AIDS Cohort Collaboration on Research and Design. They identified first presentation for HIV care as the time of first CD4 (+) T lymphocyte (CD4) count and excluded patients who, prior to this date, had HIV RNA measurements, evidence of antiretroviral exposure, or a history of AIDS-defining illness. Trends in mean CD4 count (measured as cells/mm (3)) and 95% confidence intervals were determined using linear regression, adjusted for age, sex, race/ethnicity, HIV transmission risk, and cohort. Median age at first presentation for HIV care increased over time (range, 40-43 years), whereas the percentage of patients with injection drug use HIV transmission risk decreased (from 26% to 14%) and heterosexual transmission risk increased (from 16% to 23%). Median CD4 count at presentation increased from 256 cells/mm (3) (interquartile range, 96-455 cells/mm (3)) to 317 cells/mm (3) (interquartile range, 135-517 cells/mm (3)) from 1997 to 2007. The percentage of patients with a CD4 count > or = 350 cells/mm (3) at first presentation also increased from 1997 to 2007 (from 38% to 46%). The estimated adjusted mean CD4 count increased at a rate of 6 cells/mm (3) per year (95% confidence interval, 5-7 cells/mm (3) per year). CD4 count at first presentation for HIV care has increased annually over the past 11 years but has remained <350 cells/mm (3), which suggests the urgent need for earlier HIV diagnosis and treatment. Althoff K, Gange S, Klein M, Brooks J, Hogg R, Bosch R, Horberg M, Saag M, Kitahata M, Justice A, Gebo K, Eron J, Rourke S, Gill M, Rodriguez B, Sterling T, Calzavara L, Deeks S, Martin J, Rachlis A, Napravnik S, Jacobson L, Kirk G, Collier A, Benson C, Silverberg M, Kushel M, Goedert J, McKaig R, Van Rompaey S, Zhang J, Moore R. Late Presentation For HIV Care In The United States And Canada. Clin Infect Dis. 2010; 50(11): 1512-1520.

Heterosexual HIV and Sexual Partnerships between Injection Drug Users and Noninjection Drug Users

Sex partnerships with injection drug users (IDU) are an understudied network-level risk factor for heterosexual HIV infection. Heterosexuals with no history of injection were recruited from high-risk areas in New York City through

respondent-driven sampling. Researchers examined the prevalence of IDU sex partnerships among these non-IDU, factors associated with having a past year IDU partner, and the independent association of HIV infection and IDU sex partnerships in multiple logistic regression. Of the 601 non-IDU in this analysis, 13.8% had a sex partner in the past year with a history of injection. IDU partnerships were significantly more common among women and those with higher levels of unprotected sex and drug and alcohol use. Overall, 7.0% tested positive for HIV. HIV prevalence was higher ($p = 0.07$) for participants with IDU partners (9.6%) compared to those with no IDU partners (4.6%). In multiple logistic regression, participants with IDU partners were over twice as likely to be HIV-infected ($p = 0.08$). Sex partnerships with IDU were common and may play an important role in heterosexual HIV transmission in areas with large IDU populations. Prevention interventions to encourage the disclosure of injection history and risk reduction specifically for those with IDU partners are indicated. Jenness S, Neaigus A, Hagan H, Murrill C, Wendel T. Heterosexual HIV And Sexual Partnerships Between Injection Drug Users And Noninjection Drug Users. AIDS Patient Care STDS. 2010; 24(3): 175-181.

Hepatitis Vaccination of Men who have Sex with Men at Gay Pride Events

Prevention researchers have advocated primary prevention such as vaccination in alternative venues. However, there have been major questions about both the attendance of, and the ability to, vaccinate high-risk individuals in such settings. The current study seeks to assess the feasibility of vaccinating high-risk men who have sex with men (MSM) at Gay Pride events. The research questions are: Do gay men who are sampled at Gay Pride events engage in more or less risky behavior than gay men sampled at other venues? Do the gay men who receive hepatitis vaccinations at Gay Pride events engage in more or less risky behavior than gay men at these events who do not receive hepatitis vaccination? Of the 3689 MSM that completed the Field Risk Assessment (FRA), 1095/3689 = 29.68% were recruited at either the 2006 or 2007 Long Beach, California Gay Pride events. The remaining, 2594/3689 = 70.32% were recruited at Long Beach gay bars, gay community organizations and institutions, and through street recruitment in various gay enclaves in the Long Beach area. Logistic regression analysis yielded eight factors that were associated with non-attendance of Gay Pride: Age, had sex while high in the last 12 months, had unprotected anal intercourse (UAI) in the last 12 months, had sex for drugs/money in the last 12 months, been diagnosed with a sexually transmitted infection (STI) in the last 12 months, used nitrites (poppers) in the last 12 months, and used methamphetamine in the last 12 months. Identifying as White, Asian, or African American compared to Hispanic was also associated with non-attendance. Bivariate analysis indicated that, of the MSM sampled at Gay Pride, 280/1095 = 25.57% received a hepatitis vaccination there. The MSM sampled at Gay Pride who reported engaging in UAI or having used any stimulant (cocaine, crack-cocaine, or methamphetamine) in the last 12 months were more likely to receive hepatitis vaccination on-site. The results provide evidence for the viability of successfully vaccinating high-risk MSM at Gay Pride events. However, it is vital that no-cost vaccinations are also funded in other community settings such as STI clinics, drug treatment programs, prisons, universities, and other community resource centers in order to reach those additional high-risk MSM who do not attend Gay Pride. Storholm E, Fisher D, Reynolds G, Napper L, Morrisse T, Kochems L. Hepatitis Vaccination Of Men Who Have Sex With Men At Gay Pride Events. Prev Sci. 2010; 11(2): 219-227.

Modeling the Effect of High Dead-Space Syringes on the HIV Epidemic among Injecting Drug Users

Researchers sought to illustrate the impact of different proportions of injecting drug users (IDUs) sharing high dead-space syringes (HDSS) or low dead-space

syringes (LDSS) on the probability of HIV transmission, and thus the impact on injection-related HIV prevalence and incidence. A stochastic mathematical model was used to evaluate the impact of HDSS use in high- and low-risk IDU populations. Model parameters were obtained from peer-reviewed publications. Analytical solutions of a simplified deterministic model were obtained to explain the effect of HDSS on HIV endemic states. Simulation analysis showed that the HIV epidemic could be sustained even when a small percentage of sharing (10%) involved HDSS. The effect is much stronger in high-risk compared with low-risk populations. Steady state HIV prevalence increases with the proportion of HDSS, and for high- and low-risk populations reaches around 80% and 20%, respectively. For low-risk populations, the use of LDSS could result in the virtual elimination of HIV. These results are dependent upon an evidence-supported assumption of a significant difference in HIV transmission risk associated with HDSS versus LDSS. These models suggest that injection-related HIV epidemics may not occur in situations where most (e.g. 95% or more) IDUs use LDSS. While the results are based on indirect risk measures and a number of simplifying assumptions, the effect of blood retained in high dead-space syringes on HIV prevalence is strong, even under relatively conservative assumptions. These findings have potential implications for needle exchange programs and the types of syringes produced and distributed world-wide. Bobashev GV, Zule WA. Modeling the Effect of High Dead-Space Syringes on the HIV Epidemic among Injecting Drug Users. Addiction. 2010; e1-e9.

Cost-Effectiveness of Strategies to Improve HIV Testing and Receipt of Results: Economic Analysis of a Randomized Controlled Trial

CDC recommends routine voluntary HIV testing of all patients 13-64 years of age. Despite this recommendation, HIV testing rates are low even among those at identifiable risk, and many patients do not return to receive their results. This study sought to examine the costs and benefits of strategies to improve HIV testing and receipt of results by analyzing cost-effectiveness based on a Markov model. Data on acceptance of testing, return rates, and related costs were derived from a randomized trial of 251 primary care patients with unknown HIV status; data on long-term costs and health outcomes were derived from the literature. The analysis compared three intervention models for HIV counseling and testing: Model A = traditional HIV counseling and testing; Model B = nurse-initiated routine screening with traditional HIV testing and counseling; Model C = nurse-initiated routine screening with rapid HIV testing and streamlined counseling. The main measures were life-years, quality-adjusted life-years (QALYs), and costs and incremental cost-effectiveness. Researchers found that, without consideration of the benefit from reduced HIV transmission, Model A resulted in per-patient lifetime discounted costs of $48,650 and benefits of 16.271 QALYs. Model B increased lifetime costs by $53 and benefits by 0.0013 QALYs (corresponding to 0.48 quality-adjusted life days). Model C cost $66 more than Model A with an increase of 0.0018 QALYs (0.66 quality-adjusted life days) and an incremental cost-effectiveness of $36,390/QALY. When the benefit was included from reduced HIV transmission, Model C cost $10,660/QALY relative to Model A. The cost-effectiveness of Model C was robust in sensitivity analyses. In a primary-care population, nurse-initiated routine screening with rapid HIV testing and streamlined counseling increased rates of testing and receipt of test results and was cost-effective compared with traditional HIV testing strategies. Sanders G, Anaya H, Asch S, Hoang T, Golden J, Bayoumi A, Owens D. Cost-Effectiveness Of Strategies To Improve HIV Testing And Receipt Of Results: Economic Analysis Of A Randomized Controlled Trial. J Gen Intern Med. 2010; 25(6): 556-563.

Parent Alcoholism Impacts the Severity and Timing of Children's Externalizing Symptoms

Although previous studies show that children of alcoholic parents have higher rates of externalizing symptoms compared to their peers, it remains unclear whether the timing of children's externalizing symptoms is linked to that of their parent's alcohol-related symptoms. Data were from 3 cohorts in the Michigan Longitudinal Study of children from alcoholic parents as well as children from matched, contrasting families without an alcoholic parent. In total, 596 children from 338 families provided four waves of data (ages 2-17). Using a multilevel modeling approach, researchers tested whether the children showed elevated mother-, father- and child-reported externalizing symptoms (a) at the same time that parents showed alcohol-related consequences (time-varying effects), (b) if parents showed greater alcohol-related consequences during the study period (proximal effects), and (c) if parents had a lifetime diagnosis of alcoholism that predated the study period (distal effects). Findings indicated that distal effects of parent alcoholism on increases in child externalizing symptoms were large and consistent. Proximal and time-varying effects of parent alcohol symptoms were found, but were not as large as distal effects. The implications of these findings for preventing escalations in externalizing symptoms among the children of alcoholic parents include the need for family-based programs that consider both distal and proximal impacts of parental alcoholism on children's functioning over development. Hussong A, Huang W, Curran P, Chassin L, Zucker R. Parent Alcoholism Impacts The Severity And Timing Of Children's Externalizing Symptoms. J Abnorm Child Psychol. 2010; 38(3): 367-380.

Developmental Associations between Depression and SUD

The association between depression and substance dependence is poorly understood; examinations of these two disorders over time during key developmental periods can provide insight into how they relate to each other. The goal of this study was to examine longitudinal associations between depression and substance (alcohol and illicit drug) dependence during the period from adolescence through early adulthood. Data from the Minnesota Twin Family Study, a community-based sample of 1252 youth and their families, were used. Youth were first assessed at age 17; they returned to the study at ages 20 and 24. Major depression and drug and alcohol dependence were assessed via structured interviews. Gender was examined as a possible moderator. The results indicated that both substance dependence and depression showed stability over time -- that is, each disorder was associated with increased risk for the same disorder later. Substance dependence between ages 17 and 20 predicted increased risk of depression between ages 20 and 24. These associations did not differ significantly by gender. The authors conclude that substance dependence during late adolescence predicts the subsequent occurrence of major depression. Marmorstein N, Iacono W, Malone S. Longitudinal Associations Between Depression And Substance Dependence From Adolescence Through Early Adulthood. Drug Alcohol Depend. 2010; 107(2-3): 154-160.

The Causal Impact of Childhood-Limited Maltreatment and Adolescent Maltreatment on Early Adult Adjustment

This study used full-matching propensity score models to test whether developmentally specific measures of maltreatment, in particular childhood-limited maltreatment versus adolescent maltreatment, are causally related to involvement in crime, substance use, health-risking sex behaviors, and internalizing problems during early adulthood. The design included 907 participants (72% male) in the Rochester Youth Development Study, a community sample followed from age 14 to age 31 with 14 assessments, including complete maltreatment histories from Child Protective Services records. After balancing the data sets, childhood-limited maltreatment was

found to be significantly related to drug use, problem drug use, depressive symptoms, and suicidal thoughts. Maltreatment during adolescence had a significant effect on a broader range of outcomes: official arrest or incarceration, self-reported criminal offending, violent crime, alcohol use, problem alcohol use, drug use, problem drug use, risky sex behaviors, self-reported sexually transmitted disease diagnosis, and suicidal thoughts. The causal effect of childhood-limited maltreatment was focused on internalizing problems, whereas adolescent maltreatment had a stronger and more pervasive effect on later adjustment. Increased vigilance by mandated reporters, especially for adolescent victims of maltreatment, along with provision of appropriate services, may prevent a wide range of subsequent adjustment problems. Thornberry T, Henry K, Ireland T, Smith C. The Causal Impact Of Childhood-Limited Maltreatment And Adolescent Maltreatment On Early Adult Adjustment. J Adolesc Health. 2010; 46(4): 359-365.

Impact of Adolescent Exposure to Intimate Partner Violence on Substance Use in Early Adulthood

Youth exposure to intimate partner violence has been theorized to increase the risk of adverse outcomes in adulthood including substance-use problems. However, research on the association between early exposure to intimate partner violence and later alcohol- or drug-use problems is limited and inconclusive. Using a prospective design, this study investigates whether adolescent exposure to intimate partner violence increases the risk for problem substance use in early adulthood and whether this relationship differs by gender. The study is based on a subsample (n = 508) of participants from the Rochester Youth Development Study, a longitudinal study of urban, largely minority adolescents that oversampled youth at high risk for antisocial behavior and drug use. Logistic regression analyses were conducted to assess whether adolescent exposure to intimate partner violence predicted increased odds of four indicators of problem substance use in early adulthood, controlling for parental substance use, adolescent maltreatment, and socio-demographic risk factors. Exposure to severe intimate partner violence as an adolescent significantly increased the odds of alcohol-use problems in early adulthood for young women (OR = 5.63, $p < .05$) but not for young men. Exposure to intimate partner violence did not increase the odds of other substance-use indicators for either gender. Girls exposed to intimate partner violence may be at increased risk for problems with alcohol use in adulthood and should be targeted for prevention and intervention efforts. Overall, however, the association between exposure to intimate partner violence and later substance-use problems was less than expected in this high-risk community sample. Smith C, Elwyn L, Ireland T, Thornberry T. Impact of Adolescent Exposure To Intimate Partner Violence on Substance Use In Early Adulthood. J Stud Alcohol Drugs. 2010; 71(2): 219-230.

A Parallel Process Model of the Development of Positive Smoking Expectancies and Smoking Behavior During Early Adolescence in Girls

This study examined the development of positive smoking expectancies and smoking behavior in an urban cohort of girls followed annually over ages 11-14. Longitudinal data from the oldest cohort of the Pittsburgh Girls Study (N = 566, 56% African American, 44% Caucasian) were used to estimate a parallel process growth model of positive smoking expectancies and smoking behavior. Average level of positive smoking expectancies was relatively stable over ages 11-14, although there was significant variability in initial level and rate of change in positive smoking expectancies. Ethnicity was associated with expectancy intercept and slope, such that African American, relative to Caucasian, girls initially had more positive expectancies, and less rapid change in positive expectancies. Ethnic differences in past year smoking prevalence

emerged at age 14, with greater smoking prevalence among Caucasian (17%), compared to African American (8%), girls. Initial level of positive smoking expectancies and initial smoking behavior were positively associated, but positive expectancies did not predict growth in smoking behavior. Depression at age 11 was concurrently and positively associated with both positive expectancies and smoking. Study results suggest the potential utility of culturally tailored smoking prevention efforts, and the potential secondary benefit of depression treatment to prevent smoking among at-risk girls. Chung T, White H, Hipwell A, Stepp S, Loeber R. A Parallel Process Model Of The Development Of Positive Smoking Expectancies And Smoking Behavior During Early Adolescence In Caucasian And African American Girls. Addict Behav. 2010; 35(6): 647-650.

An Item Response Theory Analysis of DSM-IV Criteria for Hallucinogen Abuse and Dependence in Adolescents

This study applied both item response theory (IRT) and multiple indicators-multiple causes (MIMIC) methods to evaluate item-level psychometric properties of diagnostic questions for hallucinogen use disorders (HUDs), differential item functioning (DIF), and predictors of latent HUD. Data were drawn from 2004-2006 National Surveys on Drug Use and Health. Analyses were based on 1548 past-year hallucinogen users aged 12-17 years. Substance use and symptoms were assessed by audio computer-assisted self-interviewing methods. Analyses revealed that abuse and dependence criteria empirically were arrayed along a single continuum of severity. All abuse criteria indicated middle-to-high severity on the IRT-defined HUD continuum, while dependence criteria captured a wider range from the lowest (tolerance and time spent) to the highest (taking larger amounts and inability to cut down) severity levels. There was indication of DIF by hallucinogen users' age, gender, race/ethnicity, and ecstasy use status. Adjusting for DIF, ecstasy users (vs. non-ecstasy hallucinogen users), females (vs. males), and whites (vs. Hispanics) exhibited increased odds of HUD. The authors conclude that, empirically, symptoms of hallucinogen abuse and dependence do not reflect two discrete conditions in adolescents. Trends and problems related to hallucinogen use among girls and whites should be examined further to inform the designs of effective gender-appropriate and culturally sensitive prevention programs. Wu L, Pan J, Yang C, Reeve B, Blazer D. An Item Response Theory Analysis Of DSM-IV Criteria For Hallucinogen Abuse And Dependence In Adolescents. Addict Behav. 2010; 35(3): 273-277.

Genetic and Environmental Influences on Cannabis Use Initiation and Problematic Use: a Meta-Analysis of Twin Studies

Because cannabis use is associated with social, physical and psychological problems, it is important to know what causes some individuals to initiate cannabis use and a subset of those to become problematic users. Previous twin studies found evidence for both genetic and environmental influences on vulnerability, but due to considerable variation in the results it is difficult to draw clear conclusions regarding the relative magnitude of these influences. A systematic literature search identified 28 twin studies on cannabis use initiation and 24 studies on problematic cannabis use. The proportion of total variance accounted for by genes (A), shared environment (C) and unshared environment (E) in the initiation of cannabis use and in problematic cannabis use was calculated by averaging corresponding A, C and E estimates across studies from independent cohorts and weighting by sample size. For cannabis use initiation, A, C and E estimates were 48%, 25% and 27% in males and 40%, 39% and 21% in females. For problematic cannabis use A, C and E estimates were 51%, 20% and 29% for males and 59%, 15% and 26% for females. Confidence intervals of these estimates are considerably narrower than those in the source studies. These results suggest that vulnerability to

both cannabis use initiation and problematic use is influenced significantly by genes, shared, and non-shared environmental factors, with a t trend for a greater non-shared environment and lesser genetic influence on cannabis use initiation compared to problematic use for females. Verweij K, Zietsch B, Lynskey M, Medland S, Neale M, Martin N, Boomsma D, Vink J. Genetic and Environmental Influences on Cannabis Use Initiation and Problematic Use: A Meta-Analysis Of Twin Studies. Addiction. 2010; 105(3): 417-430.

Circumstances, Pedagogy and Rationales for Injection Initiation among New Drug Injectors

Injection drug use is especially risky for new injectors. To understand the social and environmental contexts in which risks occur, researchers interviewed individuals who had initiated injection within the past 3 years (n = 146, 69.2% male) about the circumstances and rationales for their initial injection events. Respondents typically initiated injection due to tolerance (49.3%) and/or for experimentation (61.1%). Most (86.2%) did not possess the technical skills required to self-inject, and relied on the assistance of someone older (58.5%). While low levels of syringe sharing (5.8%) were reported, a majority of respondents (60.5%) engaged in at least one type of behavioral risk. Female injectors were more likely than male injectors to rely on another individual (95.5 vs. 82.2%), often a sex partner (40.5 vs. 7.2%), for assistance. The diversity seen in early injection practices highlights the need for tailored prevention messages to reach this population prior to the onset of injection risk. Goldsamt L, Harocopos A, Kobrak P, Jost J, Clatts M. Circumstances, Pedagogy And Rationales For Injection Initiation Among New Drug Injectors. J Community Health. 2010; 35(3): 258-267.

Factors Associated with Sex in the Context of Methamphetamine Use in Different Sexual Venues among HIV-positive Men who have Sex with Men

Harm reduction has focused primarily on reduction of high-risk substance using behaviors rather than reductions in high-risk sexual behaviors. Furthermore, most studies focus on individual behavior change, with less attention paid to the social and environmental context. This paper examines the interplay between the individual and social context by examining the psychosocial and behavioral characteristics of 321 methamphetamine-using HIV-positive men who have sex with men (MSM) in San Diego based on the locations or venues of their sexual activities when "high" on methamphetamine. Participants in a safer-sex intervention study underwent a baseline assessment that queried demographic and psychosocial characteristics as well as drug use and sexual risk behaviors. For purposes of analysis, respondents were classified by their preference of sexual venue: private (e.g., home), commercial (e.g., bathhouse), or public (e.g., public park or restroom). The commercial venue group was found to be younger, better educated, more likely to identify as gay, and significantly more likely to have used "club drugs" as compared to the other two groups. Men in the commercial- and public-venue groups reported more high-risk sex compared to the private-venue group. The public-venue group reported heavier drug and alcohol use, had significantly higher Beck depression scores, reported more experiences of stigma, and scored higher on a measure of sexual compulsivity than did the other two groups. In an effort to reduce HIV/STI risk-behaviors, future studies should investigate the feasibility of modifying personal, psychosocial and structural factors associated with the use of risky sexual venues where HIV-positive methamphetamine users engage in sexual activity when "high" on methamphetamine. Semple S, Strathdee S, Zians J, Patterson T. Factors Associated With Sex In The Context Of Methamphetamine Use In Different Sexual Venues Among HIV-Positive Men Who Have Sex With Men. BMC Public Health. 2010; 10: 178-184.

Barriers to Pharmacy-Based Syringe Purchase among Injection Drug Users in Tijuana, Mexico: A Mixed Methods Study

Injection drug users (IDUs) may be denied purchase of sterile syringes even where purchase without a prescription is legal. This study examined barriers to over-the-counter (OTC) syringe purchase among IDUs in Tijuana, Mexico. A quantitative survey and subsequent focus groups were used to quantify barriers to purchase, identify their correlates and provide in-depth exploration of syringe purchase experiences. Of 627 IDUs, 81% purchased a syringe in the past 6 months and 16% were refused or overcharged. Factors independently associated with refusal/overcharging were homelessness, receptive syringe sharing, >5 uses per syringe, and number of lifetime abscesses. Few pharmacies sold syringes to IDUs, who adapted by limiting purchase attempts to pharmacies known to sell syringes consistently. Failed purchases occurred when drug withdrawal required purchase at unusual times or locations, often following release from jail. IDUs reported syringe sharing, syringe reuse, and searching through unsecured medical waste for syringes in response to failed purchase attempts. Interventions to expand OTC syringe sales to IDUs, particularly near detention facilities, will facilitate safer injection practices. Pollini R, Lozada R, Gallardo M, Rosen P, Vera A, Macias A, Palinkas L, Strathdee S. Barriers To Pharmacy-Based Syringe Purchase Among Injection Drug Users In Tijuana, Mexico: A Mixed Methods Study. AIDS Behav. 2010; 14(3): 679-687.

Methamphetamine Use and Malnutrition among Street-Involved Youth

Researchers sought to explore the effect of crystal methamphetamine use on the risk of experiencing malnutrition among street-involved youth in Vancouver, Canada. Risk of malnutrition was defined as being hungry but not having enough money to buy food. Socio-demographic and drug use factors associated with risk of malnutrition were investigated using univariate and multivariate analysis among a prospective cohort of street-involved youth known as the At-Risk Youth Study (ARYS). Between September 2005 and December 2006, 509 street-involved youth were enrolled in ARYS, among whom 21% reported being at risk of malnutrition as defined above in the previous six months. In multivariate analysis, only non-injection crystal methamphetamine was significantly associated with being at risk of malnutrition among this cohort (Adjusted Odds Ratio [AOR] = 1.60, 95% Confidence Interval [CI]: 1.03 - 2.48, p = 0.036). Interventions seeking to address food insecurity among street youth may benefit from considering drug use patterns since methamphetamine use predicted higher risk in this setting. Werb D, Kerr T, Zhang R, Montaner J, Wood E. Methamphetamine Use And Malnutrition Among Street-Involved Youth. Harm Reduct J. 2010; 7: 5-9.

Evaluating Respondent-Driven Sampling in a Major Metropolitan Area: Comparing Injection Drug Users in the 2005 Seattle Area National HIV Behavioral Surveillance System Survey with Participants in the RAVEN and Kiwi Studies

Researchers sought to empirically evaluate respondent-driven sampling (RDS) recruitment methods, which have been proposed as an advantageous means of surveying hidden populations. The National HIV Behavioral Surveillance system used RDS to recruit 370 injection drug users (IDU) in the Seattle area in 2005 (NHBS-IDU1). The researchers compared NHBS-IDU1 estimates of participants' area of residence, age, race, sex, and drug most frequently injected to corresponding data from two previous surveys, the NIDA-funded RAVEN and Kiwi Studies, and to persons newly diagnosed with HIV/AIDS and reported from 2001 through 2005. They found that the NHBS-IDU1 population was more

likely to reside in downtown Seattle (52%) than participants in the other 2 studies (22%-25%), be older than 50 years of age (29% vs. 5%-10%), and report multiple races (12% vs. 3%-5%). The NHBS-IDU1 population resembled persons using the downtown needle exchange in age and race distribution. An examination of cross-group recruitment frequencies in NHBS-IDU1 suggested barriers to recruitment across different areas of residence, races, and drugs most frequently injected. The substantial differences found in age and area of residence between NHBS-IDU1 and the other studies suggest that RDS may not have accessed the full universe of Seattle area injection networks. Further empirical data are needed to guide evaluations of RDS-generated samples. Burt R, Hagan H, Sabin K, Thiede H. Evaluating Respondent-Driven Sampling In A Major Metropolitan Area: Comparing Injection Drug Users In The 2005 Seattle Area National HIV Behavioral Surveillance System Survey With Participants In The RAVEN And Kiwi Studies. Ann Epidemiol. 2010; 20(2): 159-167.

Intimate Partner Violence Perpetration and Condom Use-Related Factors: Associations with Heterosexual Men 's Consistent Condom Use

Intimate partner violence victimization has been linked to sexual HIV risk behavior among heterosexual women. The unique role of perpetration of intimate partner violence (IPV) in sexual risk behavior among men has not been studied as well. Based on interviews with 518 heterosexual men recruited via street-intercept between 2005 and 2007 in New York City, the researchers assessed the relationship between perpetration of IPV against a main female partner and inconsistent condom use with that same partner, while controlling for condom use-related factors. Multivariate logistic regression revealed that men who perpetrated physical IPV were half as likely to report consistent condom use as compared with men who did not use violence, while controlling for sociodemographic, condom use-related and other factors. Physical IPV perpetration by heterosexual men makes an independent contribution to consistent condom use. Designing interventions for heterosexual men that simultaneously address both IPV and sexual risk behaviors is critical. Frye V, Panchanadeswaran S, Nandi V, Galea S, Vlahov D, Ompad D. Intimate Partner Violence Perpetration And Condom Use-Related Factors: Associations With Heterosexual Men 'S Consistent Condom Use. AIDS Behav. 2010; 50(2): 107-124.

Trajectories of Cigarette Smoking from Adolescence to Young Adulthood as Predictors of Obesity in the Mid-30s

The purpose of this longitudinal study was to examine the relationship between two major health problems, smoking and obesity, and to determine to what extent trajectories of cigarette smoking from early adolescence to young adulthood are related to obesity in the mid-30s. Participants (N = 806) were interviewed using a structured questionnaire at 6 points in time over a period of 23 years. Semiparametric group-based modeling and logistic regression analyses were used to analyze the data. The main outcome measure was obesity, assessed by body mass index in the mid-30s. Five distinct trajectories of tobacco use were identified (N = 806): heavy/continuous smokers, late starters, quitters/decreasers, occasional smokers, and nonsmokers. Compared with nonsmokers, heavy/continuous smokers or late starters had a significantly lower likelihood of obesity. Also, compared with nonsmokers or occasional smokers, heavy/continuous smokers or late starters had a significantly lower likelihood of being overweight or obese. Smoking cessation programs should focus on weight control methods, such as physical exercise and learning healthy habits. In addition, weight control programs should incorporate smoking cessation efforts as integral components. Brook D, Zhang C, Brook J, Finch S. Trajectories Of Cigarette Smoking From Adolescence To Young

Adulthood As Predictors of Obesity In The Mid-30s. Nicotine Tob Res. 2010; 12(3): 263-270.

Epidemiology of HIV among Injecting and Non-injecting Drug Users: Current Trends and Implications for Interventions

Injecting drug use is a major driver of HIV infections in Eastern Europe, the Commonwealth of Independent States, North Africa, the Middle East, and many parts of Asia and North America. In this review paper, researchers provide a global overview of the epidemiology of HIV infection among drug users and present current drug use trends that may constitute important epidemic drivers. They describe trends in ethnic disparities among injecting drug using (IDU) populations in the United States, and comment upon how these trends may now be changing. They present examples where HIV infection among non-IDUs who use cocaine, crack, and methamphetamine by other routes of administration is similar to that among IDUs, and discuss potential mechanisms of HIV spread in this overlooked population. Finally, they comment upon the potential implications of these observations for HIV interventions among IDU and non-IDU populations, taking into account different strategies that are needed in settings where HIV and/or injecting drug use has been established, or threatens to emerge. Strathdee S, Stockman J. Epidemiology Of HIV Among Injecting And Non-Injecting Drug Users: Current Trends And Implications For Interventions. Curr HIV/AIDS Rep. 2010; 7(2): 99-106.

Young Adult Ecstasy Users who Forego Necessary Medical Care: a Fairly Common Occurrence with Important Health Implications

This study examined the practice of foregoing necessary medical care in a population of young adult Ecstasy users. The objectives were to (1) investigate how the failure to receive needed medical care is related to drug-related outcomes, and (2) identify factors that are associated with receiving versus foregoing needed medical care. Face-to-face, computer-assisted, structured interviews were conducted with 283 active young adult Ecstasy users in Atlanta, Georgia between August 2002 and October 2007. Study participants were recruited using a targeted sampling approach. Results indicated that almost one-third of the young adult Ecstasy users interviewed did not receive the medical care that they needed during the preceding year. Foregoing such care was associated with a variety of adverse drug-related outcomes, including experiencing a greater number of negative effects from using Ecstasy, experiencing a larger number of drug dependency symptoms, a greater likelihood of ever having binged on Ecstasy, and a greater likelihood of being classified as a "high end" polydrug abuser. Several factors were found to be associated with a greater tendency not to receive the medical care they needed, including race (not being African American), educational attainment (having completed at least high school), self-identification as belonging to the lowest socioeconomic status grouping, low self-esteem, and having experienced sexual abuse during one's formative years. Elifson K, Klein H, Sterk C. Young Adult Ecstasy Users Who Forego Necessary Medical Care: A Fairly Common Occurrence With Important Health Implications. J Psychoactive Drugs. 2010; 42(1): 63-71.

Differential Racial/Ethnic Patterns in Substance Use Initiation Among Young, Low-Income Women

Substance abuse has been associated with a host of health problems, as well as impaired social, relationship, and vocational functioning. The current study examines racial and ethnic differences in patterns of initiation of licit and illicit substance use among low-income women. A cross-sectional survey was conducted among 696 low-income women between the ages of 18 and 31 who

sought gynecological care between December, 2001 and May, 2003 in southeast Texas. Overall, White women fit the classic profile of drug use initiation patterns, with those initiating tobacco and beer/wine at earlier ages being more likely to use illicit drugs. Conversely, African-American and Hispanic women initiated tobacco and beer/wine at much later ages than White women, but they were as likely to use illicit drugs. This study extends the literature by examining patterns of drug initiation among a critically underserved sample of low-income, ethnically-diverse women. Initiation of licit substance use at earlier ages was generally a risk factor for later illicit use. These findings further emphasize the importance of implementing substance use prevention programs at an early age, and focusing on the elevated risk of early initiation on later substance use disorders. Wu Z, Temple J, Shokar N, Nguyen-Oghalai T, Grady J. Differential Racial/Ethnic Patterns In Substance Use Initiation Among Young, Low-Income Women. Am J Drug Alcohol Abuse. 2010; 36(2): 123-129.

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Research Findings - Prevention Research

Twelve-Year Follow-up of Prenatal Nurse Home Program: Enduring Effects on Mothers and Children

These two studies report on the 12-year follow-up outcomes of a randomized trial of prenatal and infancy nurse home visiting (Nurse Family Partnership), conducted with an urban primarily African American sample of first time mothers and their firstborn children. Participants were recruited through a public system of obstetric and pediatric care in Memphis, Tennessee. A total of 594 urban primarily African American economically disadvantaged mothers (among 743 who registered during pregnancy) enrolled in the study and were randomized to receive the nurse home visiting intervention or to a control group. Mothers in the control condition (n=515) were provided free transportation for scheduled prenatal care plus developmental screening and referral services for their child at age 6, 12, and 24 months. Mothers in the nurse-visited condition (n=228) were provided the same services as those in the control group plus prenatal and infancy home visiting through their child's second birthday. Combined, these two studies demonstrate the importance and value of long-term follow-up for determining the impact of early intervention approaches on families and their children.

- Positive Impact on Maternal Life Course and Government Spending This study focused on mothers' fertility, partner relationships, economic self-sufficiency, and on government spending through age 12 years of the target child. Specifically, they measured mothers' cohabitation with and marriage to the child's biological father, intimate partner violence, duration (stability) of partner relationships, role impairment due to alcohol and other drug use, use and cost of welfare benefits, arrests, mastery, child foster care placements, and cumulative subsequent births. By the time the firstborn child was 12 years old, nurse-visited mothers compared with control subjects reported less role impairment owing to alcohol and other drug use (0.0% vs 2.5%, P = .04), longer partner relationships (59.58 vs 52.67 months, P = .02), and greater sense of mastery (101.04 vs 99.60, P = .005). During this 12-year period, government spent less per year on food stamps, Medicaid, and Aid to Families with Dependent Children and Temporary Assistance for Needy Families for nurse-visited than control families ($8772 vs $9797, P = .02); this represents $12,300 in discounted savings compared with a program cost of $11,511 (both expressed in 2006 US dollars). No statistically significant program effects were noted on mothers' marriage, partnership with the child's biological father, intimate partner violence, alcohol and other drug use, arrests, incarceration, psychological distress, or reports of child foster care placements. The authors conclude that the program improved maternal life course and reduced government spending among children through age 12 years. Olds

D, Kitzman H, Cole R, Hanks C, Arcoleo K, Anson E, Luckey D, Knudtson M, Henderson C, Bondy J, Stevenson A. Enduring Effects Of Prenatal And Infancy Home Visiting By Nurses On Maternal Life Course And Government Spending: Follow-Up Of A Randomized Trial Among Children At Age 12 Years. Arch Pediatr Adolesc Med. 2010; 164(5): 419-424.

- Positive Impact on Children's Substance Use, Internalizing Problems and Academic Achievement This study reports on the12-year-old, firstborn children's use of substances, behavioral adjustment, and academic achievement. Primary outcomes focused on use of cigarettes, alcohol, and marijuana; internalizing, externalizing, and total behavioral problems; and academic achievement. By the time the firstborn child was 12 years of age, those visited by nurses, compared with those in the control group, reported fewer days of having used cigarettes, alcohol, and marijuana during the 30-day period before the 12-year interview (0.03 vs 0.18, P = .02) and were less likely to report having internalizing disorders that met the borderline or clinical threshold (22.1% vs 30.9%, P = .04). Nurse-visited children born to mothers with low psychological resources, compared with their control group counterparts, scored higher on the Peabody Individual Achievement Tests in reading and math (88.78 vs 85.70, P = .009) and, during their first 6 years of education, scored higher on group-administered standardized tests of math and reading achievement (40.52 vs 34.85, P = .02). No statistically significant program effects were found on children's externalizing or total behavioral problems. This study demonstrates that an early intervention, can have a long-term impact, in this case, on children's use of substances and internalizing mental health problems, improvements in academic achievement of children born to mothers with low psychological resources at baseline. Kitzman H, Olds D, Cole R, Hanks C, Anson E, Arcoleo K, Luckey D, Knudtson M, Henderson C, Holmberg J. Enduring Effects Of Prenatal And Infancy Home Visiting By Nurses On Children: Follow-Up Of A Randomized Trial Among Children At Age 12 Years. Arch Pediatr Adolesc Med. 2010; 164 (5): 412-418.

Fast Track Preventive Intervention Associated with Reduced Use of Health Services 12 Years Later

This analysis tested the impact of the Fast Track conduct disorder prevention program on the use of pediatric, general health, and mental health services in adolescence. Participants were 891 public kindergarten boys and girls screened from a population of 9594 children and found to be at risk for conduct disorder. They were assigned randomly (by school) to intervention or control conditions and were followed for 12 years. The final sample included 891 children divided into intervention (n = 445) and control groups (n = 446) and equally spread among sites (Durham, NC: n = 219; Nashville, TN: n = 230; Central, PA: n = 225; Seattle, WA: n = 217). Across all sites, the sample primarily comprised black and white participants (51% black, 47% white, and 2% of other ethnicity) and gender mixed (69% boys). The sample was skewed toward socioeconomic disadvantage: 58% were from single parent families and 40% of the families were in the lowest socioeconomic class. The intervention lasted 10 years and included parent training, child social-cognitive skills training, reading tutoring, peer-relations enhancement, and classroom curricula and management. Service use was assessed through annual interviews of parents and youth. Youth assigned to receive the preventive intervention had significantly reduced use of professional general health, pediatric, and emergency department services relative to control youth on the basis of parent-report data. For control-group youth, the odds of greater use of general health services for any reason and general health services use for mental health purposes were roughly 30% higher and 56% higher, respectively. On the basis of self-report data, the intervention reduced the likelihood of outpatient mental health services among older adolescents for whom odds of services use were more than 90% higher among control-group youth. No

Publications

Staff Highlights

Grantee Honors

differences were found between intervention and control youth on the use of inpatient mental health services. Statistical models controlled for key study characteristics, and potential moderation of the intervention effect was assessed. This investigation indicates that random assignment to the Fast Track prevention program was associated with reduced use of general health and outpatient mental health services in adolescents. Jones D, Godwin J, Dodge K, Bierman K, Coie J, Greenberg M, Lochman J, McMahon R, Pinderhughes E. Impact Of The Fast Track Prevention Program On Health Services Use By Conduct-Problem Youth. Pediatrics. 2010; 125(1): e130-e136.

Long-Term Effects of the Strong African American Families Program on Youth Alcohol Use

This report extends earlier accounts by addressing the effects of the Strong African American Families (SAAF) preventive intervention program across 65 months (approximately 5 years and 4 months). Two hypotheses were tested: (a) Rural African American youths randomly assigned to participate in SAAF would demonstrate lower rates of alcohol use than would control youths more than 5 years later, and (b) SAAF's effects on deterring the onset of alcohol use in early adolescence would carry forward to mediate the program's long-term effects. African American youths in rural Georgia (mean age at pretest = 10.8 years; 53% girls) were assigned randomly to the SAAF group (n = 369) or to a control group (n = 298). Past-month alcohol use was assessed at pretest and at 9, 18, 29, 53, and 65 months after pretest. SAAF participants increased their alcohol use at a slower rate than did adolescents in the control condition across the follow-up assessments. At the 65-month assessment, SAAF participants reported having drunk alcohol half as often as did youths in the control group. Consistent with the second hypothesis, SAAF's effects on deterring initiation carried forward to account for its effects on alcohol use across time. This research indicates that training in protective parenting processes and self-regulatory skills during preadolescence may contribute to a self-sustaining trajectory of disinterest in and avoidance of alcohol use during adolescence when peers begin to model and sanction it. Brody G, Chen Y, Kogan S, Murry V, Brown A. Long-Term Effects Of The Strong African American Families Program On Youths' Alcohol Use. J Consult Clin Psychol. 2010; 78(2): 281-285.

Impact of Brief Image-Based Preventive Intervention is Greatest for Drug-using Adolescents

This study evaluated the efficacy of a brief image-based prevention intervention and assessed current drug use as a moderator of intervention effects. In a clinical trial, 416 high school-age adolescents were randomized to either the brief intervention or usual care control. Data were collected at baseline and 3-month follow-up. The brief intervention consisted of a tailored in-person communication (i.e., screening survey, consultation, and goal plan) that occurred during regular school hours and was followed up one week later by a 3-week series of parent/guardian print materials comprised of tailored messages that paralleled those in the consultation. Health behavior goal setting increased for participants receiving the brief intervention, with an effect size in the small range (d = 0.33). Overall effect sizes for cigarette smoking frequency and quantity and alcohol use frequency and quantity were small (ds = 0.16-0.21) and in favor of the brief intervention. However, adolescents reporting current substance use who received the brief intervention reduced their frequency and heavy use of alcohol, frequency and quantity of cigarette smoking, and reported fewer alcohol/drug problems, with larger effects ranging from small to approaching medium in size (ds = 0.32-0.43, ps < .01). The findings from this study suggest that brief image-based messages may increase health behavior goal setting and reduce substance use in high school-age adolescents, particularly among those using drugs. Werch C, Bian H, Diclemente C, Moore M, Thombs D, Ames S, Huang I, Pokorny S. A Brief

Image-Based Prevention Intervention For Adolescents. Psychol Addict Behav. 2010; 24(1): 170-175.

15 Minutes with a Video Doctor and Provider Cueing Reduces Smoking among Pregnant Women

This study examined the use of a Video Doctor plus provider cueing to promote provider advice and smoking cessation outcomes in pregnancy, through a randomized controlled trial conducted from 2006 to 2008. Five community prenatal clinics in the San Francisco Bay Area of the United States were recruited for the trial. A total of 410 pregnant patients in these clinics completed screening for behavioral risks including tobacco use in the past 30 days. Pregnant smokers (n = 42) were identified and randomized regardless of their intention to quit smoking. Participants were assigned to either usual care or to the Video Doctor intervention. Intervention participants received a 15-minute Video Doctor session. The Video Doctor delivered interactive tailored messages, an educational worksheet for participants and a cueing sheet for providers. The main outcomes focused on receipt of advice from the provider and 30-day smoking abstinence, both by self-report. Results indicated that intervention participants were more likely to receive provider advice on tobacco use at both prenatal visits during the intervention period (60.9 % vs. 15.8%, p = 0.003). The intervention yielded a significantly greater decrease in the number of days smoked and in cigarettes smoked per day. Although not statistically significant, the 30-day abstinence rate at two months post baseline was 2.5 times greater in the intervention group (26.1% vs. 10.5%, p = 0.12). The authors conclude that the Video Doctor plus provider cueing is an efficacious adjunct to routine prenatal care by promoting provider advice and smoking reduction among pregnant smokers. Tsoh J, Kohn M, Gerbert B. Promoting Smoking Cessation In Pregnancy With Video Doctor Plus Provider Cueing: A Randomized Trial. Acta Obstet Gynecol Scand. 2010; 89(4): 515-523.

Effects of a Social and Emotional Learning Program on Aggression, Prosocial Behavior and Academic Engagement in Children

This article examines the impact of a universal social-emotional learning program, the Fast Track PATHS (Promoting Alternative Thinking Strategies) curriculum and teacher consultation, embedded within the Fast Track selective prevention model. The longitudinal analysis involved 2,937 children of multiple ethnicities who remained in the same intervention or control schools for Grades 1, 2, and 3. The study involved a clustered randomized controlled trial involving sets of schools randomized within 3 U.S. locations (i.e., rural Pennsylvania, Seattle, & Nashville). Measures assessed teacher and peer reports of aggression, hyperactive-disruptive behaviors, and social competence. Beginning in first grade and through 3 successive years, teachers received training and support and implemented the PATHS curriculum in their classrooms. The study examined the main effects of intervention as well as how outcomes were affected by characteristics of the child (baseline level of problem behavior, gender) and by the school environment (student poverty). Modest positive effects of sustained program exposure included reduced aggression and increased pro-social behavior (according to both teacher and peer report) and improved academic engagement (according to teacher report). Peer report effects were moderated by gender, with significant effects only for boys. Most intervention effects were moderated by school environment, with effects stronger in less disadvantaged schools, and effects on aggression were larger in students who showed higher baseline levels of aggression. The authors conclude that a major implication of the findings is that well-implemented multiyear social-emotional learning programs can have significant and meaningful preventive effects on the population-level rates of

aggression, social competence, and academic engagement in the elementary school years. The Effects Of A Multiyear Universal Social-Emotional Learning Program: The Role Of Student And School Characteristics. Conduct Problems Prevention Research Group. J Consult Clin Psychol. 2010; 78(2): 156-168.

Initial Findings from the Dissemination of Project Toward No Drug Abuse into Real-World Conditions

This study describes the immediate outcomes of a dissemination and implementation trial of Project Toward No Drug Abuse (TND), an evidence-based prevention program for high school students. A total of 65 high schools in 14 school districts across the USA were recruited and randomly assigned to one of three experimental conditions: comprehensive implementation support for teachers implementing TND, regular workshop training only for teachers implementing TND, or standard care control where TND was not implemented. The comprehensive intervention was comprised of on-site coaching, web-based support, and technical assistance, in addition to the regular workshop. It was hypothesized that this comprehensive training and support model compared to standard pre-implementation training workshops would result in higher implementation fidelity and improved student outcomes. High school students (mean age = 14.8 years; SD = 1.0 years) (n = 2,983) completed self-report surveys before and immediately after program implementation. Fidelity of implementation was assessed with a classroom observation procedure that focused on program process. Results indicated that relative to the controls, both intervention conditions produced effects on hypothesized program mediators, including greater gains in program-related knowledge; greater reductions in cigarette, marijuana and hard drug use intentions; and more positive changes in drug-related beliefs. There were stronger effects on implementation fidelity in the comprehensive, relative to the regular, training condition. However, seven of the ten immediate student outcome measures showed no significant differences between the two training conditions. These results suggest that comprehensive training approaches may improve implementation fidelity, but these improvements in fidelity may not result in stronger program outcomes. In sum, these findings contribute to a small, but growing, body of evidence for the effectiveness of school-based substance abuse prevention programs that have been tested under real-world conditions. Rohrbach L, Gunning M, Sun P, Sussman S. The Project Towards No Drug Abuse (TND) Dissemination Trial: Implementation Fidelity And Immediate Outcomes. Prev Sci. 2010; 11(1): 77-88.

Addressing Selection Effects In Drug Abuse Prevention Interventions Delivered Under Real World Circumstances

This study focused on improving the estimates of the costs and benefits of substance abuse through identification and correction of selection effects in community-implemented interventions. A supplemental comparison sample is typically used for this purpose, but in community-based program implementations, such a sample is often not available. The authors present an evaluation design and analytic approach that can be used in program evaluations of real-world implementations to identify selection effects, which in turn can help inform recruitment strategies, pinpoint possible selection influences on measured program outcomes, and refine estimates of program costs and benefits. The approach is illustrated with data from a multisite implementation of a popular substance abuse, family-based, prevention program. Results indicate that the program's participants differed significantly from the population at large-having a female child and being of White race/ethnicity were associated with greater participation of families with younger adolescents. Families with highest levels of opportunity for positive family interaction were less likely to participate. Weaker family management skills, lower levels of adolescent drug use, and Latino or American Indian/Alaska

Native ethnicity were all associated with greater participation of families with older youth. Taken together, these findings demonstrate that there were selection effects in this community-based implementation of an evidence-based practice. Hill L, Goates S, Rosenman R. Detecting Selection Effects In Community Implementations Of Family-Based Substance Abuse Prevention Programs. Am J Public Health. 2010; 100(4): 623-630.

Generally Healthy Behaviors are Diminished Among Multigenerational Caregivers

The current study examined the association between membership in the "sandwich" generation, defined as providing care to both children and parents or in-laws, and five health behaviors: checking the food label for health value when buying foods, using a seat belt, choosing foods based on health value, exercising regularly, and cigarette smoking. Participants were from the Indiana University Smoking Survey, an ongoing cohort-sequential study of the natural history of cigarette smoking. Between 1980 and 1983, all consenting 6th-12th graders in a Midwestern county school system completed annual surveys. The total sample size of those who were assessed at least once was 8487. Follow-up surveys were conducted in 1987, 1993, 1999, and 2005. Because the sample is 96% non-Hispanic Caucasian, ethnic differences are not considered. Demographically, the sample is similar to the community from which it was drawn. For example, the marriage rate is 64% in this sample compared to 66% among similarly aged adults in the Midwest, and the high school graduation rate is 97% in this sample compared to 92% among similarly aged adults in the Midwest. At the most recent follow-up conducted in 2005, the smoking rate in the sample was 23% compared to a 2006 statewide rate of 24% and regional rate of 17%. For the current study, participants were selected from the most recent follow-up survey (2005) who provided data on the number of hours per week spent providing unpaid help to their children, to their parents or the people who raised them, and to their in-laws. This yielded a sample of 4943 (mean age = 37.8, SD = 2.7, range 32-47. Although there is great variability in the definition of midlife, with age boundaries ranging from 30 to 60, this sample might best be considered to represent entry into midlife. Regression analyses tested the unique effect of sandwich generation membership on health behaviors above and beyond demographic factors and prior levels of the same behavior. Compared to other caregivers and non-caregivers, multigenerational caregivers were less likely to check food labels and to choose foods based on health values. Multigenerational caregivers were less likely than non-caregivers and those who cared for children only to use seat belts, and they smoked marginally more cigarettes per day than those groups. Multigenerational caregivers were less likely than non-caregivers and those who cared for parents/in-laws only to exercise regularly. Thus, in general, healthy behaviors were diminished for multigenerational caregivers. Chassin L, Macy JT, Seo D, Presson CC, Sherman SJ. The Association Between Membership In The Sandwich Generation And Health Behaviors: A Longitudinal Study. J Appl Dev Psychol. 2010; 31(1): 38-46.

Person-Centered Modeling Approach Reveals Risk Factors for Negative Child Outcomes

This study relied on data from Fast Track, a multisite, multi-cohort research project designed to study and change the development of serious conduct problems among aggressive children. This study included children and their families from the schools assigned to the control condition in Fast Track. Fast Track recruited children and families from four distinct communities in the United States. These communities were (a) Durham, North Carolina, a small city with many low- to middle- socioeconomic status (SES) African American families; (b) Nashville, Tennessee, a moderate-sized city with many low- to middle-SES African American and European American families; (c) Seattle,

Washington, a moderate-sized city with many low- to middle-SES, ethnically diverse families, including European Americans, African Americans, Asian and Pacific Islanders, Latinos, and Native Americans; and (d) Central Pennsylvania, a rural area with mostly low- to middle-SES, two-parent, European American families. Fifty-eight percent of the children in this sample were male, and 42% were female. At the beginning of the study, children were an average of 6 years, 5 months old (SD = 5 months). At the end of this study, they were 5 years older. This study identified profiles of 13 risk factors across child, family, school, and neighborhood domains in a diverse sample of children in kindergarten from four US locations (n = 750; 45% minority). It then examined the relation of those early risk profiles to externalizing problems, school failure, and low academic achievement in Grade 5. A person-centered approach, latent class analysis, revealed four unique risk profiles, which varied considerably across urban African American, urban White, and rural White children. Profiles characterized by several risks that cut across multiple domains conferred the highest risk for negative outcomes. Compared to a variable-centered approach, such as a cumulative risk index, these findings provide a more nuanced understanding of the early precursors to negative outcomes. For example, results suggested that urban children in single-parent homes that have few other risk factors (i.e., show at least average parenting warmth and consistency and report relatively low stress and high social support) are at quite low risk for externalizing problems, but at relatively high risk for poor grades and low academic achievement. These findings provide important information for refining and targeting preventive interventions to groups of children who share particular constellations of risk factors. Lanza S, Rhoades B, Nix R, Greenberg M. Modeling The Interplay Of Multilevel Risk Factors For Future Academic And Behavior Problems: A Person-Centered Approach. Dev Psychopathol. 2010; 22(2): 313-335.

Use of Text Messaging to Contact Difficult-to-Reach Study Participants

The authors investigated use of text messaging for contacting study participants expected to be difficult to reach. The authors pilot tested a program that trained secondary exchangers - methamphetamine injectors who frequent a syringe exchange program and regularly provide syringes to others- to be peer educators who delivered HIV risk reduction messages to methamphetamine-injecting recipients who do not regularly attend syringe exchange programs. The evaluation involved baseline and 3-month follow interviewers with recipients identified by secondary exchangers. Forty-eight (75%) of 64 recipients who were eligible completed a baseline interview. All of these participants reported having injected methamphetamine within the past 60 days. Their drug use and other characteristics suggested that they would be difficult to reach. Text messaging was an important way to reach enrolled participants during the study. Thirty-five (73%) indicated text messaging was a way to reach them. Generally, study staff first tried to reach participants by calling them, and then tried text messaging, if possible. Staff attempted to reach 15 (31%) of the 48 enrolled participants by text messaging, and 8 of them (53%) responded to the text. Text messaging was the only way for staff to contact 3 participants at least 1 point during the study. Overall, 43 (90%) of the 48 enrolled participants completed 3-month follow-up interviews. Text messaging was an acceptable means of communication for study participants and much cheaper than in-person field visits to participants. Given the authors' success with text messaging and its extensive use, they recommend other studies consider using it as part of their comprehensive tracking protocol for contacting populations expected to be difficult to reach. Maher J, Pranian K, Drach L, Rumptz M, Casciato C, Guernsey J. Using Text Messaging To Contact Difficult-To-Reach Study Participants. Am J Public Health. 2010; 100(6): 969-970.

How Prenatal Care Providers Approach Counseling about Excessive Weight Gain in Pregnancy

Excessive weight gain during pregnancy is becoming more common and is associated with many adverse maternal and infant outcomes. There is a paucity of data on how weight gain counseling is actually provided in prenatal care settings. This qualitative study focused on prenatal care providers and their knowledge, attitudes, and practices regarding prevention of excessive weight gain during pregnancy and, secondarily, their approach to nutrition and physical activity counseling during pregnancy. Seven focus groups were conducted with general obstetrician/ gynecologists, midwives, and nurse practitioners. Providers agreed to participate because they were unsure of the effectiveness of their counseling efforts and wanted to learn new techniques for counseling patients about weight gain, nutrition, and physical activity. Several barriers to weight gain counseling were identified, including insufficient training, concern about the sensitivity of the topic, and the perception that counseling is ineffective. Providers all agreed that weight gain was an important topic with short-term and long-term health consequences, but they described widely disparate counseling styles and approaches. The authors conclude that prenatal care providers are deeply concerned about excessive weight gain and its sequelae in their patients but encounter barriers to effective counseling. Moreover, findings indicate that providers want new tools to help them address weight gain counseling during pregnancy. Stotland N, Gilbert P, Bogetz A, Harper C, Abrams B, Gerbert B. Preventing Excessive Weight Gain In Pregnancy: How Do Prenatal Care Providers Approach Counseling? J Womens Health. 2010; 19(4): 807-814.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - Behavioral and Integrative Treatment Research

Single versus Recurrent Depression History: Differentiating Risk Factors among Current US Smokers

Dr. David Strong from Butler Hospital and colleagues conducted this study to examine risk factors that contribute to persistent smoking among US smokers with a history of Major Depressive Disorder (MDD) and to differentiate between those with recurrent MDD, those with a single episode of MDD, and those with no MDD. The National Comorbidity Survey - Replication (NCS-R) included a survey of 1560 smokers aged 18 and older in the United States. Lifetime history of MDD was categorized according to chronicity: No history (No MDD), single episode (MDD-S) and recurrent depression (MDD-R). The relationship between the chronicity of MDD, smoking characteristics, cessation history, nicotine dependence, comorbidity with psychiatric disorders, and current functional impairments were examined. MDD-R smokers reported fewer lifetime cessation efforts, smoked more cigarettes, had higher levels of nicotine dependence, had higher rates of comorbid psychiatric disorders and greater functional impairment than smokers with No MDD. MDD-S smokers were not consistently distinguished from No MDD smokers on cessation attempts, level of daily smoking, nicotine dependence or functional impairment indices. The study highlights the importance of chronicity when characterizing depression-related risk of persistent smoking behavior. Although, clinical trials suggest MDD-R smokers specifically benefit from specialized behavioral treatments, these services are not widely available and more efforts are needed to engage MDD-R smokers in efficacious treatments. Strong DR, Cameron A, Feuer S, Cohn A, Abrantes AM, Brown RA. Single versus recurrent depression history: differentiating risk factors among current US smokers. Drug Alcohol Depend. 2010 Jun 1; 109(1-3): 90-95.

Effects of Cigarette Smoking Cessation on Breastfeeding Duration

Dr. Higgins and colleagues from the University of Vermont used data from controlled trials to examine whether smoking cessation increases breastfeeding duration. Correlational studies have confirmed associations between smoking status and breastfeeding duration, but whether smoking cessation increases breastfeeding duration has not been established. Participants (N = 158) were smokers at the start of prenatal care who participated in controlled trials on smoking cessation. Women were assigned to either an incentive-based intervention wherein they earned vouchers exchangeable for retail items by abstaining from smoking or a control condition where they received comparable vouchers independent of smoking status. Treatments were provided antepartum through 12-week postpartum. Maternal reports of breastfeeding collected at 2-, 4-, 8-, 12-, and 24-weeks postpartum were compared between

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treatment conditions. The results showed that the incentive-based treatment significantly increased breastfeeding duration compared with rates observed among women receiving the control treatment, with significant differences between treatment conditions observed at 8-weeks (41% vs. 26%; odds ratio [OR] = 2.7, 95% CI = 1.3-5.6, p = .01) and 12-weeks (35% vs. 17%; OR = 3.4, 95% CI = 1.5-7.6, p = .002) postpartum. No significant treatment effects on breastfeeding were observed at other assessments. Changes in smoking status mediated the effects of treatment condition on breastfeeding duration. These results provide evidence from controlled studies that smoking cessation increases breastfeeding duration. Higgins TM, Higgins ST, Heil SH, Badger GJ, Skelly JM, Bernstein IM, Solomon LJ, Washio Y, Preston AM. Effects of cigarette smoking cessation on breastfeeding duration. Nicotine Tob Res. 2010 May; 12(5): 483-488.

A Randomized, Controlled Trial of NRT-Aided Gradual vs. Abrupt Cessation in Smokers Actively Trying to Quit

Most smoking cessation programs advise abrupt rather than gradual cessation. Dr. Hughes and colleagues conducted a randomized, controlled trial of gradual cessation (n = 297) vs. abrupt cessation (n = 299) vs. minimal treatment (n = 150) among smokers who wanted to quit now and preferred to quit gradually. The gradual and abrupt conditions received five phone calls (total = 90 min) and the minimal treatment condition received two calls (25 min total). The gradual condition received nicotine lozenge (via mail) to reduce smoking prior to their quit date. After the quit day, all participants received lozenge. The primary outcome was prolonged abstinence from 2 weeks post-quit day through 6 months. Prior to the quit day, the gradual condition decreased cigarettes/day by 54%, whereas the other two conditions decreased by 1% and 5%. Prolonged abstinence rates (CO < 10 ppm) did not differ among gradual, abrupt and minimal treatment conditions (4%, 7% and 5%), nor did 7-day point prevalence rates (7%, 11% and 11%). Fewer smokers in the gradual condition (48%) made a quit attempt than in the abrupt (64%) or minimal (60%) conditions (p<.001). In the gradual condition, every week delay to the quit date increased the probability of lapsing by 19% (p<.001). The authors conclude that among smokers who want to stop gradually in the near future, gradual cessation with nicotine pre-treatment does not produce higher quit rates than abrupt cessation. One liability of gradual reduction may be that it allows smokers to delay their quit date. Hughes JR, Solomon LJ, Livingston AE, Callas PW, Peters EN. A randomized, controlled trial of NRT-aided gradual vs. abrupt cessation in smokers actively trying to quit. Drug Alcohol Depend. 2010 May 25. [Epub ahead of print].

Effect of Smoking Scenes in Films on Immediate Smoking: A Randomized Controlled Study

Investigators from the University of California, San Francisco conducted this study to investigate whether exposure of young adult smokers to images of smoking in films stimulated smoking behavior. One-hundred cigarette smokers aged 18-25 years were randomly assigned to watch a movie montage with or without smoking scenes and paraphernalia followed by a 10-minute recess. The outcome was whether or not participants smoked during the recess. Data were collected and analyzed in 2008 and 2009. The results showed that smokers who watched the smoking scenes were more likely to smoke during the break (OR=3.06, 95% CI=1.01, 9.29). In addition to this acute effect of exposure, smokers who had seen more smoking in movies before the day of the experiment were more likely to smoke during the break (OR=6.73, 95% CI=1.00, 45.25, comparing the top to bottom 5th percentiles of exposure). Level of nicotine dependence, contemplation and precontemplation stages of change, and impulsivity were also associated with smoking during the break.

Participants who watched the montage with smoking scenes and those with a higher level of nicotine dependence were also more likely to have smoked within 30 minutes after the study. The authors concluded that there is a direct link between viewing smoking scenes and immediate subsequent smoking behavior. This finding suggests that individuals attempting to limit or quit smoking should be advised to refrain from or reduce their exposure to movies that contain smoking. Shmueli D, Prochaska JJ, Glantz SA. Effect of smoking scenes in films on immediate smoking: a randomized controlled study. Am J Prev Med. 2010 Apr;38(4): 351-358.

Promoting Smoking Cessation in Pregnancy with Video Doctor Plus Provider Cueing: A Randomized Trial

Investigators from the University of California San Francisco conducted this study to examine the use of a Video Doctor plus provider cueing to promote provider advice and smoking cessation outcomes in pregnancy. This was a randomized clinical trial conducted from 2006 to 2008 in five community prenatal clinics in the San Francisco Bay Area of the United States. A total of 410 pregnant patients completed screening for behavioral risks including tobacco use in the past 30 days. Pregnant smokers (n = 42) were randomized regardless of their intention to quit smoking. Participants were assigned to either usual care or intervention. Intervention participants received 15-minute Video Doctor sessions plus provider cueing, at baseline and one month, prior to their routine prenatal visit. The Video Doctor delivered interactive tailored messages, an educational worksheet for participants, and a cueing sheet for providers. The main outcome measure was receipt of advice from the provider and 30-day smoking abstinence. The results indicated that intervention participants were more likely to receive provider advice on tobacco use at both prenatal visits during the intervention period (60.9 vs. 15.8%, p = 0.003). The intervention yielded a significantly greater decrease in the number of days smoked and in cigarettes smoked per day. The 30-day abstinence rate at two months post baseline was 2.5 times greater in the intervention group; the difference was not significant (26.1 vs. 10.5%, p = 0.12). The authors conclude that The Video Doctor plus provider cueing is an efficacious adjunct to routine prenatal care by promoting provider advice and smoking reduction among pregnant smokers. Tsoh JY, Kohn MA, Gerbert B. Promoting smoking cessation in pregnancy with Video Doctor plus provider cueing: a randomized trial. Acta Obstet Gynecol Scand. 2010;89(4): 515-523.

The Effectiveness of Functional Family Therapy for Youth with Behavioral Problems In A Community Practice Setting

The study examined the effectiveness of Functional Family Therapy (FFT), as compared to probation services, in a community juvenile justice setting 12 months post-treatment. The study also provides specific insight into the interactive effects of therapist model specific adherence and measures of youth risk and protective factors on behavioral outcomes for a diverse group of adolescents. The findings suggest that FFT was effective in reducing youth behavioral problems, although only when the therapists adhered to the treatment model. High-adherent therapists delivering FFT had a statistically significant reduction (35%) in felony, (30%) in violent crime, and a marginally significant reduction (21%) in misdemeanor recidivisms, as compared to the control condition. The results represent a significant reduction in serious crimes 1 year after treatment, when delivered by a model adherent therapist. The low-adherent therapists were significantly higher than the control group in recidivism rates. There was an interaction effect between youth risk level and therapist adherence demonstrating that the most difficult families (those with high peer and family risk) had a higher likelihood of successful outcomes when their therapist demonstrated model-specific adherence. These results are discussed within the context of the need and importance of measuring and

accounting for model specific adherence in the evaluation of community-based replications of evidence-based family therapy models like FFT. Sexton T, Turner CW. The effectiveness of functional family therapy for youth with behavioral problems in a community practice setting. J Fam Psychol. 2010 Jun;24 (3): 339-348.

Using Treatment Process Data to Predict Maintained Smoking Abstinence

The purpose of this study was to identify distinct subgroups of treatment responders and non-responders to aid in the development of tailored smoking-cessation interventions for long-term maintenance using signal detection analysis (SDA). The secondary analyses (n = 301) are based on data obtained in a randomized clinical trial by the authors designed to assess the efficacy of extended cognitive behavior therapy for cigarette smoking cessation. Model 1 included only pretreatment factors, demographic characteristics, and treatment assignment. Model 2 included all Model 1 variables, as well as clinical data measured during treatment. SDA was successfully able to identify smokers with varying probabilities of maintaining abstinence from end-of-treatment to 52-week follow-up; however, the inclusion of clinical data obtained over the course of treatment in Model 2 yielded very different partitioning parameters. The findings from this study may enable researchers to target underlying factors that may interact to promote maintenance of long-term smoking behavior change. Bailey SR, Hammer SA, Bryson SW, Schatzberg AF, Killen JD. Using treatment process data to predict maintained smoking abstinence. Am J Health Behav. 2010 Nov-Dec;34(6): 801-810.

Retention in Depression Treatment among Ethnic and Racial Minority Groups in the United States

Premature discontinuation of psychiatric treatment among ethnic-racial minorities is a persistent concern. Previous research on identifying factors associated with ethnic-racial disparities in depression treatment has been limited by the scarcity of national samples with adequate representation of minority groups and especially non-English speakers. In this article, the authors aim to identify variations in the likelihood of retention in depression treatment among ethnic-racial minority groups in the United States as compared to non-Latino whites. Second, they aim to identify the factors that are related to treatment retention. They use data from the Collaborative Psychiatric Epidemiology Surveys to examine differences and correlates of depression treatment retention among a representative sample (n=564) of non-Latino whites, Latinos, African-American, and Asian respondents with last 12-month depressive disorder and who report receiving formal mental health treatment in the last year. They define retention as attending at least four visits or remaining in treatment during a 12-month period. Being seen by a mental health specialist as opposed to being seen by a generalist and having received medication are correlates of treatment retention for the entire sample. However, after adjusting for demographics, clinical factors including number of co-occurring psychiatric disorders and level of disability, African-Americans are significantly less likely to be retained in depression treatment as compared to non-Latino whites. Availability of specialized mental health services or comparable treatment within primary care could improve treatment retention. Low retention suggests persistent problems in the delivery of depression treatment for African-Americans. Fortuna LR, Alegria M, Gao S. Retention in depression treatment among ethnic and racial minority groups in the United States. Depress Anxiety. 2010 May;27(5): 485-494.

Prospective Study of Externalizing and Internalizing Subtypes of Posttraumatic Stress Disorder and their Relationship to Mortality

among Vietnam Veterans

Posttraumatic stress disorder (PTSD) can be a complex disorder, and some studies have found that samples of individuals with PTSD contain subtypes that may relate to health outcomes. The goals were to replicate previously identified PTSD subtypes and examine how subtype membership relates to mortality. Data from the Vietnam Experience Study and a clinical sample of Vietnam veterans were combined (n = 5248) to address these research questions. Consistent with previous studies, 3 PTSD subtypes emerged: externalizers (n = 317), internalizers (n = 579), and low pathology (n = 280). Posttraumatic stress disorder diagnosis was associated with increased risk of all-cause and behavioral-cause (e.g., homicide, suicide) mortality. Both externalizing and internalizing subtypes had higher mortality and were more likely to die from cardiovascular causes than those without PTSD. Externalizers were more likely to die from substance-related causes than those without PTSD. The value of considering possible PTSD subtypes is significant in that it may contribute to identifying more specific targets for treatment and rehabilitation in veterans with PTSD. Flood AM, Boyle SH, Calhoun PS, Dennis MF, Barefoot JC, Moore SD, Beckham JC. Prospective study of externalizing and internalizing subtypes of posttraumatic stress disorder and their relationship to mortality among Vietnam veterans. Compr Psychiatry. 2010 May-Jun; 51 (3): 236-242.

Posttraumatic Stress Disorder, Cardiovascular, and Metabolic Disease: A Review of the Evidence

Posttraumatic stress disorder (PTSD) is a significant risk factor for cardiovascular and metabolic disease. The purpose of the current review is to evaluate the evidence suggesting that PTSD increases cardiovascular and metabolic risk factors, and to identify possible biomarkers and psychosocial characteristics and behavioral variables that are associated with these outcomes. A systematic literature search in the period of 2002-2009 for PTSD, cardiovascular disease, and metabolic disease was conducted. The literature search yielded 78 studies on PTSD and cardiovascular/metabolic disease and biomarkers. Although the available literature suggests an association of PTSD with cardiovascular disease and biomarkers, further research must consider potential confounds, incorporate longitudinal designs, and conduct careful PTSD assessments in diverse samples to address gaps in the research literature. Research on metabolic disease and biomarkers suggests an association with PTSD, but has not progressed as far as the cardiovascular research. Dedert EA, Calhoun PS, Watkins LL, Sherwood A, Beckham JC. Posttraumatic stress disorder, cardiovascular, and metabolic disease: a review of the evidence. Ann Behav Med. 2010 Feb;39(1): 61-78.

Substance Abuse in Women

Gender differences in substance use disorders (SUDs) and treatment outcomes for women with SUDs have been a focus of research in the last 15 years. This article reviews gender differences in the epidemiology of SUDs, highlighting the convergence of male/female prevalence ratios of SUDs in the last 20 years. The telescoping course of SUDs, recent research on the role of neuroactive gonadal steroid hormones in craving and relapse, and sex differences in stress reactivity and relapse to substance abuse are described. The role of co-occurring mood and anxiety, eating, and posttraumatic stress disorders is considered in the epidemiology, natural history, and treatment of women with SUDs. Women's use of alcohol, stimulants, opioids, cannabis, and nicotine are examined in terms of recent epidemiology, biologic and psychosocial effects, and treatment. Although women may be less likely to enter substance abuse treatment than men over the course of the lifetime, once they enter treatment, gender itself is not a predictor of treatment retention, completion, or outcome.

Research on gender-specific treatments for women with SUDs and behavioral couples treatment has yielded promising results for substance abuse treatment outcomes in women. Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. Psychiatr Clin North Am. 2010 Jun;33(2): 339-355.

Topiramate in the Treatment of Substance-related Disorders: A Critical Review of the Literature

This paper critically reviews the literature on topiramate in the treatment of substance-related disorders. A PubMed search of human studies published in English through January 2009 was conducted using the following search terms: topiramate and substance abuse, topiramate and substance dependence, topiramate and withdrawal, topiramate and alcohol, topiramate and nicotine, topiramate and cocaine, topiramate and opiates, and topiramate and benzodiazepines. Twenty-six articles were identified and reviewed. These studies examined topiramate in disorders related to alcohol, nicotine, cocaine, methamphetamine, opioids, Ecstasy, and benzodiazepines. Study design, sample size, topiramate dose and duration, and study outcomes were reviewed. There is compelling evidence for the efficacy of topiramate in the treatment of alcohol dependence. Two trials show trends for topiramate's superiority over oral naltrexone in alcohol dependence, while one trial suggests topiramate is inferior to disulfiram. Despite suggestive animal models, evidence for topiramate in treating alcohol withdrawal in humans is slim. Studies of topiramate in nicotine dependence show mixed results. Human laboratory studies that used acute topiramate dosing show that topiramate actually enhances the pleasurable effects of both nicotine and methamphetamine. Evidence for topiramate in the treatment of cocaine dependence is promising, but limited by small sample size. The data on opioids, benzodiazepines, and Ecstasy are sparse. Topiramate is efficacious for the treatment of alcohol dependence, but side effects may limit widespread use. While topiramate's unique pharmacodynamic profile offers a promising theoretical rationale for use across multiple substance-related disorders, heterogeneity both across and within these disorders limits topiramate's broad applicability in treating substance-related disorders. Recommendations for future research include exploration of genetic variants for more targeted pharmacotherapies. Shinn AK, Greenfield SF. Topiramate in the treatment of substance-related disorders: a critical review of the literature. J Clin Psychiatry. 2010 May;71(5): 634-648.

Evidence-Based Practices in Addiction Treatment: Review and Recommendations for Public Policy

The movement in recent years towards evidence-based practice (EBP) in health care systems and policy has permeated the substance abuse treatment system, leading to a growing number of federal and statewide initiatives to mandate EBP implementation. Nevertheless, due to a lack of consensus in the addiction field regarding procedures or criteria to identify EBPs, the optimal processes for disseminating empirically based interventions into real-world clinical settings have not been identified. Although working lists of interventions considered to be evidence-based have been developed by a number of constituencies advocating EBP dissemination in addiction treatment settings, the use of EBP lists to form policy-driven mandates has been controversial. This article examines the concept of EBP, critically reviews criteria used to evaluate the evidence basis of interventions, and highlights the manner in which such criteria have been applied in the addictions field. Controversies regarding EBP implementation policies and practices in addiction treatment are described, and suggestions are made to shift the focus of dissemination efforts from manualized psychosocial interventions to specific skill sets that are broadly applicable and easily learned by clinicians. Organizational and workforce barriers to EBP implementation are delineated, with corresponding recommendations to facilitate successful dissemination of

evidence-based skills. Glasner-Edwards S, Rawson R. Evidence-based practices in addiction treatment: review and recommendations for public policy. Health Policy. 2010 Jun. [Epub ahead of print].

Cognitive Behavioral Therapy for Substance Use Disorders

Cognitive behavioral therapy (CBT) for substance use disorders has shown efficacy as a monotherapy and as part of combination treatment strategies. This article provides a review of the evidence supporting the use of CBT, clinical elements of its application, novel treatment strategies for improving treatment response, and dissemination efforts. Although CBT for substance abuse is characterized by heterogeneous treatment elements such as operant learning strategies, cognitive and motivational elements, and skills-building interventions, across protocols several core elements emerge that focus on overcoming the powerfully reinforcing effects of psychoactive substances. These elements, and support for their efficacy, are discussed. McHugh RK, Hearon BA, Otto MW. Cognitive behavioral therapy for substance use disorders. Psychiatr Clin North Am 2010 Sept; 33(3): 511-525.

Neurocognitive Impairment and HIV Risk Factors: A Reciprocal Relationship

Cognitive impairment among populations at risk for HIV poses a significant barrier to managing risk behaviors. The impact of HIV and several cofactors, including substance abuse and mental illness, on cognitive function is discussed in the context of HIV risk behaviors, medication adherence, and risk-reduction interventions. Literature suggests that cognitive impairment is intertwined in a close, reciprocal relationship with both risk behaviors and medication adherence. Not only do increased risk behaviors and suboptimal adherence exacerbate cognitive impairment, but cognitive impairment also reduces the effectiveness of interventions aimed at optimizing medication adherence and reducing risk. In order to be effective, risk-reduction interventions must therefore take into account the impact of cognitive impairment on learning and behavior. Anand P, Springer SA, Copenhaver MM, Altice FL. Neurocognitive impairment and HIV risk factors: a reciprocal relationship. AIDS Behav. 2010 Mar. [Epub ahead of print].

Psychiatric Symptom Improvement in Women Following Group Substance Abuse Treatment: Results from the Women's Recovery Group Study The Women's Recovery

Group study was a Stage I randomized clinical trial comparing a new manual-based group treatment for women with substance use disorders with Group Drug Counseling. Data from this study were examined to determine whether co-occurring symptoms of depression and anxiety would improve with treatment and whether these improvements would demonstrate durability over the follow-up period. The sample consisted of 36 women (29 Women's Recovery Group, 7 Group Drug Counseling) who were administered self-report and clinician-rated measures of anxiety, depression, and general psychiatric symptoms. Although there were no group differences in psychiatric symptom improvement, analyses demonstrated significant within-subject improvement in depression, anxiety, and general psychiatric symptoms. Symptom reduction was not mediated by changes in substance use. This study demonstrated significant psychiatric symptom reduction that remained durable through 6 month follow-up for women receiving group therapy focused on substance abuse relapse prevention. Reduction in psychiatric symptoms may be an additional benefit of substance abuse group therapy for women. McHugh RK, Greenfield S. Psychiatric symptom improvement in women following group substance abuse treatment: results from the Women's Recovery Group Study.

J Cogn Psychother. 2010 Apr;24(1): 26-36.

Improved HIV and Substance Abuse Treatment Outcomes for Released HIV-Infected Prisoners: The Impact of Buprenorphine Treatment

HIV-infected prisoners fare poorly after release. Though rarely available, opioid agonist therapy (OAT) may be one way to improve HIV and substance abuse treatment outcomes after release. Of the 69 HIV-infected prisoners enrolled in a randomized controlled trial of directly administered antiretroviral therapy, 48 (70%) met DSM-IV criteria for opioid dependence. Of these, 30 (62.5%) selected OAT, either as methadone (N = 7, 14.5%) or buprenorphine/naloxone (BPN/NLX; N = 23, 48.0%). Twelve-week HIV and substance abuse treatment outcomes are reported as a sub-study for those selecting BPN/NLX. Retention was high: 21 (91%) completed BPN/NLX induction and 17 (74%) remained on BPN/NLX after 12 weeks. Compared with baseline, the proportion with a non-detectable viral load (61% vs 63% log (10) copies/mL) and mean CD4 count (367 vs 344 cells/mL) was unchanged at 12 weeks. Opiate-negative urine testing remained 83% for the 21 who completed induction. Using means from 10-point Likert scales, opioid craving was reduced from 6.0 to 1.8 within 3 days of BPN/NLX induction and satisfaction remained high at 9.5 throughout the 12 weeks. Adverse events were few and mild. BPN/NLX therapy was acceptable, safe and effective for both HIV and opioid treatment outcomes among released HIV-infected prisoners. Future randomized controlled trials are needed to affirm its benefit in this highly vulnerable population. Springer SA, Chen S, Altice FL. Improved HIV and substance abuse treatment outcomes for released HIV-infected prisoners: the impact of buprenorphine treatment. J Urban Health. 2010 Jul;87(4): 592-602.

Menstrual Cycle Effects on Smoking Behavior of Women

Emerging research suggests potential effects of the menstrual cycle on various aspects of smoking behavior in women, but results to date have been mixed. The present study sought to explore the influence of menstrual cycle phase on reactivity to smoking in vivo and stressful imagery cues in a sample of non-treatment-seeking women smokers. Via a within-subjects design, nicotine-dependent women (N = 37) participated in a series of four cue reactivity sessions, each during a distinct biologically verified phase of the menstrual cycle (early follicular [EF], mid-follicular [MF], mid-luteal [ML], and late luteal [LL]). Subjective (Questionnaire of Smoking Urges-Brief; QSU-B) and physiological (skin conductance and heart rate) measures of craving and reactivity were collected and compared across phases. Subjective reactive craving (QSU-B) to smoking in vivo cues varied significantly across the menstrual cycle (p = .02) and was higher in both EF and MF phases versus ML and LL phases, but this finding was not sustained when controlling for reactivity to neutral cues. Heart rate reactivity to stressful imagery cues (p = .01) and skin conductance reactivity to smoking in vivo cues (p = .05) varied significantly across the men-strual cycle upon controlling for reactivity to neutral cues, with highest reactivity during the MF phase. Menstrual cycle phase may have an effect on reactivity to smoking-related and stressful cues among women smokers. These findings contribute to an expanding literature, suggesting menstrual cycle effects on smoking behaviors in women. Gray KM, DeSantis SM, Carpenter MJ, Saladin ME, LaRowe SD, Upadhyaya HP. Menstrual cycle and cue reactivity in women smokers. Nicotine Tob Res. 2010 Feb;12(2): 174-178.

Effects of Exposure to Parental Drug Abuse and Interparental Violence on Children's Development

This review examines what have been, to this point, generally two divergent lines of research: (a) effects of parental drug abuse on children, and (b) effects of children's exposure to interparental violence. A small, but growing body of literature has documented the robust relationship between drug use and intimate partner violence. Despite awareness of the interrelationship, little attention has been paid to the combined effect of these deleterious parent behaviors on children in these homes. It is argued that there is a need to examine the developmental impact of these behaviors (both individually and combined) on children in these homes and for treatment development to reflect how each of these parent behaviors may affect children of substance abusers. Kelley ML, Klostermann K, Doane AN, Mignone T, Lam WK, Fals-Stewart W, Padilla MA. The case for examining and treating the combined effects of parental drug use and interparental violence on children in their homes. Aggress Violent Behav. 2010; 15(1): 76-82.

Childhood Trauma Linked to Poor Health Outcomes among Adults with Comorbid Substance Abuse and Mental Health Disorders

This study describes the prevalence of childhood traumatic events (CTEs) among adults with comorbid substance use disorders (SUDs) and mental health problems (MHPs) and assesses the relation between cumulative CTEs and adult health outcomes. Adults with SUDs/MHPs (N=402) were recruited from residential treatment programs and interviewed at treatment admission. Exposures to 9 types of adverse childhood experiences were summed and categorized into 6 ordinal levels of exposure. Descriptive analyses were conducted to assess the prevalence and range of exposure to CTEs in comparison with a sample from primary health care. Logistic regression analyses were conducted to examine the association between the cumulative exposure to CTEs and adverse health outcomes. Most of the sample reported exposure to CTEs, with higher exposure rates among the study sample compared with the primary health care sample. Greater exposure to CTEs significantly increased the odds of several adverse adult outcomes, including PTSD, alcohol dependence, injection drug use, tobacco use, sex work, medical problems, and poor quality of life. Study findings support the importance of early prevention and intervention and provision of trauma treatment for individuals with SUDs/MHPs. Wu NS, Schairer LC, Dellor E, Grella C. Childhood trauma and health outcomes in adults with comorbid substance abuse and mental health disorders. Addict Behav. 2010 Jan;35(1): 68-71.

Greater Cue Reactivity among Low-Dependent vs. High-Dependent Smokers

Cue reactivity paradigms are well-established laboratory procedures used to examine subjective craving in response to substance-related cues. For smokers, the relationship between nicotine dependence and cue reactivity has not been clearly established. The main aim of the present study was to further examine this relationship. Participants (N=90) were between the ages of 18-40 years and smoked >=10 cigarettes per day. Average nicotine dependence (Fagerstroem Test for Nicotine Dependence; FTND) at baseline was 4.9 (SD=2.1). Participants completed four cue reactivity sessions consisting of two in vivo cues (smoking and neutral) and two affective imagery cues (stressful and relaxed), all counterbalanced. Craving in response to cues was assessed following each cue exposure using the Questionnaire of Smoking Urges-Brief (QSU-B). Differential cue reactivity was operationally defined as the difference in QSU scores between the smoking and neutral cues, and between the stressful and relaxed cues. Nicotine dependence was significantly and negatively associated with differential cue reactivity scores in regard to hedonic craving (QSU factor 1) for both in vivo and imagery cues, such that those who had low FTND scores demonstrated greater differential cue reactivity than those with higher FTND scores (β=-.082; p=.037; β=-.101; p=.023,

respectively). Similar trends were found for the Total QSU and for negative reinforcement craving (QSU factor 2), but did not reach statistical significance. Under partially sated conditions, less dependent smokers may be more differentially cue reactive to smoking cues as compared to heavily dependent smokers. These findings offer methodological and interpretative implications for cue reactivity studies. Watson NL, Carpenter MJ, Saladin ME, Gray KM, Upadhyaya HP. Evidence for greater cue reactivity among low-dependent vs. high-dependent smokers. Addict Behav. 2010 Jul;35(7): 673-677.

Meditation Pilot Study for Addiction Treatment

Treatment programs offer a variety of programming in addition to counseling including alternative treatments such as meditation, but it is not clear to what extent adding these components is beneficial. The objective of this study was to determine the acceptability and possible benefits of adding meditation to residential treatment. Three hundred fifty patients in residential substance abuse treatment were introduced to Qigong meditation which blends mindfulness relaxation, and guided imagery to induce a tranquil state. Later they were offered the option of participating in either meditation or Stress Management and Relaxation Training (SMART) twice a day as part of the scheduled treatment. Weekly questionnaires were completed for up to 4 weeks to assess treatment outcomes differences and 248 individuals provided evaluable data. Participants in the meditation group were also assessed for quality of meditation to evaluate the association between quality and treatment outcome. Most clients found meditation to be an acceptable part of their treatment program and a majority participated in daily meditation. While both groups reported significant improvement in treatment outcome, the meditation group reported a significantly higher treatment completion rate (92% versus 78%, $p < 01$) and more reduction in craving than did the SMART group. Among those electing meditation practice, participants whose meditation was of acceptable quality reported greater reductions in craving, anxiety, and withdrawal symptoms than did those whose meditation was of low quality. Female meditation participants reported significantly more reduction in anxiety and withdrawal symptoms than did any other group. These findings suggest there may be value in adding meditation to inpatient treatment. However, additional randomized trials are needed. Chen KW, Comerford A, Shinnick P, Ziedonis DM. Introducing Qigong meditation into residential treatment: a pilot study where gender makes a difference. J Altern Complement Med. 2010 Jul 22. [Epub ahead of print].

Computerized Cognitive Behavioral Therapy: Cost-Effectiveness

Computerization of psychosocial therapies to deliver skills training directly to patients offers a means to ensure that evidence based treatments are delivered consistently but it is not known to what extent these treatments are cost-effective. The main objective of this study was to examine the cost-effectiveness of a computerized version of cognitive behavioral addiction treatment when added to outpatient addiction treatment. Data for this cost study came from a randomized trial in which 77 individuals seeking treatment for substance dependence at an outpatient community setting were randomly assigned to treatment as usual (TAU) or TAU plus biweekly access to computer-based training in CBT (TAU plus CBT4CBT). The primary patient outcome measure was the total number of drug-free specimens provided during treatment. Incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) were used to determine the cost-effectiveness of TAU plus CBT4CBT relative to TAU alone. From the clinic (patient) perspective, TAU plus CBT4CBT is likely to be cost-effective when the threshold value to decision makers of an additional drug-free specimen is greater than approximately $21 ($15), and TAU alone is likely to be cost-effective when the threshold value is less than approximately $21 ($15).

Overall TAU plus CBT4CBT appears to be a good value from both the clinic and patient perspectives. However whether CBT4CBT is likely to be cost-effective depends on the value that decision makers place on an additional unit of effect. At this time, no consensus threshold values exist for any patient outcomes in substance abuse treatment; that is, there are no generally accepted values associated with an additional drug-free specimen or any other treatment outcome, from either the clinic or patient perspectives. The ICERs for TAU plus CBT4CBT compare favorably to ICERs reported elsewhere for other empirically validated therapies. Olmstead TA, Ostrow CD, Carroll KM. Cost-effectiveness of computer-assisted training in cognitive-behavioral therapy as an adjunct to standard care for addiction. Drug Alcohol Depend. 2010 Aug 1;110(3): 200-207.

Exercise May be Promising as an Adjunctive Treatment to Usual Care for Addiction

Drug addiction treatment programs sometimes include exercise as one component of their treatment. However, the efficacy of exercise as a component of addiction treatment is not known. This study examined the feasibility of assigning addiction treatment participants to an exercise program. Participants were 16 drug dependent patients who participated in a 12-week, moderate-intensity aerobic exercise intervention. Participants demonstrated a significant increase in percent days abstinent for both alcohol and drugs at the end of treatment, and those who attended at least 75% of the exercise sessions had significantly better substance use outcomes than those who did not. In addition, participants showed a significant increase in their cardiorespiratory fitness by the end of treatment. Conclusions regarding this study are limited due to the lack of randomization and a control group. However, results suggest exercise is feasible and may augment addiction treatment in a dose response fashion. Results also suggest exercise can have positive effects on addiction patient's cardiorespiratory fitness which is one predictor of mortality in the general population. Brown RA, Abrantes AM, Read JP, Marcus BH, Jakicic J, Strong DR, Oakley JR, Ramsey SE, Kahler CW, Stuart GG, Dubreuil ME, Gordon AA. A pilot study of aerobic exercise as an adjunctive treatment for drug dependence. Ment Health Phys Act. 2010 Jun 1;3(1): 27-34.

Additional Risk of Opioid Use in Marijuana and Alcohol Abusing Youth

This study was designed to determine the added risk of opioid problem use (OPU) in youth with marijuana/alcohol problem use (MAPU). A total of 475 youth (ages 14-21 years) with OPU + MAPU were compared to a sample of 475 youth with MAPU only (i.e., no OPU). Youth were recruited from 88 drug treatment sites participating in eight Center for Substance Abuse Treatment-funded grants. At treatment intake, participants were administered the Global Appraisal of Individual Need to elicit information on demographic, social, substance use, mental health, human immunodeficiency virus (HIV), physical and legal characteristics. Odds ratios with confidence intervals were calculated. Results suggest that the added risk of OPU among MAPU youth was associated with greater comorbidity; higher rates of psychiatric symptoms and trauma/victimization; greater needle use and sex-related HIV risk behaviors; and greater physical distress. The OPU + MAPU group was less likely to be African American or other race. This group was more likely to be aged 15-17 years, Caucasian, report weekly drug use at home and among peers, engage in illegal behaviors, have greater substance abuse severity and poly drug use, and use mental health and substance abuse treatment services. These findings expand upon the existing literature and highlight the substantial incremental risk of OPU on multiple comorbid areas among treatment-seeking youth. Further evaluation is needed to assess their outcomes following standard drug

treatment and to evaluate specialized interventions for this subgroup of severely impaired youth. Subramaniam GA, Ives ML, Stitzer ML, Dennis ML. The added risk of opioid problem use among treatment-seeking youth with marijuana and/or alcohol problem use. Addiction. 2010 Apr;105(4): 686-698.

Exploring Relations among Traumatic, Posttraumatic, and Physical Pain Experiences in Methadone-Maintained Patients

Differences in lifetime trauma exposure and screened symptoms of posttraumatic stress disorder (PTSD) were examined in methadone maintenance treatment (MMT) patients with a variety of pain experiences. In this study, parametric and nonparametric statistical tests were performed on data obtained from 150 patients currently enrolled in MMT. 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 comparable levels of trauma involving sexual assault but reported significantly higher levels of trauma involving physical assault, number of traumatic events, and screened symptoms of PTSD. A third group, non-CSP MMT patients reporting some pain in the past week, differed significantly from the CSP group on number of traumatic events but reported comparable levels of sexual assault and physical assault. In comparison to men, women reported higher levels of sexual assault and were more likely to score above the cutoff on the PTSD screener but reported comparable levels of physical assault and number of traumatic events. Pain-related differences in trauma and screened symptoms of PTSD exist in MMT patients and may have implications for program planning and outreach efforts. Barry DT, Beitel M, Cutter CJ, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Exploring relations among traumatic, posttraumatic, and physical pain experiences in methadone-maintained patients. J Pain. 2010 Jun 19. [Epub ahead of print].

Opioids, Chronic Pain, and Addiction in Primary Care

Research has largely ignored the systematic examination of physicians' attitudes towards providing care for patients with chronic noncancer pain. The objective of this study was to identify barriers and facilitators to opioid treatment of chronic noncancer pain patients by office-based medical providers. Barry and colleagues at Yale University used a qualitative study design using individual and group interviews. Participants were 23 office-based physicians in New England. Interviews were audiotaped, transcribed, and systematically coded by a multidisciplinary team using the constant comparative method. Physician barriers included absence of objective or physiological measures of pain; lack of expertise in the treatment of chronic pain and coexisting disorders, including addiction; lack of interest in pain management; patients' aberrant behaviors; and physicians' attitudes toward prescribing opioid analgesics. Physician facilitators included promoting continuity of patient care and the use of opioid agreements. Physicians' perceptions of patient-related barriers included lack of physician responsiveness to patients' pain reports, negative attitudes toward opioid analgesics, concerns about cost, and patients' low motivation for pain treatment. Perceived logistical barriers included lack of appropriate pain management and addiction referral options, limited information regarding diagnostic workup, limited insurance coverage for pain management services, limited ancillary support for physicians, and insufficient time. Addressing these barriers to pain treatment will be crucial to improving pain management service delivery. Barry DT, Irwin KS, Jones ES, Becker WC, Tetrault JM, Sullivan LE, Hansen H, O'Connor PG, Schottenfeld RS, Fiellin DA. Opioids, Chronic Pain, and Addiction in Primary Care. J Pain. 2010 Jun 1. [Epub ahead of print].

Injection of Buprenorphine and Buprenorphine/Naloxone Tablets in Malaysia

Buprenorphine maintenance is efficacious for treating opioid dependence, but problems with diversion and misuse of buprenorphine (BUP) may limit its acceptability and dissemination. The buprenorphine/naloxone combination tablet (BNX) was developed to reduce potential problems with diversion and abuse. This paper provides data regarding the characteristics of BUP injection drug users in Malaysia and preliminary data regarding the impact of withdrawing BUP and introducing BNX. BUP was introduced in 2002 and subsequently withdrawn from the Malaysian market in 2006. BNX was introduced in 2007. A two wave survey of BUP IDUs was conducted shortly prior to BUP withdrawal from the Malaysian market (n=276) and six months after BNX was introduced (n=204). Six focus groups with BUP and/or BNX IDUs were also conducted shortly before the second wave. In addition to current BUP or BNX IDU, 96% of first wave participants and 97% second wave participants reported lifetime heroin IDU preceding the onset of their BUP/BNX IDU. Additionally, 58% of first and 64% of second wave survey participants reported current heroin IDU. Benzodiazepine abuse, often injected with BUP, was reported in both the surveys. Focus group participants reported that BNX was not as desirable as BUP, nonetheless, the results of the second wave survey suggest a continuing widespread BNX IDU, at least in Kuala Lumpur. In Malaysia, BUP and BNX IDU occur among heroin IDUs. The introduction of BNX and withdrawal of BUP may have helped to reduce, but did not eliminate the problems with diversion and abuse. Vicknasingam B, Mazlan M, Schottenfeld RS, Chawarski MC. Injection of buprenorphine and buprenorphine/naloxone tablets in Malaysia. Drug Alcohol Depend. 2010 May 15. [Epub ahead of print].

Brief Cognitive-Behavioral Treatment for TMD Pain: Long-term Outcomes and Moderators of Treatment

The purpose of this study was to determine whether a brief (6-8 sessions) cognitive-behavioral treatment for temporomandibular dysfunction-related pain could be efficacious in reducing pain, pain-related interference with lifestyle and depressive symptoms. The patients were 101 men and women with pain in the area of the temporomandibular joint of at least 3 months duration, randomly assigned to either standard treatment (STD; n=49) or standard treatment + cognitive-behavioral skills training (STD+CBT; n=52). Patients were assessed at post-treatment (6 weeks), 12 weeks, 24 weeks, 36 weeks, and 52 weeks. Linear mixed model analyses of reported pain indicated that both treatments yielded significant decreases in pain, with the STD+CBT condition resulting in steeper decreases in pain over time compared to the STD condition. Somatization, self-efficacy and readiness for treatment emerged as significant moderators of outcome, such that those low in somatization, or higher in self-efficacy or readiness, and treated with STD+CBT reported lower pain over time. Somatization was also a significant moderator of treatment effects on pain-related interference with functioning, with those low on somatization reporting less pain interference over time when treated in the STD+CBT condition. It was concluded that brief treatments can yield significant reductions in pain, life interference and depressive symptoms in TMD sufferers, and that the addition of cognitive-behavioral coping skills will add to efficacy, especially for those low in somatization, or high in readiness or self-efficacy. Litt MD, Shafer DM, Kreutzer DL. Brief cognitive-behavioral treatment for TMD pain: long-term outcomes and moderators of treatment. Pain. 2010 Jul 22. [Epub ahead of print].

Men in Methadone Maintenance vs Psychosocial Outpatient Treatment: Differences in Sexual Risk Behaviors and Intervention Effectiveness

The effectiveness of the Real Men Are Safe (REMAS) HIV prevention intervention was examined as a function of treatment program modality. REMAS was associated with significantly larger decreases in unprotected sexual occasions than an HIV education control condition in both treatment modalities. REMAS had superior effectiveness for reducing unprotected sexual occasions in the psychosocial outpatient compared to methadone. At the 6-month follow-up, the adjusted mean change for REMAS completers in psychosocial outpatient (M=6.4, d=0.38) was greater than for REMAS completers in methadone programs (M=2.3, d=0.25). Reasons for why REMAS appears to be especially effective in psychosocial outpatient programs are explored. Calsyn DA, Campbell AN, Crits-Christoph P, Doyle SR, Tross S, Hatch-Maillette MA, Mandler R. Men in methadone maintenance versus psychosocial outpatient treatment: differences in sexual risk behaviors and intervention effectiveness from a multisite HIV prevention intervention trial. J Addict Dis. 2010 Jul;29(3): 370-382.

Randomized Trial of Continuing Care Enhancements for Cocaine-Dependent Patients Following Initial Engagement

Dr. McKay and colleagues from the University of Pennsylvania evaluated the effects of cognitive-behavioral relapse prevention (RP), contingency management (CM), and their combination (CM+RP) in a randomized trial with 100 cocaine-dependent patients (58% female, 89% African American) who were engaged in treatment for at least 2 weeks and had an average of 44 days of abstinence at baseline. The participants were from intensive outpatient programs, which provide 10 hr per week of group counseling. The CM protocol provided gift certificates (maximum value $1,150; mean received = $740) for cocaine-free urines over 12 weeks on an escalating reinforcement schedule, and weekly individual RP sessions were offered for up to 20 weeks. Average number of RP sessions attended was 3 in RP and 13 in CM+RP. Results over 18 months postrandomization showed significant effects for CM (but not RP) on urine toxicology and self-reported cocaine use (p =.05), with no significant CMxRP interactions. Secondary analyses indicated CM+RP produced better cocaine urine toxicology outcomes at 6 months than treatment as usual, odds ratio [OR]=3.96 (1.33, 11.80), p<.01, and RP, OR=4.89 (1.51, 15.86), p< .01, and produced better cocaine urine toxicology outcomes at 9 months than treatment as usual, OR=4.21 (1.37, 12.88), p<.01, and RP, OR = 4.24 (1.32, 13.65), p<.01. Trends also favored CM+RP over CM at 6 months, OR=2.93 (0.94, 9.07), p=.06, and 9 months, OR=2.93 (0.94, 9.10), p=.06. Differences between the conditions were not significant after 9 months. These results suggest CM can improve outcomes in cocaine-dependent patients in intensive outpatient programs who have achieved initial engagement, particularly when it is combined with RP. McKay J, Lynch K, Coviello D, Morrison R, Cary M, Skalina L, Plebani J. Randomized trial of continuing care enhancements for cocaine-dependent patients following initial engagement. J Consult Clin Psychol. 2010 Feb;78(1): 111-120.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - Research on Pharmacotherapies for Drug Abuse

Infant Neurobehavior Following Prenatal Exposure to Methadone or Buprenorphine: Results from the Neonatal Intensive Care Unit Network Neurobehavioral Scale

This study examined the neurobehavioral functioning of neonates prenatally exposed to methadone (n = 11) or buprenorphine (n = 10), who underwent the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) examinations on days 3, 5, 7, 10, and 14 post-delivery. Linear mixed model analyses revealed that NNNS scores of arousal and excitability showed significant differences between medications over time. Compared to neonates who did not require medication to treat neonatal abstinence syndrome (NAS), neonates receiving pharmacotherapy for NAS showed differences over time in quality of movement, excitability, and lethargy. Results suggest the NNNS may detect subtle differences over time between both neonates prenatally exposed to methadone or buprenorphine and neonates pharmacologically treated or untreated for NAS. Jones HE, O'Grady KE, Johnson RE, Velez M, Jansson LM. Infant neurobehavior following prenatal exposure to Methadone or Buprenorphine: results from the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Subst Use Misuse. 2010 May 19. (Epub ahead of print).

Excretion of Methadone in Sweat of Pregnant Women Throughout Gestation After Controlled Methadone Administration

Sweat patches (n = 350) were collected throughout gestation from 29 opioid-dependent pregnant women participating in an outpatient methadone-assisted therapy program. Volunteers provided informed consent to participate in institutional review board-approved protocols. Methadone was eluted from sweat patches with sodium acetate buffer, followed by solid-phase extraction and quantification by gas chromatography mass spectrometry (limit of quantification >/= 10 ng/patch). Methadone was present in all weekly patches (n = 311) in concentrations ranging from 10.2 to 12,129.7 nanograms per patch and in 92.3% of short-term patches (n = 39, worn for 12 or 24 hours) in concentrations up to 3303.9 nanograms per patch. Correlation between patch concentrations and total amount of drug administered (r = 0.224), and concentrations and duration of patch wear (r = 0.129) were both weak. Although there were large intra- and intersubject variations in sweat drug concentrations, sweat testing was an effective alternative technique to qualitatively monitor illicit drug use and simultaneously document methadone medication-assisted treatment. Barnes AJ, Brunet BR, Choo RE, Mura P, Johnson RE, Jones HE, Huestis MA. Excretion of methadone in sweat of pregnant women throughout gestation after controlled methadone administration. Ther Drug Monit. 2010 June 29. (Epub ahead of print).

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Clonidine Clearance Matures Rapidly During the Early Postnatal Period: A Population Pharmacokinetic Analysis in Newborns With Neonatal Abstinence Syndrome

The population pharmacokinetic (PK) profile of oral clonidine was characterized in newborns with neonatal abstinence syndrome, and significant covariates affecting its PK parameters were identified. Plasma clonidine concentration data were obtained from a clinical trial in which 36 newborns, aged 1 to 25 days (postnatal age, PNA) and weighing 2.1 to 3.9 kg, were enrolled to take multiple oral doses of clonidine. The population PK model of clonidine was developed by NONMEM, and significant covariates were identified, followed by nonparametric bootstraps (2000 replicates) and simulation experiments. A 1-compartment open linear PK model was chosen to describe plasma concentrations of clonidine, and body weight and PNA were significant covariates for apparent clearance (CL/F) as follows: CL/F (L/h) = 15.2 x [body weight (kg)/70](0.75) x [PNA (day)(0.441)/(4.06(0.441) + PNA (day)(0.441))]. Furthermore, CL/F of clonidine increased rapidly with PNA during the first month of life after body weight was adjusted. Any optimal dosage regimen for clonidine in term neonates should be based on infant's age and body weight, and 1.5 mug/kg every 4 hours is proposed starting the second week of life based on the simulation results. Xie HG, Cao YJ, Gauda EB, Agthe AG, Hendrix CW, Lee H. Clonidine clearance matures rapidly during the early postnatal period: a population pharmacokinetic analysis in newborns with neonatal abstinence syndrome. J Clin Pharmacol. 2010 May 19. (Epub ahead of print).

Effects of Repeated Tramadol and Morphine Administration on Psychomotor and Cognitive Performance in Opioid-Dependent Volunteers

Tramadol is an atypical, mixed mechanism analgesic used to treat moderate to severe pain. Based on evidence that tramadol has relatively low abuse potential and can relieve opioid withdrawal, tramadol may be useful for treating opioid dependence. The purpose of this study was to assess the performance side-effect profile of tramadol. Nine opioid-dependent volunteers completed a performance battery following 5-7 days of subcutaneous morphine (15mg, 4 times/day) and two doses of oral tramadol (50, 200mg, 4 times/day) in a within subject cross-over design. Morphine was always the first condition, and the order of the two tramadol doses was randomized and double blind. Performance was significantly worse in the morphine condition relative to one or both tramadol doses on measures of psychomotor speed/coordination (circular lights task), psychomotor speed/pattern recognition (DSST speed measure) and psychomotor speed/set shifting (trail-making tasks). There were no significant differences among conditions in DSST accuracy, simple reaction time, divided attention, working memory, episodic memory, metamemory, or time estimation. Neither tramadol dose was associated with worse performance than morphine on any measure. Although practice sessions were conducted prior to the first session to reduce order effects, the possibility that residual practice effects contributed to the differences between tramadol and morphine cannot be ruled out. The high tramadol dose produced worse performance than the low dose only on the balance measure. These findings suggest that tramadol is generally a safe medication with respect to cognitive and psychomotor measures and support tramadol's further evaluation as an opioid-dependence treatment. Mintzer, MZ, Lanier RK, Lofwall MR, Bigelow GE, Strain EC. Effects of repeated tramadol and morphine administration on psychomotor and cognitive performance in opioid-dependent volunteers. Drug Alcohol Depend. 2010 Jun 8. (Epub ahead of print).

Abuse Liability of Intravenous Buprenorphine/Naloxone and

Buprenorphine Alone in Buprenorphine-Maintained Intravenous Heroin Abusers

Sublingual buprenorphine is an effective maintenance treatment for opioid dependence, yet intravenous buprenorphine misuse occurs. A buprenorphine/naloxone formulation was developed to mitigate this misuse risk. This randomized, double-blind, cross-over study was conducted to assess the intravenous abuse potential of buprenorphine/naloxone compared with buprenorphine in buprenorphine-maintained injection drug users (IDUs). Intravenous heroin users (n = 12) lived in the hospital for 8-9 weeks and were maintained on each of three different sublingual buprenorphine doses (2 mg, 8 mg, 24 mg). Under each maintenance dose, participants completed laboratory sessions during which the reinforcing and subjective effects of intravenous placebo, naloxone, heroin and low and high doses of buprenorphine and buprenorphine/naloxone were examined. Every participant received each test dose under the three buprenorphine maintenance dose conditions. The study results showed that intravenous buprenorphine/naloxone was self-administered less frequently than buprenorphine or heroin ($P < 0.0005$). Participants were most likely to self-administer drug intravenously when maintained on the lowest sublingual buprenorphine dose. Subjective ratings of 'drug liking' and 'desire to take the drug again' were lower for buprenorphine/naloxone than for buprenorphine or heroin ($P = 0.0001$). Participants reported that they would pay significantly less money for buprenorphine/naloxone than for buprenorphine or heroin ($P < 0.05$). Seven adverse events were reported; most were mild and transient. These data suggest that although the buprenorphine/ naloxone combination has intravenous abuse potential, that potential is lower than it is for buprenorphine alone, particularly when participants received higher maintenance doses and lower buprenorphine/naloxone challenge doses. Buprenorphine/naloxone may be a reasonable option for managing the risk for buprenorphine misuse during opioid dependence treatment Comer SD, Sullivan MA, Vosburg SK, Manubay J, Amass L, Cooper ZD, Saccone P, Kleber HD. Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers. Addiction. 2010 April; 105(4): 709-718.

Physical Dependence Potential of Daily Tramadol Dosing in Humans

Tramadol is an atypical, mixed-mechanism analgesic involving both opioid and catecholamine processes that appears to have low abuse potential and may be useful as a treatment for opioid dependence. The current study assessed the level of physical dependence and opioid blockade efficacy produced by daily maintenance on oral tramadol. Nine residential opioid-dependent adults were maintained on two doses of daily oral tramadol (200 and 800 mg) for approximately 4-week intervals in a randomized, double-blind, crossover design. The acute effects of intramuscular placebo, naloxone (0.25, 0.5, and 1.0 mg), and hydromorphone (1.5, 3.0, and 6.0 mg) were tested under double-blind, randomized conditions. Outcomes included observer- and subject-rated measures and physiologic indices. Challenge doses of naloxone resulted in significantly higher mean peak withdrawal scores compared to placebo. Withdrawal intensity from naloxone was generally greater during 800 versus 200 mg/day tramadol maintenance. Mean peak ratings of agonist effects were elevated at higher hydromorphone challenge doses, but did not differ significantly between tramadol doses. Physiologic measures were generally affected by challenge conditions in a dose-dependent manner, with few differences between tramadol maintenance dose conditions. Chronic tramadol administration produces dose-related opioid physical dependence, without producing dose-related attenuation of agonist challenge effects. Tramadol may be a useful treatment for patients with low levels of opioid dependence or as a treatment for withdrawal during opioid detoxification, but

does not appear to be effective as a maintenance medication due to a lack of opioid cross-tolerance. Lanier RK, Loftwall MR, Mintzer MZ, Bigelow GE, Strain EC. Physical dependence potential of daily tramadol dosing in humans. Psychopharmacology (Berl). 2010 Jun 30.(Epub ahead of print).

Feasibility and Acceptability of a Phase II Randomized Pharmacologic Intervention for Methamphetamine Dependence in High Risk Men Who Have Sex with Men

To determine whether actively using, methamphetamine (meth)-dependent men who have sex with men (MSM) could be enrolled and retained in a pharmacologic intervention trial, and the degree to which participants would adhere to study procedures, including medication adherence. This study was a phase 2 randomized, double-blind trial of bupropion vs. placebo. Thirty meth-dependent, sexually active MSM were randomized to receive daily bupropion XL 300 mg or placebo for 12 weeks. Participants received weekly substance use counseling, provided weekly urine specimens, and completed monthly audio-computer assisted self-interview (ACASI) behavioral risk assessments. Adherence was measured by medication event monitoring systems (MEMS) caps (the number of distinct MEMS cap openings divided by the number of expected doses) and self-report. Ninety percent completed the trial: 89% of monthly ACASIs were completed, 81% of study visits were attended, and 81% of urine samples were collected. Adherence by MEMS cap was 60% and by self-report was 81% and did not differ significantly by treatment assignment. The median number of positive urine samples was 5.5 out of a possible 11 (50%). Participants in both arms reported similar declines in the median number of sex partners (P = 0.52). No serious adverse events occurred and there were no significant differences in adverse events by treatment assignment (P = 0.11). It is feasible to enroll and retain actively using, meth-dependent MSM in a pharmacologic intervention. Bupropion was well tolerated. Study participation and retention rates were high, however, study drug medication adherence was only moderate. Findings support a larger trial with improved adherence support to evaluate the efficacy of bupropion and other pharmacologic interventions for meth dependence in this population. Das M, Santos D, Matheson T, Santos GM, Chu P, Vittinghoff E, Shoptaw S, Colfax GN. Feasibility and acceptability of a phase II randomized pharmacologic intervention for methamphetamine dependence in high risk men who have sex with men. AIDS. 2010 April 24;24(7): 991-1000.

The Angiotensin-converting Enzyme Inhibitor Perindopril Treatment Alters Cardiovascular and Subjective Effects of Methamphetamine in Humans

A variety of medications have been assessed for their potential efficacy for the treatment of methamphetamine dependence. This study was conducted in an attempt to evaluate the potential of a novel class of medications, angiotensin-converting enzyme inhibitors, as treatments for methamphetamine dependence. All participants met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, third revision (DSM-IV-TR) criteria for methamphetamine abuse or dependence and were not seeking treatment at the time of study entry. The study was conducted using a double-blind design. Subjects received a baseline series of intravenous (IV) doses of methamphetamine (15mg and 30mg) and placebo. Subjects received a second identical series of methamphetamine doses 3 and 5 days after initiation of once-daily oral placebo or perindopril treatment. The dose of perindopril was 2mg, 4mg, or 8mg administered in the morning. Thirty participants completed the study. Perindopril treatment was tolerated well. There were no main effects of perindopril on methamphetamine-induced changes in cardiovascular or subjective effects. There were significant perindopril-methamphetamine

interactions for diastolic blood pressure and for ratings of "Any Drug Effect", indicating inverted U dose-effect functions for these indices. Newton TF, De La Garza R 2nd, Grasing K. The agiotensin-converting enzyme inhibitor perindopril treatment alters cardiovascular and subjective effects of methamphetamine in humans. Psychiatry Res. 2010 May 19. (EPub ahead of print).

Estimating the Intake of Abused Methamphetamine Using Experimenter Administered Deuterium Labeled R-methamphetamine Selection of the R-methamphetamine Dose

All addictive drugs produce tolerance and addicts compensate by increasing drug exposure. Thus, the quantity of illicit drug ingested is related to the severity of addiction. Unfortunately, there are no objective methods to estimate intake for most addictive drugs. Using experimenter-administered doses of deuterium-labeled R-methamphetamine (R-[-]-MA-d3), a method was developed to estimate the amount of abused methamphetamine intake in addicts enrolled in clinical trials. This study assessed the pharmacokinetics, pharmacodynamics, and tolerability of single oral doses of R-MA in healthy adults to select a dose of R-MA-d3 to be used as a biomarker for estimating the amount of methamphetamine abuse. This was a five-session randomized, double-blind, placebo-controlled, balanced crossover study in eight subjects. Oral R-(-)-MA was dosed at 0 mg, 1 mg, 2.5 mg, 5 mg, or 10 mg; bioavailability was estimated by slow intravenous dosing (30 minutes) of 2.5 mg R-(-)-MA-d3 given with the 2.5 mg R-(-)-MA oral dose condition. Pharmacokinetic and pharmacodynamic measures were obtained. No serious adverse events occurred during the study and all doses of R-MA were well tolerated. Linear pharmacokinetics was observed within the oral dose range of 1 to 10 mg. Complete bioavailability and pharmacologic inactivity were found for all oral doses. These characteristics indicate the advantage of using a small oral R-(-)-MA-d3 dose as a biomarker to estimate exposure to abused methamphetamine. Based on these results, 5 mg R-(-)-MA-d3 has been selected as the biomarker dose in future studies. Preliminary findings from this study indicate that experimenter-administered oral R-(-)-MA-d3 may allow estimation of abused methamphetamine intake and exposure. Knowledge of the quantity of methamphetamine intake may allow better estimation of disease severity and treatment efficacy. Experience gained from this study also can be applied to the management of other drug dependence problems such as cocaine, cannabinoid, and opiate addiction. Li L, Lopez JC, Galloway GP, Baggott MJ, Everhart T, Mendelson J. Estimating the intake of abused methamphetamine using experimenter administered deuterium labeled R-methamphetamine selection of the R-methamphetamine dose. Ther Drug Monit. 2010 Jun 25. (Epub ahead of print).

Behavioral Effects of D-amphetamine in Humans: Influence of Subclinical Levels of Inattention and Hyperactivity

Several studies suggest a link between stimulant abuse and attention-deficit hyperactivity disorder (ADHD) symptoms (e.g., inattention and hyperactivity). To further assess the nature of this relationship, the present study examined the association between subclinical symptoms of inattention and hyperactivity and the behavioral effects of d-amphetamine. Participants were classified into a High- (n = 8) or Low-Score (n = 9) group based on their responses on a rating scale that assessed inattention and hyperactivity symptoms. The participants did not differ across the High-Score and Low-Score groups in their ability to discriminate d-amphetamine. The participants in the High-Score group were significantly more sensitive to the positive participant-rated effects of d-amphetamine (e.g., Good Effects, Like Drug), but less sensitive to drug-induced increases in blood pressure and heart rate. The selective increase in positive subjective effects of d-amphetamine suggests that individuals with subclinical inattention and hyperactivity symptoms may have increased

vulnerability to stimulant abuse. Sevak RJ, Stoops WW, Rush CR. Am J Drug Alcohol Abuse. 2010 Jul;36(4): 220-227.

Cocaine Choice in Humans During D-amphetamine Maintenance

The results of preclinical laboratory experiments and clinical trials indicate that agonist replacements such as d-amphetamine may be a viable option for managing cocaine dependence. This study determined the effects of d-amphetamine maintenance on cocaine choice behavior in human participants. It was predicted that d-amphetamine maintenance would reduce cocaine choice. Nine cocaine-dependent participants completed the study. Two d-amphetamine maintenance conditions were completed in a counterbalanced order (0 and 40 mg/d). After 3 to 5 days of placebo or d-amphetamine maintenance, the participants completed 5 experimental sessions. During these sessions, the participants first sampled the placebo (i.e., 4 mg of intranasal cocaine) identified as drug A. The participants then sampled a second intranasal drug dose (4, 10, 20, or 30 mg of cocaine) identified as drug B. The participants then made 6 discrete choices between drugs A and B. Drug choices were separated by 45 minutes. The primary outcome measure was the number of cocaine choices. All doses of cocaine were chosen significantly more than placebo during both maintenance conditions (i.e., placebo and d-amphetamine). Choice of the 20-mg dose of cocaine was significantly lower during d-amphetamine maintenance relative to when this cocaine dose was tested during placebo-d-amphetamine maintenance. Cocaine produced prototypical subject-rated drug effects (eg., good effects, like drug, willing to take again). These effects were not altered to a significant degree by d-amphetamine maintenance. Cocaine was well tolerated during D-amphetamine maintenance, and no unexpected or serious adverse events occurred. These results are concordant with those of previous preclinical experiments, human laboratory studies, and clinical trials that suggest that agonist replacement therapy may be a viable strategy for managing cocaine dependence. Rush CR, Stoops WW, Sevak RJ, Hays LR. Cocaine choice in humans during D-amphetamine maintenance. J Clin Psychopharmacol. 2010; 30(2): 152-159.

Intranasal Cocaine Functions as a Reinforcer on a Progressive Ratio Schedule in Humans

Cocaine dependence continues to be a worldwide public health concern. Although the majority of individuals reporting cocaine use do so via the intranasal route, relatively few laboratory experiments have examined the reinforcing effects of cocaine administered intranasally. The purpose of this experiment was to measure the reinforcing effects of intranasal cocaine using a progressive ratio schedule in which eight cocaine-using subjects chose between doses of cocaine (4 [placebo], 15, 30 and 45mg) and an alternative reinforcer ($0.25). During each session, subjects first sampled the dose of cocaine available that day and then made six choices between that dose and money, which were available on concurrent progressive ratio schedules of responding. Break points for active cocaine doses were higher than those for placebo but no statistically significant active versus placebo dose effects were observed on subject-rated or physiological measures. These data demonstrate that intranasal cocaine functions as a reinforcer under a progressive ratio schedule in humans. Future research should test higher cocaine doses and larger values of the alternative reinforcer. These procedures may be useful for examining the influence of putative pharmacological and behavioral interventions on intranasal cocaine self-administration. Stoops WW, Lile JA, Glaser PE, Hays LR, Rush CR. Eur J Pharmacol. 2010 Jul 15. (Epub ahead of print).

Review of Treatment for Cocaine Dependence

Cocaine dependence is a complicated, destructive, and often chronic illness that is difficult to treat. This article reviews the challenges in treating cocaine dependence, as well as recent developments and future directions in psychosocial and pharmacological treatment relevant to treatment of cocaine dependence. Cocaine is one of the most addictive drugs because of its immediate and powerful rewarding effects. Often, cocaine dependent individuals experience difficulty abstaining due to cognitive impairments from repeated cocaine use, strong use-related social and environmental cues, and high levels of life stress. Cocaine use also affects areas of the brain related to motor function, learning, emotion, and memory, further complicating the administration of effective interventions. In addition, development of treatments for cocaine dependence has been complicated by the tendency for abusers not to complete treatment programs and their propensity for relapse. Despite these challenges, some treatment approaches, such as cognitive behavioral therapy (CBT) and medications have shown promise in successfully treating cocaine dependence. However, individually, each of these treatments exhibit weakness in longitudinal studies where long-term abstinence is the primary outcome of interest. Although other treatments are being explored, thus far, the combination of CBT and pharmacotherapy has elicited the best results for treating cocaine dependence with respect to patient retention and relapse prevention following abstinence. No treatment method has yet been shown to completely and effectively treat cocaine dependence. More research is necessary to test treatment programs and garner further information in order to better understand and treat cocaine dependence. Penberthy JK, Ait-Daoud N, Vaughan M, Fanning T. Curr Drug Abuse Rev. 2010 Mar;3(1): 49-62.

Contingency Management and Levodopa-Carbidopa for Cocaine Treatment: A Comparison of Three Behavioral Targets

New data support use of levodopa pharmacotherapy with behavioral contingency management (CM) as one efficacious combination in cocaine dependence disorder treatment. A potential mechanism of the combined treatment effects may be related to dopamine-induced enhancement of the saliency of contingently delivered reinforcers. Evidence to support this mechanism was sought by evaluating levodopa-enhancing effects across distinct CM conditions that varied in behavioral targets. A total of 136 treatment-seeking, cocaine dependent subjects participated in this 12-week, randomized, placebo-controlled trial of levodopa (vs. placebo) administered in combination with one of three behavioral CM conditions. In the CM-URINE condition, subjects received cash-valued vouchers contingent on cocaine-negative urine toxicology results. In the CM-ATTEND condition, the same voucher schedule was contingent on attending thrice weekly clinic visits. In the CM-MEDICATION condition, the same voucher schedule was contingent on Medication Event Monitoring Systems- and riboflavin-based evidence of pill-taking behavior. Primary outcomes associated with each CM target behavior were analyzed using generalized linear mixed models for repeated outcomes. CM responding in the CM-ATTEND and CM-MEDICATION conditions showed orderly effects, with each condition producing corresponding changes in targeted behaviors, regardless of medication condition. In contrast, CM responding in the CM-URINE condition was moderated by medication, with levodopa-treated subjects more likely to submit cocaine-negative urines. These findings specify the optimal target behavior for CM when used in combination with levodopa pharmacotherapy. Schmitz JM, Lindsay JA, Stotts AL, Green CE, Moeller FG. Contingency management and levodopa-carbidopa for cocaine treatment: a comparison of three behavioral targets. Exp Clin Psychopharmacol. 2010 June 18(3): 238-244.

Association Analysis Between Polymorphisms in the Dopamine D2 Receptor (DRD2) and Dopamine Transporter (DAT1) Genes With Cocaine Dependence

Genetic research on cocaine dependence (CD) may help clarify in understanding the disorder as well as provide novel insights for effective treatment. Since dopamine neurotransmission has been shown to be involved in drug reward, related genes are plausible candidates for susceptibility to CD. The dopamine receptor D(2) (DRD2) protein and dopamine transporter (DAT1) protein play regulatory roles in dopamine neurotransmission. The TaqI A single-nucleotide polymorphism (SNP) in the DRD2 gene and the 3' variable number tandem repeat (VNTR) polymorphism in the DAT1 gene have been implicated in psychiatric disorders and drug addictions. In this study, the investigators hypothesized that these polymorphisms contribute to increased risk for CD. Cocaine-dependent individuals (n=347) and unaffected controls (n=257) of African descent were genotyped for the polymorphisms in the DRD2 and DAT1 genes. No statistically significant differences or trends in allele or genotype frequencies between cases and controls for either of the tested polymorphisms were observed. The study suggests that there is no association between the DRD2 and DAT1 polymorphisms and CD. However, additional studies using larger sample sizes and clinically homogenous populations are necessary before confidently excluding these variants as contributing genetic risk factors for CD. Lohoff FW, Bloch PJ, Hodge R, Nall AH, Ferraro TN, Kampman KM, Dackis CA, O'Brien CP, Pettinati HM, Oslin DW. Association analysis between polymorphisms in the dopamine D2 receptor (DRD2) and dopamine transporter (DAT1) genes with cocaine dependence. Neuroscience Letters. 2010 473: 87-91.

Opioid Antagonism Enhances Marijuana's Effects in Heavy Marijuana Smokers

Preclinical studies in rats suggest that there may be reciprocal modulation of the opioidergic and endocannabinoid systems, a relationship that has not been demonstrated in humans. This study sought to clarify this interaction by assessing how a range of naltrexone doses altered the subjective, cognitive, and cardiovascular effects of marijuana. The sample was 29 daily marijuana smokers in a within-subject, randomized, double-blind, placebo-controlled study. Naltrexone (0, 12, 25, 50, or 100 mg) was administered before active or inactive marijuana (3.27 or 0% THC) was smoked. Active marijuana increased subjective ratings of marijuana 'Strength', 'High', and positive subjective ratings of marijuana quality and drug effect including 'Liking', 'Good', and 'Take Again' compared to inactive marijuana. Naltrexone alone decreased ratings of 'Liking', 'Take Again' and 'Stimulated' compared with placebo, but increased ratings of drug 'Strength', 'High', 'Good', 'Liking', 'Stimulated' and 'Take Again' when administered under active marijuana conditions. Active marijuana did not affect performance on cognitive tasks relative to inactive marijuana, whereas naltrexone decreased performance when administered alone or in combination with active marijuana. Active marijuana increased heart rate compared to inactive marijuana under placebo naltrexone conditions. Although naltrexone alone decreased heart rate, it further increased marijuana's cardiovascular effect. The conclusions from the study were that in heavy marijuana smokers opioid-receptor blockade enhanced the subjective and cardiovascular effects of marijuana, suggesting that endogenous opioids dampen cannabinoid effects in this population. These findings demonstrate that a broad range of clinically used doses of naltrexone potentially increases the abuse liability and cardiovascular effects of cannabinoids. Cooper ZD, Haney M. Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. Psychopharmacology. 2010 211: 141-148.

Effects of Baclofen and Mirtazapine on a Laboratory Model of Marijuana Withdrawal and Relapse

Only a small percentage of individuals seeking treatment for their marijuana

use achieves sustained abstinence, suggesting more treatment options are needed. The objective of this study was to investigate the effects of baclofen (study 1) and mirtazapine (study 2) in a human laboratory model of marijuana intoxication, withdrawal, and relapse. In study 1, daily marijuana smokers (n = 10), averaging 9.4 (+/-3.9) marijuana cigarettes/day, were maintained on placebo and each baclofen dose (60, 90 mg/day) for 16 days. In study 2, daily marijuana smokers (n = 11), averaging 11.9 (+/-5.3) marijuana cigarettes/day, were maintained on placebo and mirtazapine (30 mg/day) for 14 days each. Medication administration began outpatient prior to each 8-day inpatient phase. On the first inpatient day of each medication condition, participants smoked active marijuana (study 1: 3.3% THC; study 2: 6.2% THC). For the next 3 days, they could self-administer placebo marijuana (abstinence phase), followed by 4 days in which they could self-administer active marijuana (relapse phase); participants paid for self-administered marijuana using study earnings. The results of study 1 showed that during active marijuana smoking, baclofen dose-dependently decreased craving for tobacco and marijuana, but had little effect on mood during abstinence and did not decrease relapse. Baclofen also worsened cognitive performance regardless of marijuana condition. In study 2, mirtazapine improved sleep during abstinence, and robustly increased food intake, but had no effect on withdrawal symptoms and did not decrease marijuana relapse. The conclusions are that, overall, this human laboratory study did not find evidence to suggest that either baclofen or mirtazapine showed promise for the potential treatment of marijuana dependence. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Cooper ZD, Foltin RW. Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. Psychopharmacology 2010; 211: 233-244.

Behavioral Effects of Gamma-hydroxybutyrate in Humans

Despite the therapeutic use and abuse potential of gamma-hydroxybutyrate (GHB or Xyrem), relatively few studies have examined the behavioral effects of GHB in humans under controlled laboratory conditions. This eight-session study examined in 10 non-substance-abusing volunteers the behavioral effects of GHB at each of the following doses: 0, 0.32, 0.56, 0.75, 1.0, 1.8, 2.4, 3.2 g/70 kg, orally. Order of dose testing was random, except that the first two participants received active doses in ascending order and 2.4 g/70 kg was always tested before 3.2 g/70 kg. Before drug administration and at several post-drug time points, self-report, observer report, physiological, and psychomotor performance measures were obtained. Analyses based on area under the curve showed that GHB produced dose-related increases in subjective ratings of sedative-like, stimulant-like, positive mood, and dissociative effects, but no changes in psychomotor performance measures or blood pressure. Analyses based on peak effects generally showed dose-related increases in ratings indicating sedative-like, dissociative, and drug liking, although some measures showed U-shaped dose-related changes. These initial findings suggest that GHB at doses of 0.32-3.2 g/70 kg produces dissociative, sedating and some stimulant-like effects in humans without a history of sedative abuse. Oliveto A, Gentry WB, Pruzinsky R, Gonsai K, Kosten TR, Martell B, Poling J. Behavioral effects of gamma-hydroxybutyrate in humans. Behav Pharmacol 2010 June 3. (Epub ahead of print).

A Double-Blind, Placebo-Controlled Study of N-acetyl Cysteine Plus Naltrexone for Methamphetamine Dependence

Reducing both glutamatergic and dopaminergic drive in the nucleus accumbens may offer complementary mechanisms by which to reduce drug cravings. This 8-week study sought to examine the efficacy of a combination of a glutamate modulator, N-acetyl cysteine (NAC), plus the opioid antagonist, naltrexone, compared to placebo in the treatment of methamphetamine dependence.

Thirty-one subjects with methamphetamine dependence (mean age 36.8+/-7.12years; 29% female) were randomly assigned in a 1:1 fashion to NAC plus naltrexone or placebo and returned for one post-baseline visit. The Penn Craving Scale was the primary outcome measure. Self-report methamphetamine use frequency and urine toxicology were secondary measures. NAC plus naltrexone failed to demonstrate statistically significant differences from placebo on primary and secondary outcomes. The current study failed to demonstrate greater efficacy for NAC plus naltrexone compared to placebo. Given the small sample size, the statistical power to detect significant effects of active treatment versus placebo was limited. The question of whether a larger, well-powered sample would have detected differences between NAC plus naltrexone and placebo deserves further examination. Grant JE, Odlaug BL, Kim SW. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. Eur Neuropsychopharmacol. 2010 Jul 21. [Epub ahead of print].

Introduction to Behavioral Addictions

Several behaviors, besides psychoactive substance ingestion, produce short-term reward that may engender persistent behavior, despite knowledge of adverse consequences, i.e., diminished control over the behavior. These disorders have historically been conceptualized in several ways. One view posits these disorders as lying along an impulsive-compulsive spectrum, with some classified as impulse control disorders. An alternate, but not mutually exclusive, conceptualization considers the disorders as non-substance or "behavioral" addictions. The authors review data illustrating similarities and differences between impulse control disorders or behavioral addictions and substance addictions. This topic is particularly relevant to the optimal classification of these disorders in the forthcoming fifth edition of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Growing evidence suggests that behavioral addictions resemble substance addictions in many domains, including natural history, phenomenology, tolerance, comorbidity, overlapping genetic contribution, neurobiological mechanisms, and response to treatment, supporting the DSM-V Task Force proposed new category of Addiction and Related Disorders encompassing both substance use disorders and non-substance addictions. Current data suggest that this combined category may be appropriate for pathological gambling and a few other better studied behavioral addictions, e.g., Internet addiction. There is currently insufficient data to justify any classification of other proposed behavioral addictions. Conclusions and Scientific Significance: Proper categorization of behavioral addictions or impulse control disorders has substantial implications for the development of improved prevention and treatment strategies. Grant, JE, Potenza, MN, Weinstein, A, Gorelick, DA. Introduction to Behavioral Addictions. Am J Drug Alcohol Abuse. 2010 Jun 21. [Epub ahead of print].

Monetary Incentives Promote Smoking Abstinence In Adults With Attention Deficit Hyperactivity Disorder (ADHD)

Individuals with attention deficit hyperactivity disorder (ADHD) smoke at rates significantly higher than the general population and have more difficulty quitting than non-diagnosed individuals. Currently, there are no evidence-based approaches for reducing smoking specifically in individuals with ADHD. Adult regular smokers with or without ADHD participated in a study of extended smoking withdrawal where monetary incentives were used to promote abstinence. Participants were paid according to an escalating schedule for maintaining abstinence measured as self-report of no smoking and an expired air carbon monoxide (CO) level of < or=4 parts per million. Sixty-four percent (14/22) of smokers with ADHD and 50% (11/22) of smokers without ADHD maintained complete abstinence for the 2-week duration of the study.

Twenty-two percent (5/22) and 9% (2/22) of smokers with ADHD and without ADHD, respectively, maintained continued abstinence for up to 10 days following the removal of the contingencies. Though abstinence rates were higher for the smokers with ADHD, the group differences were not statistically significant. Results suggest that monetary incentives may be a useful approach for promoting abstinence in adult smokers with ADHD, perhaps owing to altered reinforcement processes in these individuals. Kollins SH, McClernon FJ, Van Voorhees EE. Monetary incentives promote smoking abstinence in adults with attention deficit hyperactivity disorder (ADHD). Exp Clin Psychopharmacol. 2010; 18(3): 221-228.

Intravenous Oxycodone, Hydrocodone, and Morphine In Recreational Opioid Users: Abuse Potential and Relative Potencies

Nonmedical use and abuse of prescription opioids is an increasing public health problem. Intravenous (IV) administration of opioid analgesics intended for oral use is not uncommon; yet, little is known about the relative abuse potential of these drugs when administered intravenously to recreational opioid abusers without physical dependence. This inpatient study employed a double-blind, randomized, within-subject, placebo-controlled design to examine the relative abuse potential of IV doses of oxycodone, hydrocodone, and morphine. Nine healthy adult participants reporting recreational opioid use and histories of IV opioid use completed 11 experimental sessions, including one active-dose practice session. IV doses were infused over 5 min and included three identical doses of each opioid (5, 10, and 20 mg/10 ml) and saline placebo. Physiological, subjective, and performance effects were collected before and for 6 h after drug administration. All three opioids produced prototypical mu agonist effects (e.g., miosis; increased ratings of liking) that were generally dose-related. Pharmacodynamic effects were observed within 5 min of IV administration. Physiological effects were more prolonged than subjective effects for all three drugs. While the magnitude of effects was generally comparable across drugs and qualitatively similar, valid potency assays indicated the following potency relationship: oxycodone > morphine > hydrocodone. There were modest potency differences between oxycodone, hydrocodone, and morphine, but their overall profile of effects was similar, indicating significant abuse potential when administered intravenously. Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, Walsh SL. Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. Psychopharmacology (Berl). 2010 Jul 28. [Epub ahead of print].

Behavioral Effects of D-Amphetamine In Humans: Influence of Subclinical Levels of Inattention and Hyperactivity

Several studies suggest a link between stimulant abuse and attention-deficit hyperactivity disorder (ADHD) symptoms (e.g., inattention and hyperactivity). To further assess the nature of this relationship, the present study examined the association between subclinical symptoms of inattention and hyperactivity and the behavioral effects of d-amphetamine. Participants were classified into a High- (n = 8) or Low-Score (n = 9) group based on their responses on a rating scale that assessed inattention and hyperactivity symptoms. The participants did not differ across the High-Score and Low-Score groups in their ability to discriminate d-amphetamine. The participants in the High-Score group were significantly more sensitive to the positive participant-rated effects of d-amphetamine (e.g., Good Effects, Like Drug), but less sensitive to drug-induced increases in blood pressure and heart rate. The selective increase in positive subjective effects of d-amphetamine suggests that individuals with subclinical inattention and hyperactivity symptoms may have increased vulnerability to stimulant abuse. Sevak RJ, Stoops WW, Rush CR. Behavioral effects of d-amphetamine in humans: influence of subclinical levels of

inattention and hyperactivity. Am J Drug Alcohol Abuse. 2010; 36(4): 220-227.

Acute Effects of Intramuscular and Sublingual Buprenorphine and Buprenorphine/ Naloxone In Non-Dependent Opioid Abusers

Buprenorphine is a partial mu opioid receptor agonist with clinical efficacy as a pharmacotherapy for opioid dependence. A sublingual combination formulation was developed containing buprenorphine and naloxone with the intent of decreasing abuse liability in opioid-dependent individuals. However, the addition of naloxone may not limit abuse potential of this medication when taken by individuals without opioid physical dependence. The present study investigated the effects of buprenorphine alone and in combination with naloxone administered intramuscularly and sublingually to non-dependent opioid abusers. In a within-subject crossover design, non-dependent opioid-experienced volunteers (N = 8) were administered acute doses of buprenorphine (4, 8, and 16 mg) and buprenorphine/naloxone (4/1, 8/2, and 16/4 mg) via both intramuscular and sublingual routes, intramuscular hydromorphone (2 and 4 mg as an opioid agonist control), and placebo, for a total of 15 drug conditions. Laboratory sessions were conducted twice per week using a double-blind, double-dummy design. Buprenorphine and buprenorphine/ naloxone engendered effects similar to hydromorphone. Intramuscular administration produced a greater magnitude of effects compared to the sublingual route at the intermediate dose of buprenorphine and at both the low and high doses of the buprenorphine/naloxone combination. The addition of naloxone did not significantly alter the effects of buprenorphine. These results suggest that buprenorphine and buprenorphine/naloxone have similar abuse potential in non-dependent opioid abusers, and that the addition of naloxone at these doses and in this dose ratio confers no evident advantage for decreasing the abuse potential of intramuscular or sublingual buprenorphine in this population. Duke AN, Correia CJ, Walsh SL, Bigelow GE, Strain EC. Acute effects of intramuscular and sublingual buprenorphine and buprenorphine/naloxone in non-dependent opioid abusers. Psychopharmacology (Berl). 2010 Jun 25. [Epub ahead of print].

Does the Response to Cocaine Differ as a Function of Sex or Hormonal Status In Human and Non-Human Primates?

Stimulant abuse continues to be a growing problem among women. Over the last 10-15 years, an increasing number of studies have focused on factors that may be implicated in stimulant abuse in women as compared to men, including the role of hormonal fluctuations across the menstrual cycle. Numerous preclinical studies have documented that female rodents are more sensitive than male rodents to the behavioral effects of stimulant administration and the hormone estradiol is involved in the enhanced response to stimulants observed in females. In contrast, fewer studies have been conducted in humans and non-human primates addressing the role of sex and gonadal hormones on the effects of cocaine. This review paper presents a recent update on data collected in our Human Cocaine Challenge Laboratory and our Non-human Primate Laboratory, including analysis of cocaine pharmacokinetics, sex differences, the menstrual cycle, and the role of progesterone in modulating the response to cocaine. Our studies indicate that there is minimal evidence that the response to intranasal cocaine varies across the menstrual cycle or between men and women. In contrast, the response to smoked cocaine is greater in the follicular phase than the luteal phase and differences between men and women generally only emerge when men are compared to women in the luteal phase. In terms of potential hormonal mechanisms for these differences, the hormone progesterone attenuates the subjective response to cocaine. With respect to cocaine self-administration, there are minimal changes across the menstrual cycle in both humans and non-human primates. Thus, there is converging evidence across a range of species that the behavioral effects of cocaine (1)

differ between males and females, (2) differ in relation to hormonal fluctuations, (3) can be attenuated by progesterone (at least in females), and (4) do not appear to be related to differences in cocaine pharmacokinetics. Evans SM, Foltin RW. Does the response to cocaine differ as a function of sex or hormonal status in human and non-human primates? Horm Behav. 2010; 58(1): 13-21. [Epub 2009 Sep 4].

A Placebo-Controlled Trial of Memantine For Cocaine Dependence With High-Value Voucher Incentives During A Pre-Randomization Lead-In Period

Preclinical findings suggest that the inhibition of NMDA glutamatergic neurotransmission may have beneficial effects in the treatment of cocaine dependence. The authors hypothesized that memantine, a low potency, uncompetitive NMDA receptor antagonist, would be safe and effective in the treatment of cocaine dependence, particularly in preventing relapse to cocaine use in abstinent individuals. Cocaine dependent patients (N=112) were enrolled. The trial began with a 2-week placebo lead-in period during which patients received high-value voucher contingency management to induce abstinence. Participants were then randomized to receive either memantine 20mg bid (N=39) or placebo (N=42) for 12-weeks in combination with individual relapse-prevention therapy. The randomization was stratified by abstinence status during the lead-in period. The primary outcome was the weekly proportion of days of cocaine use. There were no significant differences in cocaine use outcome between the groups treated with memantine versus placebo. Thus, the efficacy of memantine 40mg/d for the treatment of cocaine dependence was not supported. Urine-confirmed abstinence during the lead-in period was achieved by 44% of participants, and was a strong predictor of subsequent cocaine abstinence during the trial. This suggests that this clinical trial design, an intensive behavioral intervention during a lead-in period, resolves cocaine dependent patients into two subgroups, one that rapidly achieves sustained abstinence and may not need a medication, and another that displays persistent cocaine use and would most likely benefit from a medication to help induce abstinence. Targeting the latter subgroup may advance medication development efforts. Bisaga A, Aharonovich E, Cheng WY, Levin FR, Mariani JJ, Raby WN, Nunes EV. A placebo-controlled trial of memantine for cocaine dependence with high-value voucher incentives during a pre-randomization lead-in period. Drug Alcohol Depend. 2010 May 25. [Epub ahead of print].

A Comparison of Psychosocial and Cognitive Functioning Between Depressed and Non-Depressed Patients With Cannabis Dependence

Cannabis use and depressive disorders are thought to impair cognitive performance and psychosocial functioning. Both disorders co-occurring may compound the negative effects of these diagnoses. In this study, the authors used the California Computerized Assessment Package as the cognitive performance measure and the Addiction Severity Index as the psychosocial functioning measure to compare individuals who were cannabis dependent and either depressed or not depressed (N= 108: 54 cannabis dependent only, 54 cannabis dependent and depressed or dysthymic). As predicted, cannabis dependent individuals with comorbid depression showed more psychosocial impairment than individuals with cannabis dependence alone. However, contrary to the authors' hypothesis, individuals who were cannabis dependent with comorbid depression showed less cognitive impairment in some California Computerized Assessment Package modules than individuals with cannabis dependence alone. Based on the authors' results, they concluded that the additive effects of cannabis dependency and depression may only be limited to

psychosocial domains and may not extend to cognitive functioning. Secora AM, Eddie D, Wyman BJ, Brooks DJ, Mariani JJ, Levin FR. A comparison of psychosocial and cognitive functioning between depressed and non-depressed patients with cannabis dependence. J Addict Dis. 2010;29(3): 325-337.

Long-Acting Injectable Versus Oral Naltrexone Maintenance Therapy With Psychosocial Intervention For Heroin Dependence: A Quasi-Experiment

A quasi-experimental comparison of early clinical outcomes between injectable, sustained-release, depot naltrexone formulation versus oral naltrexone maintenance therapy in individuals with opiate dependence was conducted. Early retention in treatment and urine-confirmed opiate use in the first 8 weeks post-detoxification were compared between patients (diagnosed as opiate-dependent according to DSM-IV criteria) participating in 2 concurrently run randomized clinical trials of oral (n = 69; patients treated from September 1999 to May 2002) and long-acting injectable (n = 42; patients treated from November 2000 to June 2003) naltrexone maintenance therapy with psychosocial therapy. Long-acting injectable naltrexone produced significantly better outcome than oral naltrexone on days retained in treatment ($F(1,106) = 6.49$, $P = .012$) and for 1 measure of opiate use ($F(1,106) = 5.26$, $P = .024$); other measures were not significantly different, but differences were in the same direction. In subanalyses, there were interaction effects between baseline heroin use severity and type of treatment. In subanalyses, heroin users with more severe baseline use showed better retention with oral naltrexone maintenance therapy combined with intensive psychotherapy (behavioral naltrexone therapy) as compared to retention shown by severe heroin users treated with long-acting naltrexone injections combined with standard cognitive-behavioral therapy ($chi(2)(1) = 9.31$, $P = .002$); less severe heroin users evidenced better outcomes when treated with long-acting injectable naltrexone. This quasi-experimental analysis provides tentative indications of superior outcomes for heroin-dependent patients treated with long-acting injectable naltrexone compared to oral naltrexone. The finding that heroin users with more severe baseline use achieved better outcomes with oral naltrexone is most probably attributable to the intensive nature of the psychosocial treatments provided and points to the opportunity for continued research in augmenting injectable naltrexone with psychosocial strategies to further improve outcome, especially in individuals with more severe use. The results should be considered exploratory given the quasi-experimental nature of the study. Brooks AC, Comer SD, Sullivan MA, Bisaga A, Carpenter KM, Raby WM, Yu E, O'Brien CP, Nunes EV. Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: a quasi-experiment. J Clin Psychiatry. 2010 Jul 13 [Epub ahead of print].

Progesterone Improves Cognitive Performance and Attenuates Smoking Urges In Abstinent Smokers

Progesterone, a steroid hormone, has been implicated in many CNS functions including reward, cognition, and neuroprotection. The goal of this study was to examine the dose-dependent effects of progesterone on cognitive performance, smoking urges, and smoking behavior in smokers. Thirty female and thirty-four male smokers participated in a double-blind, placebo-controlled study. Female smokers were in the early follicular phase of their menstrual cycle during study participation. Smokers were randomly assigned to either 200 or 400mg/day of progesterone or placebo, given in two separate doses, during clinic visit. The first 3 days of the treatment period, smokers abstained from smoking, which was verified with breath CO levels. Smokers attended an experimental session on day 4 where the number of cigarettes smoked were recorded starting 2h after the medication treatment. Progesterone treatment, 200mg/day, significantly improved cognitive performance in the Stroop and the Digit

Symbol Substitution Test. Progesterone at 400mg/day was associated with reduced urges for smoking but did not change ad lib smoking behavior. These findings suggest a potential therapeutic value of progesterone for smoking cessation. Sofuoglu M, Mouratidis M, Mooney M. Progesterone improves cognitive performance and attenuates smoking urges in abstinent smokers. Psychoneuroendocrinology. 2010 Jul 30. [Epub ahead of print].

Comparison of Available Treatments For Tobacco Addiction

Cigarette smoking is a major public health problem that causes more than 5 million deaths annually worldwide. Cigarette smoking is especially common among individuals with psychiatric comorbidity, including individuals with primary psychiatric disorders and other addictions. Effective behavioral and pharmacologic treatments for smoking cessation are available. Behavioral treatments including brief (< 3 min) counseling by physicians are effective. Seven first-line pharmacologic treatments are currently available: five nicotine replacement therapies, bupropion, and varenicline. In addition, clonidine and nortriptyline are second-line treatments for smoking cessation. These treatments increase the chances of quitting smoking by two- to threefold, supporting their use in smokers who are motivated to quit. However, effective treatments for many subpopulations, including smokers with psychiatric comorbidities as well as adolescent, pregnant, or postpartum smokers, remain to be developed and represent an important challenge. Herman AI, Sofuoglu M. Comparison of Available Treatments for Tobacco Addiction. Curr Psychiatry Rep. 2010 Jul 10. [Epub ahead of print].

Cognitive Effects of Nicotine: Genetic Moderators

Cigarette smoking is the main preventable cause of death in developed countries, and the development of more effective treatments is necessary. Cumulating evidence suggests that cognitive enhancement may contribute to the addictive actions of nicotine. Several studies have demonstrated that nicotine enhances cognitive performance in both smokers and non-smokers. Genetic studies support the role of both dopamine (DA) and nicotinic acetylcholine receptors (nAChRs) associated with nicotine-induced cognitive enhancement. Based on knockout mice studies, beta2 nAChRs are thought to be essential in mediating the cognitive effects of nicotine. alpha7nAChRs are associated with attentional and sensory filtering response, especially in schizophrenic individuals. Genetic variation in D2 type DA receptors and the catechol-O-methyltransferase enzyme appears to moderate cognitive deficits induced by smoking abstinence. Serotonin transporter (5-HTT) gene variation also moderates nicotine-induced improvement in spatial working memory. Less is known about the contribution of genetic variation in DA transporter and D4 type DA receptor genetic variation on the cognitive effects of nicotine. Future research will provide a clearer understanding of the mechanism underlying the cognitive-enhancing actions of nicotine. Herman AI, Sofuoglu M. Cognitive effects of nicotine: genetic moderators. Addict Biol. 2010;15(3): 250-265. Epub 2010 Apr 29.

Influence of Cocaine Dependence and Early Life Stress on Pituitary-Adrenal Axis Responses to CRH and the Trier Social Stressor

Long-term changes in the hypothalamic-pituitary-adrenal (HPA) axis as a result of early life stress could be related to the development of substance use disorders during adulthood. In this study, the neuroendocrine, physiologic (HR), and subjective responses to corticotropin releasing hormone (CRH) and the Trier Social Stress Task (TSST) in individuals with cocaine dependence, with (n=21)/without early life stress (n=21), non-dependent individuals with

early life stress (n=22), and a control group were examined (n=21). CRH increased cortisol and ACTH levels in all groups. However, a significant effect of early life stress on ACTH was observed indicating that the increase in ACTH was greatest in subjects with a history of childhood stress. Post hoc analysis indicated the early life stress/non-cocaine dependent individuals exhibited significantly higher levels of ACTH as compared to the early life stress/cocaine-dependent group. Despite the elevated ACTH response there was no difference between the groups in the cortisol response to CRH. The TSST produced a significant elevation in ACTH and cortisol all study groups. No significant group differences were observed. The subjective stress and peak heart rate responses to the TSST were greatest in cocaine-dependent subjects without early life stress. In response to CRH, subjective stress and craving were positively correlated in cocaine-dependent subjects regardless of early life stress history, while stress and craving following the TSST were correlated only in cocaine-dependent subjects without a history of early life stress. Findings support previous studies demonstrating that subjects with a history of childhood adversity exhibit elevated ACTH and blunted cortisol levels in response to stress. In contrast, HR and subjective stress in response to the TSST were greatest in cocaine-dependent subjects without a history of early life stress, suggesting that childhood adversity may desensitize autonomic and subjective responding to social stress in adults with cocaine dependence. Maria MM, McRae-Clark AL, Back SE, Desantis SM, Baker NL, Spratt EG, Simpson AN, Brady KT. Influence of cocaine dependence and early life stress on pituitary-adrenal axis responses to CRH and the Trier social stressor. Psychoneuroendocrinology. 2010 May 31. [Epub ahead of print].

Methylphenidate Transdermal System in Adults With Past Stimulant Misuse: An Open-Label Trial--Investigator-Supported Trial Funded by Shire Pharmaceuticals

This 8-week, open-label trial assessed the efficacy of methylphenidate transdermal system (MTS) in 14 adult individuals diagnosed with ADHD and with a history of stimulant misuse, abuse, or dependence. The primary efficacy endpoint was the Wender-Reimherr Adult ADHD Scale (WRAADS), and secondary efficacy endpoints included the Clinical Global Impression (CGI) ratings and substance abuse as quantified by urine drug screens and self-reported use. Significant improvements from baseline were found on both the WRAADS and CGI measurements. No abuse of the study medication was observed. The findings suggested that MTS may improve ADHD symptoms in adults with a history of stimulant misuse; however, there were limitations. The study data showed the need for subsequent randomized studies that further explore findings made in this study. McRae-Clark AL, Brady KT, Hartwell KJ, White K, Carter RE. Methylphenidate Transdermal System in Adults With Past Stimulant Misuse: An Open-Label Trial--Investigator-Supported Trial Funded by Shire Pharmaceuticals. J Atten Disord. 2010 Jun 10. [Epub ahead of print].

Extinction of Drug Cue Reactivity In Methamphetamine-Dependent Individuals

Conditioned responses to drug-related environmental cues (such as craving) play a critical role in relapse to drug use. Animal models demonstrate that repeated exposure to drug-associated cues in the absence of drug administration leads to the extinction of conditioned responses, but the few existing clinical trials focused on extinction of conditioned responses to drug-related cues in drug-dependent individuals show equivocal results. The current study examined drug-related cue reactivity and response extinction in a laboratory setting in methamphetamine-dependent individuals. Methamphetamine cue-elicited craving was extinguished during two sessions of repeated (3) within-session exposures to multi-modal (picture, video, and in-vivo) cues, with no evidence of spontaneous recovery between sessions. A

trend was noted for a greater attenuation of response in participants with longer (4-7 day) inter-session intervals. These results indicate that extinction of drug cue conditioned responding occurs in methamphetamine-dependent individuals, offering promise for the development of extinction- based treatment strategies. Price KL, Saladin ME, Baker NL, Tolliver BK, Desantis SM, McRae-Clark AL, Brady KT. Extinction of drug cue reactivity in methamphetamine-dependent individuals. Behav Res Ther. 2010 Sep;48(9): 860-865. Epub 2010 May 19.

Naltrexone to Treat Opioid Addiction in a Country in Which Methadone and Buprenorphine Are Not Available

Opioid dependence is one of the most severe drug dependencies. Naltrexone is a medication that completely blocks the subjective and other effects of opioids and, when administered to detoxified opioid addicts and taken as directed, prevents relapse and helps maintain abstinence. The major problem with naltrexone is poor compliance, particularly in countries in which there is a treatment alternative based on substitution of illicit opioids such as heroin with orally administered opioid agonists (methadone) or partial agonist/antagonists (buprenorphine). In Russia, substitution therapy is forbidden by law, and naltrexone is the only available pharmacotherapy for heroin dependence. Due to the lack of alternatives to naltrexone and stronger family control of compliance (adherence), naltrexone is more effective for relapse prevention and abstinence stabilization in Russia than in Western countries. Long-acting, sustained-release formulations (injectable and implantable) seem particularly effective compared with oral formulations. This article summarizes the results of studies conducted in Russia during the past 10 years that demonstrate these points. Krupitsky E, Zvartau E, Woody G. Use of Naltrexone to Treat Opioid Addiction in a Country in Which Methadone and Buprenorphine Are Not Available. Curr Psychiatry Rep. 2010 Jul 17. [Epub ahead of print].

Cost-Effectiveness of Extended Buprenorphine-Naloxone Treatment for Opioid-Dependent Youth: Data From a Randomized Trial

The objective is to estimate cost, net social cost and cost-effectiveness in a clinical trial of extended buprenorphine-naloxone (BUP) treatment versus brief detoxification treatment in opioid-dependent youth. Economic evaluation of a clinical trial conducted at six community out-patient treatment programs from July 2003 to December 2006, who were randomized to 12 weeks of BUP or a 14-day taper (DETOX). BUP patients were prescribed up to 24 mg per day for 9 weeks and then tapered to zero at the end of week 12. DETOX patients were prescribed up to 14 mg per day and then tapered to zero on day 14. All were offered twice-weekly drug counseling. Participants were 152 patients aged 15-21 years. Data were collected prospectively during the 12-week treatment and at follow-up interviews at months 6, 9 and 12. The 12-week out-patient study treatment cost was $1514 ($P < 0.001$) higher for BUP relative to DETOX. One-year total direct medical cost was only $83 higher for BUP ($P = 0.97$). The cost-effectiveness ratio of BUP relative to DETOX was $1376 in terms of 1-year direct medical cost per quality-adjusted life year (QALY) and $25,049 in terms of out-patient treatment program cost per QALY. The acceptability curve suggests that the cost-effectiveness ratio of BUP relative to DETOX has an 86% chance of being accepted as cost-effective for a threshold of $100,000 per QALY. Extended BUP treatment relative to brief detoxification is cost effective in the US health-care system for the outpatient treatment of opioid-dependent youth. Polsky D, Glick HA, Yang J, Subramaniam GA, Poole SA, Woody GE. Cost-effectiveness of extended buprenorphine-naloxone treatment for opioid-dependent youth: data from a randomized trial. Addiction. 2010 Jul 12. [Epub ahead of print].

Diffusion Tensor Imaging and Decision Making In Cocaine Dependence

Chronic stimulant abuse is associated with both impairment in decision making and structural abnormalities in brain gray and white matter. Recent data suggest these structural abnormalities may be related to functional impairment in important behavioral processes. In 15 cocaine-dependent and 18 control subjects, relationships were examped between decision-making performance on the Iowa Gambling Task (IGT) and white matter integrity as measured by diffusion tensor imaging (DTI). Whole brain voxelwise analyses showed that, relative to controls, the cocaine group had lower fractional anisotropy (FA) and higher mean of the second and third eigenvalues (lambda perpendicular) in frontal and parietal white matter regions and the corpus callosum. Cocaine subjects showed worse performance on the IGT, notably over the last 40 trials. Importantly, FA and lambda perpendicular values in these regions showed a significant relationship with IGT performance on the last 40 trials. Compromised white matter integrity in cocaine dependence may be related to functional impairments in decision making. Lane SD, Steinberg JL, Ma L, Hasan KM, Kramer LA, Zuniga EA, Narayana PA, Moeller FG. Diffusion tensor imaging and decision making in cocaine dependence. PLoS One. 2010; 5(7): e11591.

Effect of Cocaine on Structural Changes In Brain: MRI Volumetry Using Tensor-Based Morphometry

Magnetic resonance imaging (MRI) was performed in cocaine-dependent subjects to determine the structural changes in brain compared to non-drug using controls. Cocaine-dependent subjects and controls were carefully screened to rule out brain pathology of undetermined origin. Magnetic resonance images were analyzed using tensor-based morphometry (TBM) and voxel-based morphometry (VBM) without and with modulation to adjust for volume changes during normalization. For TBM analysis, unbiased atlases were generated using two different inverse consistent and diffeomorphic nonlinear registration techniques. Two different control groups were used for generating unbiased atlases. Independent of the nonlinear registration technique and normal cohorts used for creating the unbiased atlases, our analysis failed to detect any statistically significant effect of cocaine on brain volumes. These results show that cocaine-dependent subjects do not show differences in regional brain volumes compared to non-drug using controls. Narayana PA, Datta S, Tao G, Steinberg JL, Moeller FG. Effect of cocaine on structural changes in brain: MRI volumetry using tensor-based morphometry. Drug Alcohol Depend. 2010 May 28. [Epub ahead of print].

Relationship Between Impulsivity and Decision Making In Cocaine Dependence

Impulsivity and decision making are associated on a theoretical level in that impaired planning is a component of both. However, few studies have examined the relationship between measures of decision making and impulsivity in clinical populations. The purpose of this study was to compare cocaine-dependent subjects to controls on a measure of decision making (the Iowa Gambling Task or IGT), a questionnaire measure of impulsivity (the Barratt Impulsiveness Scale or BIS-11) and a measure of behavioural inhibition (the immediate memory task or IMT), and to examine the interrelationship among these measures. Results of the study showed that cocaine-dependent subjects made more disadvantageous choices on the IGT, had higher scores on the BIS and more commission errors on the IMT. Cognitive model analysis showed that choice consistency factors on the IGT differed between cocaine-dependent subjects and controls. However, there was no significant correlation between IGT performance and the BIS total score or subscales or IMT

commission errors. These results suggest that in cocaine-dependent subjects there is little overlap between decision making as measured by the IGT and impulsivity/ behavioral inhibition as measured by the BIS and IMT. Kjome KL, Lane SD, Schmitz JM, Green C, Ma L, Prasla I, Swann AC, Moeller FG. Relationship between impulsivity and decision making in cocaine dependence. Psychiatry Res. 2010 Jul 30;178(2): 299-304. Epub 2010 May 15.

Dopamine D4 Receptor Gene Variation Moderates the Efficacy of Bupropion For Smoking Cessation

Smokers (>/=10 cigarettes per day, N=331) of European ancestry taking part in a double-blind placebo-controlled randomized trial of 12 weeks of treatment with bupropion along with counseling for smoking cessation were genotyped for a variable number of tandem repeats polymorphism in exon III of the dopamine D4 receptor gene. Generalized estimating equations predicting point-prevalence abstinence at end of treatment and 2, 6 and 12 months after the end of treatment indicated that bupropion (vs placebo) predicted increased odds of abstinence. The main effect of Genotype was not significant. A Genotype x Treatment interaction (P=0.005) showed that bupropion predicted increased odds of abstinence in long-allele carriers (odds ratios (OR)=1.31, P<0.0001), whereas bupropion was not associated with abstinence among short-allele homozygotes (OR=1.06, P=0.23). The Genotype x Treatment interaction remained when controlling for demographic and clinical covariates (P=0.01) and in analyses predicting continuous abstinence (P'sSmoking Expectancies, Weight Concerns, and Dietary Behaviors In Adolescence

The objective of this study was to examine the association of cigarette smoking and weight concerns in adolescents, given that adolescents may begin smoking or have difficulty quitting because of their expectancies of the effects of smoking on body weight. This study used data from a cross-sectional survey of 4523 Connecticut high school adolescents to assess the influence of gender, smoking intensity, and dietary-restrictive behavior on smoking-related weight concerns. Heavy smokers were significantly less likely to engage in healthy dietary restrictions than nonsmokers; however, light smokers did not differ from nonsmokers. Both light and heavy smokers were significantly more likely to engage in unhealthy dietary restriction when compared with nonsmokers. In the model that was used to examine smokers only, heavy smokers were significantly less likely to engage in healthy dietary restriction than light smokers, but smoking level was not associated with unhealthy dietary restrictions. Dietary restrictions are significantly associated with smoking-related weight concerns; however, this seems to be related to type of dietary-restrictive behavior, with greater weight concerns observed only in those smokers who engaged in unhealthy dietary restrictions and not in those who engaged in healthy dietary restrictions or no restrictions. Although limited by its cross-sectional nature, the findings from this large, geographically diverse sample have clinical implications for smoking prevention and cessation interventions in adolescents. Cavallo DA, Smith AE, Schepis TS, Desai R, Potenza MN, Krishnan-Sarin S. Smoking expectancies, weight concerns, and dietary behaviors in adolescence. Pediatrics. 2010 Jul;126(1): e66-72. Epub 2010 Jun 14.

Drug-Induced Plasticity Contributing To Heightened Relapse Susceptibility: Neurochemical Changes and Augmented Reinstatement In High-Intake Rats

Previous studies have demonstrated that increased extracellular glutamate, but not dopamine, in the nucleus accumbens core (NAcc) is necessary for cocaine-induced reinstatement. In this study, rats were assigned to self-administer cocaine under conditions resulting in low or high levels of drug intake. Approximately 19 d after the last session, extracellular levels of glutamate and

dopamine in the NAcc were measured. Contrary to what has beeng reported, high-intake rats exhibited an increase in extracellular levels of dopamine but not glutamate. Further, increased reinstatement in high-intake rats was no longer observed when the D(1) receptor antagonist SCH-23390 was infused into the NAcc. The sensitized dopamine response to cocaine in high-intake rats may involve blunted cystine-glutamate exchange by system x(c(-)). Reduced (14)C-cystine uptake through system x(c(-)) was evident in NAcc tissue slices obtained from high-intake rats, and the augmented dopamine response in these rats was no longer observed when subjects received the cysteine prodrug N-acetyl cysteine. Madayag A, Kau KS, Lobner D, Mantsch JR, Wisniewski S, Baker DA. J Neurosci. 2010; 30(1): 210-217.

Behavioral and Neurochemical Effects of Amphetamine Analogs That Release Monoamines In the Squirrel Monkey

Previous preclinical and clinical studies have shown that continuous treatment with the monoamine releaser amphetamine reduces cocaine self-administration, but amphetamine selectively targets the dopamine system and is reinforcing. In the present study, the consequences of administration of amphetamine and three structurally related analogs that vary in their potencies for releasing dopamine and serotonin on behavioral-stimulant effects and nucleus accumbens dopamine levels in squirrel monkeys were examined. These results demonstrate that increasing serotonergic activity attenuates dopamine release and dopamine-mediated behavioral effects of monoamine releasers. These results support further investigation of PAL-313 and similar compounds as a potential medication for treating psychostimulant abuse. Kimmel HL, Manvich DF, Blough BE, Negus SS, Howell LL. Pharmacol Biochem Behav. 2009; 94(2): 278-284.

Synthetic Studies and Pharmacological Evaluations on the MDMA ('Ecstasy') Antagonist Nantenine

(R)- and (S)-nantenine were prepared and evaluated in a food-reinforced operant task in rats. Pretreatment with either nantenine enantiomer (0.3mg/kg ip) completely blocked the behavioral suppression induced upon administration of 3.0mg/kg MDMA. (+/-)-Nantenine displayed high affinity and selectivity for the alpha(1A) adrenergic receptor among several other receptors suggesting that this alpha(1) subtype may be significantly involved in the anti-MDMA effects of the enantiomers. Legendre O, Pecic S, Chaudhary S, Zimmerman SM, Fantegrossi WE, Harding WW. Bioorg Med Chem Lett. 2010; 20(2): 628-631.

A Novel Substituted Piperazine, CM156, Attenuates the Stimulant and Toxic Effects of Cocaine In Mice

In the present study, CM156, a novel compound, was developed and tested for interactions with sigma receptors using radioligand binding studies. It was also evaluated against cocaine-induced effects in behavioral studies. The results showed that CM156 has nanomolar affinities for each of the sigma receptor subtypes in the brain and much weaker affinities for non-sigma binding sites. Pretreatment of male Swiss-Webster mice with CM156, before administering either a convulsive or locomotor stimulant dose of cocaine, led to a significant attenuation of these acute effects. CM156 also significantly reduced the expression of behavioral sensitization and place conditioning evoked by subchronic exposure to cocaine. Xu YT, Kaushal N, Shaikh J, Wilson LL, Mésangeau C, McCurdy CR, Matsumoto RR. J Pharmacol Exp Ther. 2010; 333(2): 491-500.

A Thermally Stable Form of Bacterial Cocaine Esterase: A Potential Therapeutic Agent For Treatment of Cocaine Abuse

Rhodococcal cocaine esterase (CocE) is an attractive potential treatment for both cocaine overdose and cocaine addiction. The most thermostable form of this enzyme to date, CocE-L169K/G173Q were characterized. In vitro kinetic analyses reveal that CocE-L169K/G173Q displays a half-life of 2.9 days at 37 degrees C, which represents a 340-fold improvement over wild type (wt) and is 15-fold greater than previously reported mutants. In vivo rodent studies reveal that intravenous pretreatment with CocE-L169K/G173Q in mice provides protection from cocaine-induced lethality and prevents self-administration of cocaine in a time-dependent manner. Termination of the in vivo effects of CoCE seems to be dependent on, but not proportional to, its clearance from plasma as its half-life is approximately 2.3 h and similar to that of wt CocE (2.2 h).
Brim RL, Nance MR, Youngstrom DW, Narasimhan D, Zhan CG, Tesmer JJ, Sunahara RK, Woods JH. Mol Pharmacol. 2010; 77(4): 593-600.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

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

Human Immunodeficiency Virus Type 1 clade B and C Tat Differentially Induce Indoleamine 2, 3-dioxygenase and Serotonin in Immature Dendritic Cells: Implications for NeuroAIDS

Human immunodeficiency virus type 1 (HIV-1) is commonly associated with immune dysfunctions and the suppression of antigen-presenting cells. This results in immune alterations, which could lead to impaired neuronal functions, such as neuroAIDS. The neurotoxic factor kynurenine (KYN), the rate-limiting enzyme indoleamine 2, 3-dioxygenase (IDO), serotonin (5-HT), and serotonin transporter (5-HTT) may play a role in tryptophan deficiency and serotogenic dysfunction in neuroAIDS. HIV-1 transactivator regulatory protein (Tat) is known to play a major role in immune dysfunction. Previous studies suggest that HIV-1 B and C clades differentially manifest neuronal dysfunctions in the infected host. In the present study an examination was conducted of the effect of HIV-1 B and C clade-derived Tat on IDO and 5-HTT gene and protein expressions by dendritic cells as studied by quantitative polymerase chain reaction (qPCR) and Western blot. In addition, the intracellular IDO expression, IDO enzyme activity, and the levels of 5-HT and KYN were also measured. Results indicate that HIV-1 clade B Tat up-regulates IDO and down-regulates 5-HTT gene and protein expressions. Further, HIV-1 clade B Tat caused a reduction of 5-HT with simultaneous increase in KYN levels as compared to HIV-1 clade C Tat. These studies suggest that HIV-1 clade B and C Tat proteins may play a differential role in the neuropathogenesis of HIV-associated dementia (HAD) or HIV-associated neurocognitive disorder (HAND). Samikkannu T, Rao KV, Gandhi N, Saxena SK, Nair MP. Human immunodeficiency virus type 1 clade B and C Tat differentially induce indoleamine 2,3-dioxygenase and serotonin in immature dendritic cells: Implications for neuroAIDS. J Neurovirol. 2010 Jul 6. [Epub ahead of print].

Randomized, Controlled Clinical Trial of Zinc Supplementation to Prevent Immunological Failure in HIV-infected Adults

Adequate zinc is critical for immune function; however, zinc deficiency occurs in >50% of human immunodeficiency virus (HIV)-infected adults. The authors examined the safety and efficacy of long-term zinc supplementation in relation to HIV disease progression. A prospective, randomized, controlled clinical trial was conducted involving 231 HIV-infected adults with low plasma zinc levels (<0.75 mg/L), who were randomly assigned to receive zinc (12 mg of elemental zinc for women and 15 mg for men) or placebo for 18 months. The primary end point was immunological failure. HIV viral load and CD4(+) cell count were determined every 6 months. Questionnaires, pill counts, and plasma zinc and C-reactive protein levels were used to monitor adherence to

Publications

Staff Highlights

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study supplements and antiretroviral therapy. Intent-to-treat analysis used multiple-event analysis, treating CD4(+) cell count <200 cells/mm(3) as a recurrent immunological failure event. Cox proportional hazard models and the general-linear model were used to analyze morbidity and mortality data. Zinc supplementation for 18 months reduced 4-fold the likelihood of immunological failure, controlling for age, sex, food insecurity, baseline CD4(+) cell count, viral load, and antiretroviral therapy (relative rate, 0.24; 95% confidence interval, 0.10-0.56; P<.002). Viral load indicated poor control with antiretroviral therapy but was not affected by zinc supplementation. Zinc supplementation also reduced the rate of diarrhea by more than half (odds ratio, 0.4; 95% confidence interval, 0.183-0.981; P=.019), compared with placebo. There was no significant difference in mortality between the 2 groups. This study demonstrated that long-term (18-month) zinc supplementation at nutritional levels delayed immunological failure and decreased diarrhea over time. This evidence supports the use of zinc supplementation as an adjunct therapy for HIV-infected adult cohorts with poor viral control. Trial registration. ClinicalTrials.gov identifier: NCT00149552. Baum MK, Lai S, Sales S, Page JB, Campa A. Randomized, controlled clinical trial of zinc supplementation to prevent immunological failure in HIV-infected adults. Clin Infect Dis 2010; 50(12): 1653-1660.

Alcohol Use Accelerates HIV Disease Progression

The effects of alcohol abuse on HIV disease progression have not been definitively established. A prospective, 30-month, longitudinal study of 231 HIV(+) adults included history of alcohol and illicit drug use, adherence to antiretroviral therapy (ART), CD4(+) cell count, and HIV viral load every 6 months. Frequent alcohol users (two or more drinks daily) were 2.91 times (95% CI: 1.23-6.85, p = 0.015) more likely to present a decline of CD4 to < or=200 cells/microl, independent of baseline CD4(+) cell count and HIV viral load, antiretroviral use over time, time since HIV diagnosis, age, and gender. Frequent alcohol users who were not on ART also increased their risk for CD4 cell decline to < or=200 cells/mm(3) (HR = 7.76: 95% CI: 1.2-49.2, p = 0.03). Combined frequent alcohol use with crack-cocaine showed a significant risk of CD4(+) cell decline (HR = 3.57: 95% CI: 1.24-10.31, p = 0.018). Frequent alcohol intake was associated with higher viral load over time (beta = 0.259, p = 0.038). This significance was maintained in those receiving ART (beta = 0.384, p = 0.0457), but not in those without ART. Frequent alcohol intake and the combination of frequent alcohol and crack-cocaine accelerate HIV disease progression. The effect of alcohol on CD4(+) cell decline appears to be independent of ART, through a direct action on CD4 cells, although alcohol and substance abuse may lead to unmeasured behaviors that promote HIV disease progression. The effect of alcohol abuse on viral load, however, appears to be through reduced adherence to ART. Baum MK, Rafie C, Lai S, Sales S, Page JB, Campa A. Alcohol use accelerates HIV disease progression. AIDS Res Hum Retroviruses. 2010; 26(5): 511-518.

Methadone, Buprenorphine, and Street Drug Interactions With Antiretroviral Medications

While street drugs appear unlikely to alter the metabolism of antiretroviral (ARV) medications, several ARVs may induce or inhibit metabolism of various street drugs. However, research on these interactions is limited. Case reports have documented life-threatening overdoses of ecstasy and gamma-hydroxybutyrate after starting ritonavir, an ARV that inhibits several metabolic enzymes. For opioid addiction, methadone or buprenorphine are the treatments of choice. Because a number of ARVs decrease or increase methadone levels, patients should be monitored for methadone withdrawal or toxicity when they start or stop ARVs. Most ARVs do not cause buprenorphine withdrawal or

toxicity, even if they alter buprenorphine levels, with rare exceptions to date including atazanavir/ritonavir associated with significant increases in buprenorphine and adverse events related to sedation and mental status changes in some cases. There are newer medications yet to be studied with methadone or buprenorphine. Further, there are many frequently used medications in treatment of complications of HIV disease that have not been studied. There is need for continuing research to define these drug interactions and their clinical significance. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. Curr HIV/AIDS Rep. 2010; 7(3): 152-160.

A Critical Function of Toll-Like Receptor-3 In the Induction of Anti-Human Immunodeficiency Virus Activities In Macrophages

Summary Toll-like receptor-3 (TLR-3) recognizes double-stranded RNA and induces multiple intracellular events responsible for innate anti-viral immunity against a number of viral infections. Activation of TLR-3 inhibits human immunodeficiency virus (HIV) replication, but the mechanism(s) underlying the action of TLR-3 activation on HIV are largely unknown. The authors demonstrate that treatment of monocyte-derived macrophages with poly I:C, a synthetic ligand for TLR-3, significantly inhibited HIV infection and replication. Investigation of the mechanisms showed that TLR-3 activation resulted in the induction of type I interferon inducible antiviral factors, including APOBEC3G and tetherin, the newly identified anti-HIV cellular proteins. In addition, poly I:C-treated macrophages expressed increased levels of CC chemokines, the ligands for CCR5. Furthermore, TLR-3 activation in macrophages induced the expression of cellular microRNAs (miRNA-28, -125b, -150, -223 and -382), the newly identified intracellular HIV restriction factors. These findings indicate that TLR-3-mediated induction of multiple anti-HIV factors should be beneficial for the treatment of HIV disease where innate immune responses are compromised by the virus. Zhou Y, Wang X, Liu M, Hu Q, Song L, Ye L, Zhou D, Ho W. A critical function of toll-like receptor-3 in the induction of anti-human immunodeficiency virus activities in macrophages. Immunology. 2010 Jul 16. [Epub ahead of print].

Noninvasive Markers of Liver Fibrosis Are Highly Predictive of Liver-Related Death In a Cohort of HCV-Infected Individuals With and Without HIV Infection

Noninvasive markers of liver fibrosis correlate with the stage of liver fibrosis, but have not been widely applied to predict liver-related mortality. The authors assessed the ability of two indices of liver fibrosis, aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and Fib-4, and two markers of extracellular matrix metabolism, hyaluronic acid (HA) and YKL40, to predict liver mortality in a prospective cohort of hepatitis C virus (HCV)-infected individuals with and without HIV coinfection. These were compared with two established prognostic scores, the Child-Pugh-Turcotte (CPT) and model of end-stage liver disease (MELD) scores. A total of 303 subjects, of whom 207 were HIV positive at study entry, were followed up for a mean period of 3.1 years. There were 33 deaths due to liver disease. The ability of each test and score to predict 3-year liver mortality was expressed as the area under the receiver operator curve. The area under the receiver operator curve 95% confidence intervals were: HA 0.92 (0.86-0.96), CPT 0.91 (0.79-0.96), APRI 0.88 (0.80-0.93), Fib-4 0.87 (0.77-0.92), MELD 0.84 (71-0.91). In multivariate analyses HA, APRI, and fib-4 were independent predictors of mortality when included in models with MELD or CPT. Noninvasive markers of liver fibrosis are highly predictive of liver outcome in HCV-infected individuals with and without HIV coinfection. These markers seem to have a prognostic value independent of CPT and MELD. Nunes D, Fleming C, Offner G, Craven D, Fix O, Heeren T, Koziel MJ, Graham C, Tumilty S, Skolnik P, Stuver S, Horsburgh CR Jr, Cotton D. Noninvasive

markers of liver fibrosis are highly predictive of liver-related death in a cohort of HCV-infected individuals with and without HIV infection. Am J Gastroenterol. 2010; 105(6): 1346-1353. Epub 2010 Feb 23.

Decreased Kidney Function in a Community-based Cohort of HIV-Infected and HIV-Negative Individuals in Rakai, Uganda

High prevalences of reduced glomerular filtration rate (GFR) have been reported from HIV-infected individuals in sub-Saharan Africa when initiating antiretroviral therapy. However little is known about natural history HIV-related kidney disease or about background rates of reduced GFR in HIV-negative individuals in this region. The authors estimated GFR from first and last available stored serum samples from 1202 HIV-infected and 664 age-matched and sex-matched HIV-negative individuals in a community-based cohort of HIV-infected and HIV-negative individuals in Rakai, Uganda, between 1994 and 2003. The prevalence and incidence of mildly (60-89 ml.min.1.73 m) and moderately (<60 ml.min.1.73 m) reduced GFR using standard analytical methods was assessed. At baseline, 8.4% of HIV-infected and 4.7% of HIV-negative individuals had mildly or moderately reduced GFR (P = 0.002). During follow-up, the rates of decline to a lower GFR category were of 32.4 and 20.3 per 1000 person-years in HIV-infected and HIV-negative subjects, respectively (P = 0.019). In an unselected community sample of HIV-infected individuals followed in Rakai, Uganda, before the availability of antiretroviral therapy, the prevalence of decreased GFR and the incidence of a decline in GFR category during follow-up were both significantly higher in HIV-infected subjects compared with HIV-negative subjects, although moderately reduced GFR was uncommon. Lucas GM, Clarke W, Kagaayi J, Atta MG, Fine DM, Laeyendecker O, Serwadda D, Chen M, Wawer MJ, Gray RH. Decreased Kidney Function in a Community-based Cohort of HIV-Infected and HIV-Negative Individuals in Rakai, Uganda. J Acquir Immune Defic Syndr. 2010 Jul 6. [Epub ahead of print].

Clinic-Based Treatment of Opioid-Dependent HIV-Infected Patients Versus Referral To An Opioid Treatment Program: A Randomized Trial

Opioid dependence is common in HIV clinics. Buprenorphine-naloxone (BUP) is an effective treatment of opioid dependence that may be used in routine medical settings. The objective of this study was to compare clinic-based treatment with BUP (clinic-based BUP) with case management and referral to an opioid treatment program (referred treatment). The study design was a single-center, 12-month randomized trial. Participants and investigators were aware of treatment assignments. (ClinicalTrials.gov registration number: NCT00130819). The study site was an HIV clinic in Baltimore, Maryland. Patients were 93 HIV-infected, opioid-dependent participants who were not receiving opioid agonist therapy and were not dependent on alcohol or benzodiazepines. Clinic-based BUP included BUP induction and dose titration, urine drug testing, and individual counseling. Referred treatment included case management and referral to an opioid-treatment program. Initiation and long-term receipt of opioid agonist therapy, urine drug test results, visit attendance with primary HIV care providers, use of antiretroviral therapy, and changes in HIV RNA levels and CD4 cell counts. The average estimated participation in opioid agonist therapy was 74% (95% CI, 61% to 84%) for clinic-based BUP and 41% (CI, 29% to 53%) for referred treatment (P < 0.001). Positive test results for opioids and cocaine were significantly less frequent in clinic-based BUP than in referred treatment, and study participants receiving clinic-based BUP attended significantly more HIV primary care visits than those receiving referred treatment. Use of antiretroviral therapy and changes in HIV RNA levels and CD4 cell counts did not differ between the 2 groups. This was a small single-center study, follow-up was only moderate, and the study groups were

unbalanced in terms of recent drug injections at baseline. Management of HIV-infected, opioid-dependent patients with a clinic-based BUP strategy facilitates access to opioid agonist therapy and improves outcomes of substance abuse treatment. Lucas GM, Chaudhry A, Hsu J, Woodson T, Lau B, Olsen Y, Keruly JC, Fiellin DA, Finkelstein R, Barditch-Crovo P, Cook K, Moore RD. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized trial. Ann Intern Med. 2010; 152(11): 704-711.

HIV Risk Behavior Before and After HIV Counseling and Testing In Jail: A Pilot Study

Incarceration represents an opportunity to deliver HIV counseling and testing (C&T) services to persons at increased risk of infection. However, jails can be chaotic with rapid turnover of detainees. A pilot study to investigate the feasibility of comparing the effect of different approaches to HIV C&T in jail on subsequent HIV risk behaviors among persons testing HIV negative was conducted. Consecutive cohorts of new detainees were recruited with 132 subjects completing standard HIV C&T and 132 subjects completing rapid testing with an individualized counseling session. Risk behavior was assessed and compared at baseline and 6 weeks after jail release. Among the 264 male participants, pre-incarceration substance use and sexual risk were common. The follow-up visit was completed by 59% of eligible participants. There were no differences in post-release HIV risk behavior between the 2 arms but there was an overall decrease in risk behavior after jail release for the cohort. In addition, all participants in the rapid arm received rapid HIV test results compared with participants receiving 28% of conventional test results. Jail incarceration represents an important public health opportunity to deliver HIV C&T. This study demonstrated (1) feasibility in delivering rapid HIV testing combined with individualized counseling to jail detainees, (2) improved test result delivery rates, and (3) success with evaluating risk behaviors during the transition from jail to the community. Further research is needed to determine the optimal approach to HIV C&T in jail with the goal of increasing awareness of HIV serostatus and decreasing HIV risk behavior. Beckwith CG, Liu T, Bazerman LB, DeLong AK, Desjardins SF, Poshkus MM, Flanigan TP. HIV Risk Behavior Before and After HIV counseling and testing in Jail: a pilot study. Acquired Immune Defic Syndr. 2010 Apr 1:53(4): 485-490.

Virology and Clinical Sequelae of Drug-Resistant HBV In HIV-HBV-Coinfected Patients On Highly Active Antiretroviral Therapy

Several of the nucleoside/nucleotide analogues used to treat HIV also inhibit HBV replication, with lamivudine being the oldest of this group. Thus, prior to licensing of tenofovir, many HIV-HBV-coinfected individuals received lamivudine as the only drug active against HBV as part of an anti-HIV regimen, which set the stage for the emergence of drug-resistant HBV. In coinfected persons, lamivudine-resistant HBV develops more rapidly than in HBV-monoinfected persons, but it is not known if this is true for the newer agents. Owing to overlapping reading frames of the HBV polymerase and surface antigens, drug-resistant changes in HBV Pol can lead to mutations in the envelope. This review discusses studies of drug-resistant HBV in HIV-infected persons including drug-resistant mutations that have been identified and clinical sequelae of these mutations. Thio CL. Virology and clinical sequelae of drug-resistant HBV in HIV-HBV-coinfected patients on highly active antiretroviral therapy. Antivir Ther. 2010; 15(3 Pt B): 487-491.

Hepatitis C Virus Risk Behaviors Within the Partnerships of Young Injecting Drug Users

Young injection drug users (IDU) are at high risk for hepatitis C virus (HCV). Assessments have been conducted to evaluate the implications of partner perceptions regarding their injecting partner. An HCV positive status was associated with decreased odds of engaging in receptive needle/syringe sharing (RNS) or ancillary equipment sharing (AES) with that partner, a cross sectional study between 2003 to 2007 in San Francisco, 212 participant (under age 30) IDUs who were HCV antibody negative reported on 492 injecting partnerships measured by self-report regarding perceptions of receptive (RNS) or ancillary (AES) sharing. The odds of engaging in RNS were significantly lower for relationships in which the participant reported that his/her partner was HCV positive; an association that was attenuated when adjusted for reusing one's own needle/syringe (adjusted OR 0.57; 95% CI 0.28-1.15) (odds ratio [OR] 0.49; 95% confidence interval [CI] 0.25-0.95). The odds of engaging in AES were lower for participants who did not know the HCV status of their partner, only among non-sexual partnerships (OR 0.47; 95% CI 0.29-0.76). A partner's perception that their partner is HCV positive was associated with decreased RNS, increased HCV testing and thus, partner disclosure may be warranted. Perception of one's AES was common and was decreased only among non-sexual partnerships in which the HCV status of the partner was unknown. These assessments show the value of interventions to reduce AES in young IDU and the need that they be widespread. Hahn JA, Evans JL, Davidson PJ, Lum PJ, Page K. Hepatitis C Virus Risk behaviors within the partnerships of young injecting drug users. Addiction. 2010; 105(7): 1254-1264.

Are Young Injection Drug Users Ready and Willing To Participate In Preventive HCV Vaccine Trials?

The participation of high risk HCV seronegative injection drug users (IDUs) will be needed to evaluate the efficacy of preventive HCV vaccines. To guide clinical trial planning, these investigators have assessed willingness of young IDU in San Francisco to participate in HCV vaccine efficacy trials and have evaluated knowledge of vaccine trial concepts: placebo, randomization and blinding. During 2006 and 2007, a total of 67 participants completed the survey. A substantial proportion (88%) would definitely (44%) or probably (44%) be willing to participate in a randomized trial, but knowledge of vaccine trial concepts was low. Reported willingness to participate in an HCV vaccine trial decreased with increasing trial duration, with 67% of participants surveyed willing to participate in a trial of 1 year duration compared to 43% of participants willing to participate in a trial of 4 years duration. Willingness to enroll in HCV vaccine trials was higher in young IDU than reported by most at-risk populations in HIV vaccine trials. Educational strategies will be needed to ensure understanding of key concepts prior to implementing HCV vaccine trials. Levy V, Evans JL, Stein ES, Davidson PJ, Lum PJ, Hahn JA, Page K. Are young injection drug users ready and willing to participate in preventive HCV vaccine trials? Vaccine. 2010 Jul 16.

Dissolution of Arterial Platelet Thrombi In Vivo With A Bifunctional Platelet Gpiiia49-66 Ligand Which Specifically Targets the Platelet Thrombus

Patients with HIV-1 immune-related thrombocytopenia have a unique antibody (Ab) against integrin GPIIIa49-66 capable of inducing oxidative platelet fragmentation via Ab activation of platelet NADPH oxidase and 12-lipoxygenase releasing reactive oxygen species. Using a phage display single-chain antibody (scFv) library, a novel human monoclonal scFv Ab against GPIIIa49-66 (named A11) capable of inducing fragmentation of activated platelets was developed. In this study, the authors investigated the in vivo use of A11. The authors show that A11 does not induce significant thrombocytopenia or inhibit platelet function. A11 can prevent the cessation of carotid artery flow produced by induced artery injury and dissolve the induced thrombus 2 hours after

cessation of blood flow. In addition, A11 can prevent, as well as ameliorate murine middle cerebral artery stroke, without thrombocytopenia or brain hemorrhage. To further optimize the anti-thrombotic activity of A11, the authors produced a bifunctional A11-plasminogen 1st kringle agent (SLK), which homes to newly deposited fibrin strands within and surrounding the platelet thrombus, reducing effects on non-activated circulating platelets. Indeed, SLK is able to completely reopen occluded carotid vessels 4 hours after cessation of blood flow, whereas A11 had no effect at 4 hours. Thus, a new anti-thrombotic agent was developed for platelet thrombus clearance. Zhang W, Li YS, Nardi MA, Dang S, Yang J, Ji Y, Li Z, Karpatkin S, Wisniewski T. Dissolution of arterial platelet thrombi in vivo with a bifunctional platelet GPIIIa49-66 ligand which specifically targets the platelet thrombus. Blood. 2010 Jun 4. [Epub ahead of print].

Magnetic Nanoformulation of Azidothymidine 5'-triphosphate for Targeted Delivery Across the Blood-Brain Barrier

Despite significant advances in highly active antiretroviral therapy (HAART), the prevalence of neuroAIDS remains high. This is mainly attributed to inability of antiretroviral therapy (ART) to cross the blood-brain barrier (BBB), thus resulting in insufficient drug concentration within the brain. Therefore, development of an active drug targeting system is an attractive strategy to increase the efficacy and delivery of ART to the brain. The authors report herein development of magnetic azidothymidine 5'-triphosphate (AZTTP) liposomal nanoformulation and its ability to transmigrate across an in vitro BBB model by application of an external magnetic field. The authors hypothesize that this magnetically guided nanoformulation can transverse the BBB by direct transport or via monocyte-mediated transport. Magnetic AZTTP liposomes were prepared using a mixture of phosphatidyl choline and cholesterol. The average size of prepared liposomes was about 150 nm with maximum drug and magnetite loading efficiency of 54.5% and 45.3%, respectively. Further, magnetic AZTTP liposomes were checked for transmigration across an in vitro BBB model using direct or monocyte-mediated transport by application of an external magnetic field. The results show that apparent permeability of magnetic AZTTP liposomes was 3-fold higher than free AZTTP. Also, the magnetic AZTTP liposomes were efficiently taken up by monocytes and these magnetic monocytes showed enhanced transendothelial migration compared to normal/non-magnetic monocytes in presence of an external magnetic field. Thus, the authors anticipate that the developed magnetic nanoformulation can be used for targeting active nucleotide analog reverse transcriptase inhibitors to the brain by application of an external magnetic force and thereby eliminate the brain HIV reservoir and help to treat neuroAIDS. Saiyed ZM, Gandhi NH, Nair MP. Magnetic nanoformulation of azidothymidine 5'-triphosphate for targeted delivery across the blood-brain barrier. Int J Nanomedicine. 2010; 5: 157-166.

Pubertal Timing and Smoking Initiation In Adolescent Females: Differences By Race

The purpose of this study was to examine whether (a) early pubertal timing effects on smoking onset existed for both White and Black girls and (b) whether the association between pubertal timing and smoking onset was moderated by race. Participants included 264 girls (14.9 +/- 2.2 years, 164 White, and 100 Black) at the baseline report of a longitudinal study of whom 153 reported smoking and age at first cigarette. Kaplan-Meier analysis stratified by racial group showed a significant difference between the pubertal timing groups for Black girls only. After accounting for covariates using Cox regression, there was no significant interaction between pubertal timing and racial group. There was a main effect of pubertal timing indicating that late maturers were at significantly lower risk for smoking initiation compared with

the early and on-time groups, but the early and on-time groups were not significantly different from each other. Results point to equal risk of early smoking onset for early and on-time maturers of both racial groups, indicating the need for smoking prevention in early adolescence for both White and Black females. Negriff S, Dorn LD, Huang B. Pubertal timing and smoking initiation in adolescent females: differences by race. Nicotine Tob Res. 2010; 12(7): 748-755. Epub 2010 May 19.

Association of Anxiety and Depressive Symptoms and Adiposity Among Adolescent Females, Using Dual Energy X-Ray Absorptiometry

The purpose of this study is to evaluate the association between anxiety and depressive symptoms and obesity among adolescent females using objective measures of adiposity and evaluate for moderating effects of race and age. This is a cross-sectional analysis of 198 females aged 11, 13, 15, and 17 years (mean = 14.6, standard deviation = 2.2). Adiposity measures include BMI, BMI Z score, percentage body fat from dual energy X-ray absorptiometry (DXA), and fat distribution (fat mass upper vs lower body regions from DXA). Symptoms of anxiety are measured with the State-Trait Anxiety Inventory and depressive symptoms with the Children's Depression Inventory. Trait anxiety and depressive symptoms are positively associated with BMI and percentage body fat. No interaction of anxiety/ depressive symptoms with race or age on measures of adiposity was detected. Symptoms of anxiety and depression are associated with percentage body fat among adolescent females, linking psychological distress with a physiological measure of adiposity. Hillman JB, Dorn LD, Bin Huang. Association of anxiety and depressive symptoms and adiposity among adolescent females, using dual energy X-ray absorptiometry. Clin Pediatr (Phila). 2010; 49(7): 671-677. Epub 2010 Mar 31.

Iron Homeostasis and the Inflammatory Response

Iron and its homeostasis are intimately tied to the inflammatory response. The adaptation to iron deficiency, which confers resistance to infection and improves the inflammatory condition, underlies what is probably the most obvious link: the anemia of inflammation or chronic disease. A large number of stimulatory inputs must be integrated to tightly control iron homeostasis during the inflammatory response. In order to understand the pathways of iron trafficking and how they are regulated, this article presents a brief overview of iron homeostasis. A major focus is on the regulation of the peptide hormone hepcidin during the inflammatory response and how its function contributes to the process of iron withdrawal. The review also summarizes new and emerging information about other iron metabolic regulators and effectors that contribute to the inflammatory response. Potential benefits of treatment to ameliorate the hypoferremic condition promoted by inflammation are also considered. Wessling-Resnick M. Iron Homeostasis and the Inflammatory Response. Annu Rev Nutr. 2010; 30: 105-122.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - Services Research

New Estimates of Crime Costs Available

Understanding the costs to society of criminal behavior is essential for economic evaluations of drug abuse services and policies because of the strong estimated association between drug use and crime. This paper combines cost-of-illness and jury compensation methods using the latest available data from a variety of sources, including National Criminal Victimization Survey, the FBI's Uniform Crime Reports and National Incident-Based Reporting System, the Current Population Survey, as well as other published data to update these estimates for 13 common offenses. Murder was the most costly crime on a per offense basis, with a cost of $8.9 million. It was followed by rape/sexual assault ($240,776), aggravated assault ($107,020), robbery ($42,310), arson ($21,103), motor vehicle theft ($10,772), stolen property ($7,974), household burglary ($6,462), embezzlement ($5,480), forgery and counterfeiting ($5,265), fraud ($5,032), vandalism ($4,860), and larceny/theft ($3,532). McCollister K, French M, Fang H. The Cost Of Crime To Society: New Crime-Specific Estimates For Policy And Program Evaluation. Drug Alcohol Depend. 2010; 108(1-2): 98-109.

Termination of Federal Disability Benefits Had Few Effects on National Survey Respondents with Likely Addictive Disorders

Data on 156,000 respondents to the 1994-2002 National Household Surveys on Drug Use/National Surveys on Drug Use and Health (NHSDA/NSDUH) were used to examine the effect of the 1997 termination of Supplemental Security Income for those with addictive disorders on public program (SSI and Welfare) participation, labor market participation, health insurance status, and health care utilization (emergency use, inpatient hospitalizations, psychiatric visits, psychiatric admissions). Subjects selected were those age 18-64 years with less than 16 years of education to reflect the population that is eligible for SSI and Welfare. About 20% reported substance use and associated symptoms consistent with an addictive disorder. Multivariate Log-linear and logistic regressions were estimated using a difference-in-difference-in-difference approach with propensity score adjustments to estimate the differences in the probability of these outcomes between those with likely addictions and non-substance abusers in the period before and after the termination policy went into effect. This method is an improvement on the extant literature because unlike simple pre/post- designs it can account for secular changes between the pre- and post- years that might affect the dependent variables (e.g. economic conditions and employment). Results reveal that there was an 81% (SE=.349) reduction in the use of SSI shortly after the termination. Welfare participation was not immediately affected but had dropped by 31% (SE=.115) by 1999. The probability of employment also increased significantly in the short run for

Publications

Staff Highlights

Grantee Honors

individuals with addictive disorders, but the effect attenuated over time. There were no effects on health insurance status or healthcare utilization through 2002. Chatterji P, Meara E. Consequences Of Eliminating Federal Disability Benefits For Substance Abusers. J Health Econ. 2010; 29(2): 226-240.

Study Measures Costs of Gender-Specific, Peer-Delivered HIV-Prevention Interventions for Drug Abusing Women

Detailed information on the costs of providing one of three HIV-prevention interventions — the NIDA Cooperative Agreement Standard Intervention (SI), SI + a field-based well woman exam (WWE), and SI+WWE+ four education sessions (4ES) — for drug abusing women were measured along side a clinical trial comparing their effectiveness. Subjects were 501 women age 18 years and older who had reported sexual activity in the last four months, were using cocaine, heroin, amphetamines, or other injection drugs, and who had resided in the St. Louis metropolitan area during the study period (2000-2006). Societal and provider costs were measured using standard micro-costing techniques in which a comprehensive and detailed list of resources used to produce each intervention is identified, measured, and valued in dollar terms. Provider costs included variable cost items such as materials, tests, patient incentives, personnel costs, and fixed cost items such as building costs. Costs to society include those costs as well as patient travel and time costs. Average total costs per patient were $227.28 for the SI, 144.45 for the WWE, and $942.30 for the 4ES. Sensitivity analyses revealed that per patient costs varied according to the assumption used. For example, SI might cost as low as $98 per patient if rapid HIV tests were used instead of the enzyme immunoassay test, and 4ES costs could be as low as $549 if building rental and utility costs were half as much as those observed in the study. Ruger J, Ben Abdallah A, Cottler L. Costs Of HIV Prevention Among Out-Of-Treatment Drug-Using Women: Results Of A Randomized Controlled Trial. Public Health Rep. 2010; 125 (Suppl 1): 83-94.

Craving Opioid Medication Predicts Aberrant Drug Behavior in Chronic Pain Patients

This study was performed to examine the relationship between the self-report of opioid medication craving and subsequent misuse of opioid medications among chronic pain patients. Six hundred thirteen adult patients from 5 regional pain treatment clinics, who were prescribed opioid medication for chronic noncancer pain were asked how often they have felt a craving for their medication on a scale from 0=never to 4=very often. All participants completed a series of baseline questionnaires. After 6 months the participants were administered a structured prescription drug use interview (Prescription Drug Use Questionnaire), and submitted a urine sample for toxicology assessment. Their treating physicians also completed a substance misuse behavior checklist (Prescription Opioid Therapy Questionnaire). It was found that 337 participants (55.0%) reported that they never felt a craving for their medication, whereas 276 (45.0%) reported some degree of craving their medication (seldom to very often). Those who reported craving their medication were significantly more often male ($P<0.01$), unmarried ($P<0.05$), had lower scores on social desirability ($P<0.001$), and had been prescribed opioids for a longer time ($P<0.05$) than those who did not report craving medication. At 6-month follow-up, those who reported craving their medication showed higher scores on the Prescription Drug Use Questionnaire ($P<0.001$), had a higher incidence of physician-rated aberrant drug behavior on the Prescription Opioid Therapy Questionnaire ($P<0.05$), showed a higher frequency of abnormal urine toxicology screens ($P<0.001$), and more often had a positive Aberrant Drug Behavior Index ($P<0.001$). These results suggest that self-reported craving is a potential marker for identification of those at risk for opioid medication misuse. Wasan A, Butler S, Budman S, Fernandez K, Weiss R, Greenfield S, Jamison R.

Does Report Of Craving Opioid Medication Predict Aberrant Drug Behavior Among Chronic Pain Patients? Clin J Pain. 2009; 25(3): 193-198.

Screening for Atypical Suicide Risk Among People Presenting to Alcohol and Other Drug Treatment

Symptoms of internalizing disorders (depression, anxiety, somatic, trauma) are the major risk factors for suicide. Atypical suicide risk is characterized by people with few or no symptoms of internalizing disorders. In persons screened at intake to alcohol or other drug (AOD) treatment, this research examined whether person fit statistics would support an atypical subtype at high risk for suicide that did not present with typical depression and other internalizing disorders. Symptom profiles of the prototypical, typical, and atypical persons, as defined using fit statistics, were tested on 7408 persons entering AOD treatment using the Global Appraisal of Individual Needs (GAIN; Dennis et al., 2003a,b). Participants were 67% male, 45% white, and 73% under age 18 (mean = 19.9, SD = 8.9). In the past year, 86% had substance disorders, 51% had internalizing disorders (e.g., somatic, depression, anxiety, trauma, suicide), and 59% had externalizing disorders (ADHD, conduct disorders), Of those with suicide symptoms, the findings were as expected with the atypical group being higher on suicide and lower on symptoms of internalizing disorders. In addition, the atypical group was similar or lower on substance problems, symptoms of externalizing disorders, and crime and violence. The use of person fit statistics may be able to rapidly red-flag persons at high risk for suicide who are less likely to be identified using the usual screening methods alone. Person fit statistics were useful in identifying persons with atypical suicide profiles and in enlightening aspects of existing theory concerning atypical suicidal ideation. Conrad K, Bezruczko N, Chan Y, Riley B, Diamond G, Dennis M. Screening For Atypical Suicide Risk With Person Fit Statistics Among People Presenting To Alcohol And Other Drug Treatment. Drug Alcohol Depend. 2010; 106(2-3): 92-100.

Measuring Patient Satisfaction During Treatment May Improve Retention

Patient satisfaction surveys, widely used in health care delivery systems, may provide useful data for improving patient retention and outcomes. This study examined the relationship between methadone patients' treatment satisfaction at three months post-admission and their 3-month treatment outcomes and 12-month treatment retention. The study sample consisted of 283 opioid-addicted individuals newly enrolling in one of six Baltimore area methadone maintenance treatment programs: 48% were female, 77% were categorized as African American and the mean age was 42 years. All of the participants had reported using opiates, 70% reported using cocaine, and 24% reported using marijuana in the 30 days prior to treatment entry. New methadone treatment admissions were assessed at 3 months post-admission for satisfaction with their counselors and programs. Correlations examined the relationship between 3-month satisfaction and Addiction Severity Index (ASI) scores. Regression analysis assessed the relationship between satisfaction and drug testing at 3 months and was used to predict whether participants were retained in treatment at 12 months. Findings from this study suggest a positive association between patient satisfaction and measures of treatment outcome and retention. Participants who were more satisfied with their counselors and programs had lower Drug and Legal ASI composite scores at 3 months. Participants who were more satisfied with their programs remained in treatment for at least 12 months. The authors suggest that methadone treatment programs should consider administering measures of treatment satisfaction to their patients at 3 months post-admission to identify patients with low satisfaction scores who may be at risk for prematurely leaving treatment. Measuring patient satisfaction during treatment may help programs

meet patients' needs and improve retention. More research is needed to examine how patient satisfaction can be integrated into drug treatment program practice. Kelly S, O 'Grady K, Brown B, Mitchell S, Schwartz R. The Role of Patient Satisfaction in Methadone Treatment. Am J Drug Alcohol Abuse. 2010; 36(3): 150-154.

Social Support May Be An Important Factor in Treatment Entry

Social support has been found to be important in influencing entry into drug-addiction treatment, as well as for retention in treatment and ultimate recovery. This study was conducted to determine the psychometric properties of a measure of social support, the Community Assessment Inventory (CAI), and to examine the role of social support in recovery. The CAI and the Addiction Severity Index (ASI) were administered to 196 opioid-dependent adults in (n = 135) or out of (n = 61) methadone treatment in Baltimore, Maryland, between 2004 and 2006. Sixty percent of the total sample was male, 74% was African American, and the mean age was 41 years old. Just over half the total sample had been employed at least part-time during most of the three years prior to the baseline interview. Analyses focused on six research questions: 1) What are the relationships among the CAI scales at baseline in the total sample?; 2) What are the relationships between CAI scales at baseline and CAI scales at the 3-month assessment for the in-treatment group?; 3) What are the relationships between baseline CAI scales and baseline Addiction Severity Index (ASI) (26) composite scores in the total sample?; 4) Are there significant differences in levels of support at baseline between in- and out-of-treatment opioid-addicted individuals?; 5) What are the relationships between CAI scales at baseline and drug use and illegal activity at the 3-month follow-up for the in-treatment group?; and 6) Are there significant changes over time in perceived levels of support by individuals in treatment? Baseline CAI scale scores indicated a generally high level of internal consistency (alpha scores). Pearson correlations showed that the scales were stable and had good discriminate validity with the ASI composite scores. One-way analysis of variance indicated that in-treatment participants reported significantly more support at baseline than out-of-treatment participants. An important finding in this study was that individuals who were in treatment, as compared with those who were out of treatment, perceived significantly greater support from their partners or family with whom they lived, family members outside the home, friends, and their communities at treatment entry. This study's findings indicate the CAI may be a useful measure of social support and that such support is an important factor in treatment entry. Kelly S, O 'Grady K, Schwartz R, Peterson J, Wilson M, Brown B. The Relationship of Social Support To Treatment Entry And Engagement: The Community Assessment Inventory. Subst Abus. 2010; 31(1): 43-52.

Factors Associated with Drug Dealing Differ between White and Black Youths

Data on 13,706 Black and White youths 12-17 years of age who responded to the 2006 National Survey on Drug Use and Health were used to examine the associations between drug dealing and the use of drugs, drug availability, and the family's receipt of public assistance, all measured in the past 12 months. Separate backward stepwise logistic regressions were estimated by race to assess the factors that had the strongest associated with drug dealing. Among White youths, males were more likely to report drug dealing (AOR = 3.3; 95% CI=2.30, 4.75), as were those who used marijuana (13.9; 8.32-23.19), cocaine (1.8; 1.06-2.97), and hallucinogens (1.9; 1.26-2.86); who misused prescription drugs (2.6; 1.78-3.79), perceived easy availability of cocaine (1.5; 1.06-2.27), and had been approached by someone selling drugs (3.4; 2.39-4.81); and whose families were not on public assistance (0.3, 0.12-0.67). Among Blacks, males (3.7; 1.66—8.13), those using marijuana (12.6; 6.85-

23.27), and those who perceived easy availability of crack (1.9; 1.02-3.41) and marijuana (5.0; 1.70-14.62), were more likely to sell drugs. Floyd L, Alexandre P, Hedden S, Lawson A, Latimer W, Giles N. Adolescent Drug Dealing And Race/Ethnicity: A Population-Based Study Of The Differential Impact Of Substance Use On Involvement In Drug Trade. Am J Drug Alcohol Abuse. 2010; 36(2): 87-91.

Identifying Service Needs Across Recovery Stages to Inform Service Development

Substance use disorders (SUD) are, for many, chronic conditions that are typically associated with severe impairments in multiple areas of functioning. "Recovery" from SUD is, for most, a lengthy process; improvements in other areas of functioning do not necessarily follow the attainment of abstinence. The current SUD service model providing intense, short-term, symptom-focused services is ill-suited to address these issues. A recovery-oriented model of care is emerging, which provides coordinated recovery-support services using a chronic-care model of sustained recovery management. Information is needed about substance users' priorities, particularly persons in recovery who are not currently enrolled in treatment, to guide the development of recovery-oriented systems. As a first step in filling this gap, the authors present qualitative data on current life priorities among a sample of individuals that collectively represent successive recovery stages (N = 356). The sample consisted of 56% men, 62% African American, and 19% were of Hispanic origin. The average age was 43: Participants ranged in age from 19 to 65 years. Educational attainment averaged 12 years: Nineteen percent were employed part-time, 21% fulltime; 60% cited government or other benefits (e.g., veteran's pension) as their primary source of income. Nearly one quarter (22%) reported being seropositive for HIV antibodies and 30% for hepatitis C. Findings suggest that many areas of functioning remain challenging long after abstinence is attained, most notably employment and education, family/social relations, and housing. Although the ranking of priorities changes somewhat across recovery stages, employment is consistently the second most important priority, behind working on one's recovery. Findings suggest that individuals in recovery continue to experience many difficulties and to need support in many areas of functioning long after abstinence has been reached. Laudet A, White W. What Are Your Priorities Right Now? Identifying Service Needs Across Recovery Stages To Inform Service Development. J Subst Abuse Treat. 2010; 38(1): 51-59.

Psychiatric Disorders in Smokers Seeking Treatment for Tobacco Dependence and Relationship to Cessation

The goal of the present research is to examine the relationship of psychiatric disorders to tobacco dependence and cessation outcomes. Data were collected from 1,504 smokers (58.2% women; 83.9% White; mean age = 44.67 years, SD = 11.08) making an aided smoking cessation attempt as part of a clinical trial in the mid-west. Psychiatric diagnoses were determined with the Composite International Diagnostic Interview structured clinical interview. Tobacco dependence was assessed with the Fagerstršm Test of Nicotine Dependence (FTND) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM). Psychiatric diagnostic groups included those who were never diagnosed, those who had ever been diagnosed (at any time, including in the past year), and those with past-year diagnoses (with or without prior diagnosis). Some diagnostic groups had lower follow-up abstinence rates than did the never diagnosed group ($p < .05$). At 8 weeks after quitting, strong associations were found between cessation outcome and both past-year mood disorder and ever diagnosed anxiety disorder. At 6 months after quitting, those ever diagnosed with an anxiety disorder (OR = .72, $p = .02$) and those ever diagnosed with more than one psychiatric diagnosis (OR = .74, $p = .03$) had

lower abstinence rates. The diagnostic categories did not differ in smoking heaviness or the FTND, but they did differ in dependence motives assessed with the WISDM. This study indicates that information on recent or lifetime psychiatric disorders may help clinicians gauge relapse risk and may suggest dependence motives that are particularly relevant to affected patients. These findings also illustrate the importance of using multidimensional tobacco dependence assessments. Piper M, Smith S, Schlam T, Fleming M, Bittrich A, Brown J, Leitzke C, Zehner M, Fiore M, Baker T. Psychiatric Disorders In Smokers Seeking Treatment For Tobacco Dependence and Relationship To Cessation. J Consult Clin Psychol. 2010; 78(1): 13-23.

Persistent Gaps in Provision of HIV Counseling and Testing in Substance Abuse Treatment

This article examines the extent to which U.S. outpatient substance abuse treatment (OSAT) facilities provided HIV counseling and testing (C&T) to clients between 1995 and 2005, and the organizational and client characteristics associated with OSAT facilities' provision of HIV C&T. Data were collected from a nationally representative sample of outpatient treatment facilities in 1995 (n = 618), 2000 (n = 571), and 2005 (n = 566). Results show that in 1995, 74% of programs provided any HIV testing, but only an average of 26.8% of clients in these programs received HIV C&T. By 2005, services were offered in 82% of programs, but only 28.8% of clients, on average, received C&T. Further, results from random-effects interval regression analysis show that C&T is especially widespread in public and nonprofit facilities, in methadone facilities, and in units that serve injection drug users. HIV C&T was also more widespread in units that employed formal intake protocols. Despite widespread efforts to increase HIV C&T services in OSAT care, only a small and stable minority of clients received these services over the decade studied. The authors suggest that program adoption of formal intake procedures may provide one vehicle to increase provision of C&T services. Pollack HA, D'Aunno T. HIV Testing And Counseling In The Nation's Outpatient Substance Abuse Treatment System, 1995-2005. J Subst Abuse Treat. 2010; 38: 307-316.

Effect of Incarceration History on Outcomes of Primary Care Office-Based Buprenorphine/ Naloxone

Behaviors associated with opioid dependence often involve criminal activity, which can lead to incarceration. The impact of a history of incarceration on outcomes in primary care office-based buprenorphine/naloxone is not known. The purpose of this study is to determine whether having a history of incarceration affects response to primary care office-based buprenorphine/ naloxone treatment. In this post hoc secondary analysis of a randomized clinical trial, investigators compared demographic, clinical characteristics, and treatment outcomes among 166 participants receiving primary care office-based buprenorphine/naloxone treatment stratifying on history of incarceration. This study shows that participants with a history of incarceration have similar treatment outcomes with primary care office-based buprenorphine/naloxone than those without a history of incarceration (consecutive weeks of opioid-negative urine samples, 6.2 vs. 5.9, p = 0.43; treatment retention, 38% vs. 46%, p = 0.28). This study shows that a prior history of incarceration does not appear to impact primary care office-based treatment of opioid dependence with buprenorphine/naloxone. Wang EA, Moore BA, Sullivan LE, Fiellin DA. Effect Of Incarceration History On Outcomes Of Primary Care Office-Based Buprenorphine/Naloxone. J Gen Intern Med. 2010; 1-5.

Unobserved Versus Observed Office Buprenorphine/Naloxone Induction: A Pilot Randomized Clinical Trial

Physician adoption of buprenorphine treatment of opioid dependence may be limited in part by concerns regarding the induction process. Although national guidelines recommend observed induction, some physicians utilize unobserved induction outside the office. The aim of this pilot randomized clinical trial was to assess preliminary safety and effectiveness of unobserved versus observed office buprenorphine/naloxone induction among patients entering a 12-week primary care maintenance study. Participants (N=20) with DSM-IV opioid dependence were randomly assigned to unobserved or office induction, stratifying by past buprenorphine use. All patients received verbal and written instructions. A withdrawal scale was used during initiation and to monitor treatment response. Clinic visits occurred weekly for 4 weeks then decreased to monthly. The primary outcome, successful induction one week after the initial clinic visit, was defined as retention in buprenorphine/naloxone treatment and being withdrawal free. Secondary outcomes included prolonged withdrawal beyond 2 days after medication initiation and stabilization at week 4, defined as being in treatment without illicit opioid use for the preceding 2 weeks. Outcome results were similar in the two groups: 6/10 (60%) successfully inducted in each group, 3/10 (30%) experienced prolonged withdrawal and 4/10 (40%) stabilized by week 4. These pilot study results suggest comparable safety and effectiveness of unobserved and office induction and point toward utilization of non-inferiority design during future definitive protocol development. By addressing an important barrier for physician adoption, further validation of the unobserved buprenorphine induction method will hopefully lead to increased availability of effective opioid dependence treatment. Gunderson E, Wang X, Fiellin D, Bryan B, Levin F. Unobserved Versus Observed Office Buprenorphine/Naloxone Induction: A Pilot Randomized Clinical Trial. Addict Behav. 2010; 35(5): 537-540.

A Brief Alcohol Intervention for Hazardously Drinking Incarcerated Women

The purpose of this study is to test the hypothesis that among hazardously drinking incarcerated women who are returning to the community, a brief alcohol intervention will result in less alcohol use at follow-up relative to standard of care. Eligible participants endorsed hazardous alcohol consumption-four or more drinks at a time on at least 3 separate days in the previous 3 months or a score of 8 or above on the Alcohol Use Disorders Identification Test. Participants were randomized to either an assessment-only condition or to two brief motivationally focused sessions, the first delivered during incarceration, the second 1 month later after community re-entry. Participants recalled drinking behaviors at 3 and 6 months after the baseline interview using a 90-day time-line follow-back method. The 245 female participants averaged 34 years of age, and were 71% Caucasian. The mean percentage of alcohol use days in the 3 months prior to incarceration was 51.7% and heavy alcohol use days were 43.9%. Intervention effects on abstinent days were statistically significant at 3 months (odds ratio = 1.96, 95% confidence interval 1.17, 3.30); the percentage of days abstinent was 68% for those randomized to intervention and 57% for controls. At 6 months the effect of the intervention was attenuated and no longer statistically significant. This paper shows that among incarcerated women who reported hazardous drinking, a two-session brief alcohol intervention increased abstinent days at 3 months, but this effect decayed by 6 months. Study participants continued to drink heavily after return to the community. More intensive intervention pre-release, and after re-entry may benefit hazardously drinking incarcerated women. Stein M, Caviness C, Anderson B, Hebert M, Clarke J. A Brief Alcohol Intervention For Hazardously Drinking Incarcerated Women. Addiction. 2010; 105(3): 466-475.

A Behavioral Decision Model Testing the Association of Marijuana

Use and Sexual Risk Behavior in Young Adult Women

The authors created a model conceptualizing sexual risk as a series of discrete event-specific behavioral decisions and tested the hypothesis that marijuana use was associated with increased sexual risk-taking. Three hundred eight marijuana-using women aged 18-24 completed a 90-day time-line-follow-back to assess sexual behaviors and marijuana use. A sequential logit model estimated the effect of marijuana use on the likelihood of being sexually active, partner type when sexually active, and condom nonuse conditional on partner type. Participants had a mean age of 20.4 years, with 67% Caucasian. Marijuana use was associated with an increased likelihood of being sexually active (OR 1.6; 95% CI 1.33, 1.93) and with condom nonuse when sexually active with casual partners (OR 2.58; 95% CI 1.1, 6.09). This behavioral decision model identified where marijuana use was associated with sexual risk, and suggests where interventions designed to reduce risk may have an impact. Stein MD, Anderson BJ. A Behavioral Decision Model Testing the Association of Marijuana Use and Sexual Risk in Young Adult Women. AIDS Behav. 2010: 1-10.

Educational Outreach to Improve Emergency Medical Services Systems of Care for Stroke in Montana

The goal of this study was to improve stroke knowledge, identification, and acute care among first responders (FRs) and emergency medical technicians (EMTs) through educational outreach and support. Beginning in 2006, the Montana Stroke Initiative implemented outreach to FRs and EMTs and emergency medical services (EMS) statewide. Cross-sectional telephone surveys of FRs and EMTs were used to evaluate changes in stroke knowledge and practice in 2006 (n = 988) and 2009 (n = 944), overall and in rural and urban counties. The respondents to the 2009 survey were more likely to report the availability of a stroke protocol in their service (69% vs. 61%, $p = 0.001$), training in the use of a stroke screening tool (62% vs. 42%, $p < 0.001$), use of a stroke screening tool (62% vs. 40%, $p < 0.001$), and an adequate level of knowledge about stroke (81% vs. 66%, $p < 0.001$) compared with the respondents to the 2006 survey. Significant improvements in each of these areas were achieved for both rural and urban FRs and EMTs. Educational outreach to FRs and EMTs was associated with marked improvement in selected components of the EMS system of stroke care. Oser C, McNamara M, Fogle C, Gohdes D, Helgerson S, Harwell T. Educational Outreach To Improve Emergency Medical Services: Systems Of Care For Stroke In Montana. Prehosp Emerg Care. 2010; 14(2): 259-264.

Risk Practices Associated with Bacterial Infections Among Injection Drug Users in Denver, Colorado

There has been limited research on bacterial infections (e.g., skin and soft tissue abscesses, endocarditis) among injection drug users (IDUs), despite these infections often resulting in serious morbidity and costly medical care. Although high-risk practices that contribute to bacterial infections are not entirely clear, certain injection practices have been found to increase risk in past studies. The objectives of this study are to examine rates of bacterial infections among IDUs in Denver, Colorado, and high-risk practices that predict skin infections. Structured interviews were conducted with 51 active heroin, cocaine, and methamphetamine IDUs (over 18 years). Among all participants, 55% reported a lifetime history of at least one skin infection, and 29% reported having an infection in the last year. Those with a skin infection in the last year were significantly more likely to inject intramuscularly (OR = 1.57) and to report greater heroin injection frequency (OR = 1.08) compared to IDUs with no history of skin infections. Heroin and speedball injectors reported a

higher number of past abscesses compared to methamphetamine and cocaine injectors. Intervention strategies to reduce bacterial infections should focus on high-risk injection practices. Learning about rates of bacterial infections and high-risk practices associated with these infections can benefit researchers developing risk reduction interventions for IDUs. Phillips K, Stein M. Risk Practices Associated With Bacterial Infections Among Injection Drug Users In Denver, Colorado. Am J Drug Alcohol Abuse. 2010; 36(2): 92-97.

The Need for Culturally Appropriate, Gender-Specific Global HIV Prevention Efforts with Vulnerable Women

More than 25 years into the HIV/AIDS epidemic, women are rapidly becoming the face of the pandemic. An estimated 15.4 million women aged 15 or older are living with HIV—approximately 46% of the global total of people infected with HIV (UNAIDS, 2007). Women in Sub-Saharan Africa are among the most affected by HIV/AIDS, representing 61% of infections among adults in this region (UNAIDS, 2007). Furthermore, it is estimated that 75% of all women living with HIV are in Sub-Saharan Africa (UNAIDS, 2006). With approximately one in three people infected with HIV, Southern Africa continues to be the global epicenter of the epidemic (UNAIDS, 2006) and accounts for more than one third of HIV infections worldwide (UNAIDS, 2008). It is estimated that 52% of all women aged 15 or older living with HIV are in this region (UNAIDS, 2006). Throughout Sub-Saharan Africa, adolescent women, particularly orphans, are at increased risk for HIV. Wechsberg W, Luseno W. The Need For Culturally Appropriate, Gender-Specific Global HIV Prevention Efforts With Vulnerable Women. J Prev Interv Community. 2010; 38 (2): 85-88.

The Physician Clinical Support System-Buprenorphine (PCSS-B): A Novel Project to Expand/Improve Buprenorphine Treatment

Opioid dependence is largely an undertreated medical condition in the United States. The introduction of buprenorphine has created the potential to expand access to and use of opioid agonist treatment in generalist settings. Physicians, however, often have limited training and experience providing this type of care. Some physicians believe having a mentoring relationship with an experienced provider during their initial introduction to the use of buprenorphine would ease implementation. The authors' goal was to describe the development, implementation, resources, and evaluation of the Physician Clinical Support System-Buprenorphine (PCSS-B), a federally funded program to improve access to and quality of treatment with buprenorphine. The authors provide a description of the PCSS-B, a national network of 88 trained physician mentors with expertise in buprenorphine treatment and skills in clinical education. They provide information regarding the use the PCSS-B core services including telephone, email and in-person support, a website, clinical guidance, a warm-line and outreach to primary care and specialty organizations. Between July 2005 and July 2009, 67 mentors and 4 clinical experts reported providing mentoring services to 632 participants in 48 states, Washington DC and Puerto Rico. A total of 1,455 contacts were provided through email (45%), telephone (34%) and in-person visits (20%). Seventy-six percent of contacts addressed a clinical issue. Eighteen percent of contacts addressed a logistical issue. The number of contacts per participant ranged from 1-125. Between August 2005 and April 2009 there were 72,822 visits to the PCSS-B website with 179,678 pages viewed. Seven guidance were downloaded more than 1000 times. The warm-line averaged more than 100 calls per month. The PCSS-B model provides support for a mentorship program to assist non-specialty physicians in the provision of buprenorphine and may serve as a model for dissemination of other types of care. Egan JE, Casadonte P, Gartenmann T, Martin J, McCance-Katz EF, Netherland J, Renner JA, Weiss L, Saxon AJ, Fiellin DA. The Physician Clinical Support System-Buprenorphine (PCSS-B): A Novel Project to Expand/Improve Buprenorphine Treatment. J Gen Intern Med. 2010: 1-6.

Methamphetamine ("tik") Use and Its Association with Condom Use among Out-of-school South African Females

Little is known about the association between methamphetamine use and sexual risk behaviors among young South African women between 13 and 20 years of age. This study examined the association between methamphetamine use and condom use among out-of-school South African female adolescents. Black and Colored female adolescents were interviewed and categorized into methamphetamine user (n = 261) or non-user (n = 188) groups. Methamphetamine use was reported by 58% of the total sample. Higher methamphetamine rates were found among young Colored females (87%) than among young Black females (11%). In a multiple logistic regression analysis that adjusted for relevant confounders and included an interaction term for race and methamphetamine use, Colored female methamphetamine users were over six times more likely than other participants to report not using a condom the last time they had sex (OR = 6.21; 95% CI = 1.21, 31.94). The conclusions and scientific significance of this study are that efforts are needed to reduce methamphetamine use and related sexual risk among adolescent females in Colored communities and to prevent the spread of methamphetamine use in Black African communities. Wechsberg W, Jones H, Zule W, Myers B, Browne F, Kaufman M, Luseno W, Flisher A, Parry C. Methamphetamine ("tik") Use And Its Association With Condom Use Among Out-Of-School Females In Cape Town, South Africa. Am J Drug Alcohol Abuse. 2010; 36(4): 208-213.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - CTN-Related Research

CTN Participation Influences Innovation Adoption Beyond Clinical Trial Protocol Activities

Organizational involvement in clinical research may lead to adoption of the focal intervention by participating treatment agencies, but it is not known whether research involvement enhances innovativeness beyond the specific interventions that are tested. The authors studied programs in NIDA's Clinical Trials Network to examine this question. To date, the CTN has conducted multiple trials on buprenorphine, but none on alcohol pharmacotherapies. Using longitudinal data from a pooled sample of CTN programs and public sector treatment programs outside the CTN, the authors examined organizational adoption of tablet naltrexone and acamprosate, with CTN affiliation and buprenorphine study participation as predictors of interest. In multivariate models controlling for a variety of organizational characteristics, CTN-affiliated programs were 3.5 times more likely to have adopted acamprosate, and 3.2 times more likely to have adopted tablet naltrexone during the 2-year interval in which CTN programs were heavily exposed to research on buprenorphine. The authors suggest that participation in research networks may enhance organizational innovativeness generally to include interventions beyond the scope of the network. Abraham AJ, Knudsen HK, Rothrauff TC, Roman PM. The Adoption of Alcohol Pharmacotherapies in the Clinical Trials Network: The Influence of Research Network Participation. J Subst Abuse Treat. 2010; 38: 275-283.

Innovation in the NIDA Clinical Trials Network

The National Institute on Drug Abuse established the National Drug Abuse Treatment Clinical Trials Network (CTN) to conduct trials of promising substance abuse treatment interventions in diverse clinical settings and to disseminate results of these trials. Interviews with program administrators in 2002 and 2004 of 262 CTN community treatment programs (CTPs) across 17 CTN regional research centers (nodes) addressed CTN''s formation as a network of inter-organizational interaction among treatment practitioners and researchers. Data from Wave I to Wave II indicated strong relationships of interaction and trust (M=4.35 & 4.40 on a 5-point scale), but a decline in problem-centered inter-organizational interaction over time (from M=2.58 to M-1.72 staff hours/week of communication; p<.01). Second, adoption of buprenorphine and motivational incentives among CTN''s affiliated community treatment programs (CTPs) was examined over three waves of data. In the case of buprenorphine, CTP use rose from 15.5% at baseline to 31.8% at 24 months, and 34.5% at 48 months. However, 4.7% abandoned use at 24 months, and 7% more discontinued at 48 months. Although over time 18.6% of CTPs adopted MI/CM, gains were offset by 17.8% discontinuing MI/CM.

Publications

Staff Highlights

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Finally, 58.1% of CTPs never used buprenorphine over the four-year period and 38.7% never used MI/CM. Third, CTPs' pursuit of the CTN's dissemination goals were examined. Results indicated that such organizational outreach activities are underway, with 40% of CTPs organizing or leading training sessions for non-CTN CTPs. Considering that CTN interventions are consider state-of-the-art, it is evident that adoption did not approach 100% and that dissemination activities did not involve even half the CTPs. Organizational treatment philosophies and regulatory barriers were commonly cited reasons for non-adoption. Roman PM, Abraham AJ, Rothrauff TC, Knudsen HK. A Longitudinal Study Of Organizational Formation, Innovation Adoption, And Dissemination Activities Within The National Drug Abuse Treatment Clinical Trials Network. J Subst Abuse Treat. 2010; 38 (Suppl 1): S44-S52.

Increasing Prenatal Care and Healthy Behaviors In Pregnant Substance Users

Evidence suggests that prenatal care, healthy behaviors such as exercise and nutrition, and general stress level are associated with fetal and maternal health but there is a relative dearth of research on interventions to improve these factors in pregnant substance users. Two hundred pregnant substance users entering outpatient substance abuse treatment were randomized to receive either three individual sessions of Motivational Enhancement Therapy for pregnant substance users (MET-PS) or the first three individual sessions normally provided by the program (CTN-0013). The present study evaluated the relative efficacy of MET-PS, compared to treatment as usual on modifiable healthy behaviors, and the impact of treatment when the groups were pooled. The results suggest that MET-PS was not more effective than treatment as usual in improving modifiable healthy behaviors. When the treatment groups were pooled, the results suggest that there were significant increases in prenatal care utilization and prenatal/multi-vitamin and water consumption, and a significant decrease in stress. Limitations and recommendations for further research are discussed. Kropp F, Winhusen T, Lewis D, Hague D, Somoza E. J Psychoactive Drugs. 2010; 42(1): 73-81.

Do Therapist Cultural Characteristics Influence the Outcome of Substance Abuse Treatment For Spanish-Speaking Adults?

This secondary data analysis of the Clinical Trials Network's Motivational Enhancement Therapy effectiveness trial with Spanish-speaking substance users (CTN-0021) examined whether the degree of birthplace and acculturation similarities between clients and therapists, as well as the therapists' own level of acculturation and birthplace were related to the clients' participation in treatment and level of substance use during outpatient substance use treatment. Sixteen therapists and their 235 clients from the 480 participants in the larger effectiveness trial were included in the analyses for this study. Results of the multilevel regression models for client participation in substance use treatment and client days of substance use, taking into account within and between therapist cultural characteristics, revealed that birthplace match and acculturation similarity between each therapist and his or her clients did not predict client outcomes. Instead, therapists' birthplace ($p < 0.05$) and level of acculturation ($p < 0.001$) independently predicted days of substance use, but not treatment participation for monolingual Spanish-speaking clients. Suarez-Morales L, Martino S, Bedregal L, McCabe BE, Cuzmar IY, Paris M, Feaster DJ, Carroll KM, Szapocznik J. Cultur Divers Ethnic Minor Psychol. 2010; 16(2): 199-205.

HIV Risk Behavior In Treatment-Seeking Opioid-Dependent Youth: Results From A NIDA Clinical Trials Network Multisite Study (CTN-0010)

This study assessed baseline rates of and changes in HIV drug and sexual risk behavior as a function of gender and treatment in opioid-dependent youth. One hundred fifty four participants were randomly assigned to extended buprenorphine/naloxone therapy (BUP) for 12 weeks or detoxification for 2 weeks; all received drug counseling for 12 weeks; 150 participants were eligible for this analysis. HIV risk was assessed at baseline and 4-week, 8-week, and 12-week follow-ups. Behavioral change was examined using generalized estimating equations. Baseline rates of past-month HIV risk for females/males were non significant for injection drug use (IDU), multiple partners, unprotected intercourse and sexual activity. Baseline rates for injection risk were significant ($P < 0.001$). IDU decreased over time ($P < 0.001$), with greater decreases in BUP versus detoxification ($P < 0.001$) and females versus males in BUP ($P < 0.05$). Injection risk did not change for persistent injectors. Sexual activity decreased in both genders and conditions ($P < 0.01$), but sexual risk did not. Overall, IDU and sexual activity decreased, particularly in BUP patients and females, but injection and sexual risk behaviors persisted. Although extended BUP seems to have favorable effects on HIV risk behavior in opioid-dependent youth, risk reduction counseling may be necessary to extend its benefits. Meade CS, Weiss RD, Fitzmaurice GM, Poole SA, Subramaniam GA, Patkar AA, Connery HS, Woody GE. J Acquir Immune Defic Syndr. 2010 Apr 13. [Epub ahead of print].

Association of Race and Ethnicity With Withdrawal Symptoms, Attrition, Opioid Use, and Side-Effects During Buprenorphine Therapy

Some studies report differences in opioid withdrawal between racial/ethnic groups. However, it is not known if these differences are reflected in differential treatment response. Data from National Institute on Drug Abuse (NIDA) Clinical Trials Network trial CTN-0003 were used to examine racial/ethnic differences before and during stabilization with buprenorphine. At induction, non-Hispanic Caucasians had higher objective and subjective withdrawal scores and greater opioid craving than minority participants. No significant between-group differences were observed on these scales following buprenorphine. Non-Hispanic Caucasians and Hispanics reported more adverse events than African Americans. Although ethnic and racial differences were observed prior to buprenorphine treatment, scores following buprenorphine treatment were similar between groups. Brown ES, Tirado C, Minhajuddin A, Hillhouse M, Adinoff B, Ling W, Doraimani G, Thomas C. J Ethn Subst Abuse. 2010; 9(2): 106-114.

Survey of Eating Disorder Symptoms Among Women In Treatment For Substance Abuse

A strong association between substance use disorders (SUDs) and eating disorders (EDs) in women has been established. Yet, little is known about the rates and impact of ED symptoms in women presenting to addiction treatment. The current investigation assessed the prevalence of ED symptoms and their effect on treatment outcomes in a sample of substance abusing women with co-occurring posttraumatic stress disorder (PTSD) enrolled in outpatient substance use programs. Participants were 122 of the 353 women who participated in a multisite clinical trial (CTN-0015) comparing two behavioral treatments for co-occurring SUD and PTSD. The Eating Disorder Examination-self report, and measures of PTSD and SUD symptoms were administered at baseline, during treatment and at four follow-up points. Two subgroups emerged; those reporting binge eating in the 28 days prior to baseline (Binge group; $n = 35$) and those who reported no binge eating episodes (No Binge group; $n = 87$). Women in the Binge group endorsed significantly higher ED, PTSD, and depression symptoms at baseline than those in the No Binge group.

Although all participants showed significant reductions in PTSD symptoms and improvements in abstinence rates during the study period, the improvements for the Binge group were significantly lower. These findings suggest that a subgroup of women with co-occurring PTSD and SUDs, who endorsed binge ED symptoms, responded differently to SUD/PTSD group treatment. Identification of ED symptoms among treatment-seeking women with SUDs may be an important element in tailoring interventions and enhancing treatment outcomes. Cohen LR, Greenfield SF, Gordon S, Killeen T, Jiang H, Zhang Y, Hien D. Am J Addict. 2010; 19(3): 245-251.

The Role of Alcohol Misuse In PTSD Outcomes For Women In Community Treatment: A Secondary Analysis of NIDA's Women and Trauma Study (CTN-0015)

Individuals with comorbid substance use and posttraumatic stress disorder may differentially benefit from integrated trauma-focused interventions based on specific presenting characteristics such as substance use type and PTSD severity. The current study is a secondary analysis of a NIDA Clinical Trials Network study exploring the effectiveness of two interventions for women with comorbid PTSD and substance use disorders. Generalized estimating equations were used to examine the association of baseline alcohol misuse with PTSD outcome measures over time for all randomized participants. Women entering treatment with baseline alcohol misuse had higher Post Traumatic Stress Disorder Symptom Scale (PSS-SR) total scores ($t=2.43$, $p<.05$), cluster C (avoidance/numbing) scores ($p<.01$), and cluster D (hyper-arousal) scores ($p<.05$). For women with alcohol misuse, after treatment week 1, PSS-SR scores were significantly lower in the Seeking Safety intervention during treatment ($p<.05$) and follow-up ($p<.05$) compared to those in the health education intervention. Alcohol misusers in the Seeking Safety group who had higher baseline hyper-arousal severity improved more quickly than those with lower baseline hyper-arousal severity during treatment ($p<.05$). Hien DA, Campbell AN, Ruglass LM, Hu MC, Killeen T. Drug Alcohol Depend. 2010 May 25. [Epub ahead of print].

Gender Differences in the Rates and Correlates of HIV Risk Behaviors Among Drug Abusers

This study examined gender differences in the rates and correlates of HIV risk behaviors among 1,429 clients participating in multi-site trials throughout the United States between 2001 and 2005 as part of the National Institute on Drug Abuse-funded Clinical Trials Network. Certain risk factors differed between men and women. Women had overall higher sexual risk than men, due to multiple partners and unprotected sex. However men were more likely to inject drugs than women. Greater alcohol use and psychiatric severity were associated with higher risk behaviors for women, while impaired social relations were associated with decreased risk for men. Specific risk factors were differentially predictive of HIV risk behaviors for women and men, highlighting the need for gender-specific risk-reduction interventions. Brooks A, Meade CS, Potter JS, Lokhnygina Y, Calsyn DA, Greenfield SF. Subst Use Misuse. 2010 Jun 10. [Epub ahead of print].

Alterations In Brain Structure and Functional Connectivity In Prescription Opioid-Dependent Patients

A dramatic increase in the use and dependence of prescription opioids has occurred within the last 10 years. The consequences of long-term prescription opioid use and dependence on the brain are largely unknown, and any speculation is inferred from heroin and methadone studies. Thus, no data have directly demonstrated the effects of prescription opioid use on brain structure

and function in humans. To pursue this issue, investigators used structural magnetic resonance imaging, diffusion tensor imaging and resting-state functional magnetic resonance imaging in a highly enriched group of prescription opioid-dependent patients [(n=10); from a larger study on prescription opioid dependent patients (n=133)] and matched healthy individuals (n=10) to characterize possible brain alterations that may be caused by long-term prescription opioid use. In comparison to control subjects, individuals with opioid dependence displayed bilateral volumetric loss in the amygdala. Prescription opioid-dependent subjects had significantly decreased anisotropy in axonal pathways specific to the amygdala (i.e. stria terminalis, ventral amygdalofugal pathway and uncinate fasciculus) as well as the internal and external capsules. In the patient group, significant decreases in functional connectivity were observed for seed regions that included the anterior insula, nucleus accumbens and amygdala subdivisions. Correlation analyses revealed that longer duration of prescription opioid exposure was associated with greater changes in functional connectivity. Finally, changes in amygdala functional connectivity were observed to have a significant dependence on amygdala volume and white matter anisotropy of efferent and afferent pathways of the amygdala. These findings suggest that prescription opioid dependence is associated with structural and functional changes in brain regions implicated in the regulation of affect and impulse control, as well as in reward and motivational functions. These results may have implications for uncovering the effects of long-term prescription opioid use on brain structure and function. Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, Knudsen J, Wallin D, Pendse G, McDonald L, Griffin M, Anderson J, Nutile L, Renshaw P, Weiss R, Becerra L, Borsook D. Brain. 2010; 133(Pt 7): 2098-2114. Epub 2010 Jun 16.

Comparison of Opiate-Primary Treatment Seekers With and Without Alcohol Use Disorder

Many persons seeking opiate treatment present with complex clinical challenges, which may be exacerbated by alcohol misuse. This report details secondary data analyses aggregating treatment-seeking samples across 10 National Institute on Drug Abuse (NIDA) Clinical Trials Network treatment trials to examine alcohol-related characteristics of opiate-primary (OP) clients and compare broad pretreatment characteristics of those with and without an alcohol use disorder (AUD). Analysis of this aggregate OP client sample (n = 1,396) indicated that 38% had comorbid AUD and that a history of alcohol treatment episodes and recent alcohol problems were common. Further, comparisons of OP clients with and without AUD revealed the former were more likely to have had a history of pervasive difficulties in psychosocial functioning. Findings suggest the need for detection of and intervention for alcohol misuse at the outset of opiate treatment and support for the practice of availing medical, psychological, case management, and other support services. Hartzler B, Donovan DM, Huang Z. J Subst Abuse Treat. 2010; 39(2): 114-123. Epub 2010 Jul 3.

Substance Abuse Treatment Providers' Involvement In Research Is Associated With Willingness To Use Findings In Practice

Using a national sample (n = 571) of substance abuse treatment providers affiliated with the Clinical Trials Network, investigators examined the contribution of several factors-demographic, attitudes, and involvement in research-toward providers' willingness to use research findings in practice. The sample included medical staff, social workers, psychologists, and counselors. Using a multiple linear regression model, investigators examined the impact of involvement in research and willingness to use research findings in practice. Providers involved in research were more willing to use findings in practice ($p < .001$). Latino/Latinas were less willing ($p < .05$). Providers with favorable

attitudes toward evidence-based practices and whose agencies supported professional growth were more willing to use findings ($p < .01$). Involvement in research may enhance providers' willingness to use findings in practice and improve quality of services. Pinto RM, Yu G, Spector AY, Gorroochurn P, McCarty D. J Subst Abuse Treat. 2010; 39(2): 188-194.

Reducing HIV-Related Risk Behaviors Among Injection Drug Users in Residential Detoxification

This study of 632 drug injectors enrolled in eight residential detoxification centers within the National Drug Abuse Treatment Clinical Trials Network tested three interventions to reduce drug and sex risk behaviors. Participants were randomized to: (a) a two-session, HIV/HCV counseling and education (C&E) model added to treatment as usual (TAU), (b) a one-session, therapeutic alliance (TA) intervention conducted by outpatient counselors to facilitate treatment entry plus TAU, or (c) TAU. Significant reductions in drug and sex risk behaviors occurred for all three conditions over a 6-month follow-up period. C&E participants reported significantly greater rates of attending an HIV testing appointment, but this was not associated with better risk reduction outcomes. Reporting treatment participation within 2 months after detoxification and self-efficacy to practice safer injection behavior predicted reductions in injection risk behaviors. Findings indicate that participation in detoxification was followed by significant decreases in drug injection and risk behaviors for up to 6-months; interventions added to standard treatment offered no improvement in risk behavior outcomes. Booth RE, Campbell BK, Mikulich-Gilbertson SK, J Tillotson C, Choi D, Robinson J, Calsyn DA, Mandler RN, Jenkins LM, Thompson LL, Dempsey CL, Liepman MR, McCarty D. AIDS Behav. 2010 Jul 21. [Epub ahead of print]

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Research Findings - Intramural Research

Office of the Scientific Director

Brain Mu-Opioid Receptor Binding Predicts Treatment Outcome In Cocaine-Abusing Outpatients

Cocaine users not seeking treatment have increased regional brain mu-opioid receptor (mOR) binding that correlates with cocaine craving and tendency to relapse, but this relationship had not been evaluated in cocaine-abusing outpatients in treatment. In collaboration with the Treatment Section, Clinical Pharmacology and Therapeutics Branch, and the Johns Hopkins PET Center, IRP researchers determined whether regional brain mOR binding before treatment correlates with outcome, and compared it with standard clinical predictors of outcome, in 25 individuals seeking outpatient treatment for cocaine abuse or dependence (DSM-IV). Patients received up to 12 weeks of cognitive-behavioral therapy and cocaine abstinence reinforcement, whereby each cocaine-free urine was reinforced with vouchers redeemable for goods. Regional brain mOR binding was measured before treatment using positron emission tomography with [11C]-carfentanil (a selective mOR agonist). Elevated mOR binding in the medial frontal and middle frontal gyri before treatment correlated with greater cocaine use (higher proportion of cocaine-positive urine samples) during treatment. Elevated mOR binding in the anterior cingulate, medial frontal, middle frontal, middle temporal, and sublobar insular gyri correlated with shorter duration of cocaine abstinence during treatment. Regional mOR binding contributed significant predictive power for treatment outcome beyond that of standard clinical variables such as baseline drug and alcohol use. These findings show that elevated mOR binding in brain regions associated with reward sensitivity is a significant independent predictor of treatment outcome in cocaine-abusing outpatients. They suggest a key role for the brain endogenous opioid system in cocaine addiction and a possible role for PET scanning in predicting cocaine-abuse treatment response and improving allocation of treatment resources. Ghitza UE, Preston KL, Epstein DH, Kuwabara H, Endres CJ, Bencherif B, Boyd SJ, Copersino ML, Frost JJ, and Gorelick DA. Brain mu-opioid receptor binding predicts treatment outcome in cocaine-abusing outpatients. Biological Psychiatry. 2010 published online.

Cannabis Withdrawal Symptoms In Non-Treatment-Seeking Adult Cannabis Smokers

Cannabis withdrawal symptoms are reported in the medical literature, but a cannabis withdrawal syndrome is not recognized in DSM-IV because of doubts about its clinical significance. IRP scientists assessed the phenomenon of cannabis withdrawal and its relationship to relapse in a convenience sample of 469 nontreatment-seeking adults who had made a quit attempt without formal treatment while not in a controlled environment. Subjects completed a 176-item Marijuana Quit Questionnaire collecting information on sociodemographic characteristics, cannabis use history, and their "most difficult" cannabis quit

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attempt. 42.4% of subjects had experienced a lifetime withdrawal syndrome, of whom 70.4% reported using cannabis in response to withdrawal. During the index quit attempt, 95.5% of subjects reported ³1 individual withdrawal symptom. Number of withdrawal symptoms was significantly associated with greater frequency and amount of cannabis use, but symptoms occurred even in those using less than weekly. Symptoms were usually of at least moderate intensity and often prompted actions to relieve them. Alcohol (41.5%) and tobacco (48.2%) were used more often than cannabis (33.3%) for this purpose. There was little change during withdrawal in use of other legal or illegal substances. These findings show that cannabis withdrawal is a common syndrome among adults not seeking treatment and that withdrawal can serve as a negative reinforcer for relapse to cannabis use (as well as other substance use). Therefore, cannabis withdrawal symptoms do have clinical significance and should be a target of treatment efforts. Levin KH, Copersino ML, Heishman SJ, Liu F, Kelly DL, Boggs DL, and Gorelick DA. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. Drug and Alcohol Dependence. 2010 published online.

Clinical Pharmacology and Therapeutics

Ecological Momentary Assessment Study

The effects of an intervention cannot be understood without precise knowledge of the baseline behavior on which the intervention is superimposed. For misusers of illicit drugs, patterns of daily activities and moods have not been studied in a way that is amenable to statistical aggregation. The objective of the study was to compare hour-by-hour daily activities in cocaine-dependent outpatients during urine-verified periods of use and abstinence. In a cohort design, a volunteer sample of 112 methadone-maintained cocaine- and heroin-abusing outpatients provided ecological momentary assessment (EMA) data on handheld computers for 10,781 person-days. Drug use was monitored in three-times weekly urine drug screens. EMA responses to questions about current location, activities, companions, moods, and recent exposure to putative drug-use triggers were compared across periods of use and abstinence (defined as at least three consecutive cocaine-positive or cocaine-negative drug screens, respectively) using SAS Proc Glimmix (for binary outcomes) and Proc Mixed (for continuous outcomes). Periods of cocaine use were associated with idle, solitary, affectively negative afternoons, but, unexpectedly, were also associated with a greater likelihood of early-morning or late-evening work. The whole-day concomitants of cocaine use were often distinct from the acute predecessors of use seen in prior analyses from the same sample. Several measures of negative mood increased during abstinence. Weeks of cocaine use and abstinence in outpatients are associated with distinct patterns of mood and behavior; the detailed hourly data reported here should help inform treatment interventions aimed at changing daily activities. The findings also argue against the contention that cocaine abstinence symptoms decrease monotonically from the day of cessation. Epstein DH, Preston KL. Daily life hour by hour, with and without cocaine: an ecological momentary assessment study. Psychopharmacology, 2010; 211: 223-232. Epub 2010 June 9.

Nicotine Psychopharmacology Section/Clinical Pharmacology and Therapeutics Branch

Validity of the 12-item French version of the Tobacco Craving Questionnaire

The French version (FTCQ) of the Tobacco Craving Questionnaire (TCQ) is a valid and reliable 47-item self-report instrument that assesses tobacco craving in four factors: emotionality, expectancy, compulsivity, and purposefulness. For use in research and clinical settings, IRP researchers constructed a 12-item version of the FTCQ (FTCQ-12). The FTCQ-12 was administered to treatment-seeking French smokers (n=310) enrolled in the Adjustment of DOses of

NIcotine in Smoking Cessation (ADONIS) trial. The authors conducted confirmatory factor analysis (CFA) and examined congruence in factor loadings between the FTCQ and FTCQ-12 to determine the validity and reliability of the FTCQ-12. Measures of tobacco craving, withdrawal, smoking patterns, and smoking history were included to explore the concurrent validity of the FTCQ-12. The authors used craving scores to distinguish participants who were highly dependent on nicotine from those less dependent on nicotine. CFA indicated perfect fit for a 4-factor model, with congruence coefficients indicating moderate similarity in factor patterns and loadings between the FTCQ and FTCQ-12. Individual factors of the FTCQ-12 correlated positively with smoking history and withdrawal variables. Participants who were highly dependent on nicotine were nearly six times more likely to score >5 on the general factor (maximum: 7) than those less dependent on nicotine. Findings suggest the FTCQ-12 measures the same four factors as the FTCQ, TCQ, and TCQ-12, and these four constructs have unique properties. The FTCQ-12 yields valid and reliable indices of tobacco craving, and has potential clinical utility for rapid assessment of tobacco craving in smokers seeking treatment. Berlin I, Singleton EG, Heishman SJ. Validity of the 12-item French version of the Tobacco Craving Questionnaire in treatment-seeking smokers. Nicotine Tob Res. 2010;12: 500-507.

Meta-Analysis of the Acute Effects of Nicotine and Smoking On Human Performance

Empirical studies indicate that nicotine enhances some aspects of attention and cognition, suggesting a role in the maintenance of tobacco dependence. The purpose of this review was to update the literature since our previous review (Heishman et al. 1994) and to determine which aspects of human performance were most sensitive to the effects of nicotine and smoking. The authors conducted a meta-analysis on the outcome measures of 41 double-blind, placebo-controlled laboratory studies published from 1994 to 2008. In all studies, nicotine was administered and performance was assessed in healthy adult nonsmokers or smokers who were not tobacco deprived or minimally deprived (² 2 h). There were sufficient effect size data to conduct meta-analyses on nine performance domains, including motor abilities, alerting and orienting attention, and episodic and working memory. The authors found significant positive effects of nicotine or smoking on six domains: fine motor, alerting attention-accuracy and response time (RT), orienting attention-RT, short-term episodic memory-accuracy, and working memory-RT (effect size range = 0.16 to 0.44). The signficant effects of nicotine on motor abilities, attention, and memory likely represent true performance enhancement because they are not confounded by withdrawal relief. The beneficial cognitive effects of nicotine have implications for initiation of smoking and maintenance of tobacco dependence. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology. 2010; 210: 453-469.

Comparison of Reactivity to Smoking Cues and Smoking Imagery

Increases in self-reported craving and changes in autonomic functioning are reliably elicited when smokers are exposed to tobacco-related stimuli compared with neutral stimuli. However, few studies have reported the time course of cue-elicited craving or have directly compared the effectiveness of smoking cues versus imagery to evoke a craving response. In addition to these two issues, IRP scientists investigated the influence of tobacco deprivation and sex on craving, mood, and autonomic responses. Sixty cigarette smokers (30 men, 30 women) were tested in two counterbalanced sessions, one after overnight tobacco deprivation and one during ad libitum smoking. At each session, participants were exposed to four randomized experimental trials: smoking imagery, neutral imagery, smoking cues, and neutral cues. Tobacco craving and mood were assessed repeatedly and physiological measures were recorded continuously for 30 min after imagery or cue exposure. Compared with neutral trials, smoking cues and smoking imagery reliably increased tobacco craving,

negative mood, heart rate, and blood pressure and decreased positive mood ratings. Changes were observed immediately after cue and imagery presentation and remained unchanged for 30 min. Responding was greater in the nondeprived condition, and cues elicited more robust responding than imagery for most measures. Women responded more robustly to smoking cues only in the nondeprived condition, whereas imagery evoked greater responses in men during both conditions. These findings provide new data on the time course, magnitude, and tobacco deprivation effects on elicited craving. Sex differences were dependent on stimulus type and deprivation condition. Heishman SJ, Lee DC, Taylor RC, Singleton EG. Prolonged duration of craving, mood, and autonomic responses elicited by cues and imagery in smokers: effects of tobacco deprivation and sex. Exp Clin Psychopharmacol. 2010; 18: 245-256.

Chemical Biology Research Branch, Drug Design and Synthesis Section

Probes For Narcotic Receptor Mediated Phenomena. 40. N-Substituted Cis-4a-Ethyl-1,2,3,4,4a,9a-Hexahydrobenzofuro[2,3-C]Pyridin-8-Ols

A series of N-substituted rac-cis-4a-ethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-8-ols have been prepared using a simple synthetic route previously designed for synthesis of related cis-2-methyl-4a-alkyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ols. The new phenolic compounds, where the aromatic hydroxy moiety is situated ortho to the oxygen atom in the oxide-bridged ring, do not interact as well as the pyridin-6-ols with opioid receptors. The N-para-fluorophenethyl derivative had the highest mu-opioid receptor affinity of the examined compounds (K(i)=0.35 microM). Iyer MR, Lee YS, Deschamps JR, Rothman RB, Dersch CM, Jacobson AE, Rice KC. Bioorg Med Chem. 2010 Jan 1;18(1): 91-99. Epub 2009 Nov 18.

Identification of a Novel "Almost Neutral" Micro-Opioid Receptor Antagonist In CHO Cells Expressing the Cloned Human Mu-Opioid Receptor

The basal (constitutive) activity of G protein-coupled receptors allows for the measurement of inverse agonist activity. Some competitive antagonists turn into inverse agonists under conditions where receptors are constitutively active. In contrast, neutral antagonists have no inverse agonist activity, and they block both agonist and inverse agonist activity. The mu-opioid receptor (MOR) demonstrates detectable constitutive activity only after a state of dependence is produced by chronic treatment with a MOR agonist. IRP investigators therefore sought to identify novel MOR inverse agonists and novel neutral MOR antagonists in both untreated and agonist-treated MOR cells. CHO cells expressing the cloned human mu receptor (hMOR-CHO cells) were incubated for 20 h with medium (control) or 10 microM (2S,4aR,6aR,7R,9S,10aS,10bR)-9-(benzoyloxy)-2-(3-furanyl) dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho-[2,1-c]pyran-7-carboxylic acid methyl ester (herkinorin, HERK). HERK treatment generates a high degree of basal signaling and enhances the ability to detect inverse agonists. [(35)S]-GTP-gamma-S assays were conducted using established methods. The authors screened 21 MOR "antagonists" using membranes prepared from HERK-treated hMOR-CHO cells. All antagonists, including CTAP and 6beta-naltrexol, were inverse agonists. However, LTC-274 ((-)-3-cyclopropylmethyl-2,3,4,4alpha, 5,6,7,7alpha-octahydro-1H-benzofuro[3,2-e]isoquinolin-9-ol)) showed the lowest efficacy as an inverse agonist, and, at concentrations less than 5 nM, had minimal effects on basal [(35)S]-GTP-gamma-S binding. Other efforts in this study identified KC-2-009 ((+)-3-((1R,5S)-2-((Z)-3-phenylallyl)-2-azabicyclo[3.3.1]nonan-5-yl)phenol hydrochloride) as an inverse agonist at untreated MOR cells. In HERK-treated cells, KC-2-009 had the highest efficacy as an inverse agonist. In summary, the authors identified a novel and selective MOR inverse agonist (KC-2-009) and a novel MOR antagonist (LTC-274) that

shows the least inverse agonist activity among 21 MOR antagonists. LTC-274 is a promising lead compound for developing a true MOR neutral antagonist. Sally EJ, Xu H, Dersch CM, Hsin L-W, Chang L-T, Prisinzano TE, Simpson D, Giuvelis D, Rice KC, Jacobson, AE, Bilsky EJ, Rothman RB. Synapse. 2010 Apr;64(4): 280-288.

Evidence That Tricyclic Small Molecules May Possess Toll-Like Receptor and Myeloid Differentiation Protein 2 Activity

Opioids have been discovered to have Toll-like receptor (TLR) activity, beyond actions at classical opioid receptors. This raises the question whether other pharmacotherapies for pain control may also possess TLR activity, contributing to or opposing their clinical effects. IRP scientists document that tricyclics can alter TLR4 and TLR2 signaling. In silico simulations revealed that several tricyclics docked to the same binding pocket on the TLR accessory protein, myeloid differentiation protein 2 (MD-2), as do opioids. Eight tricyclics were tested for effects on TLR4 signaling in HEK293 cells over-expressing human TLR4. Six exhibited mild (desipramine), moderate (mianserin, cyclobenzaprine, imiprimine, ketotifen) or strong (amitriptyline) TLR4 inhibition, and no TLR4 activation. In contrast, carbamazepine and oxcarbazepine exhibited mild and strong TLR4 activation, respectively, and no TLR4 inhibition. Amitriptyline but not carbamazepine also significantly inhibited TLR2 signaling in a comparable cell line. Live imaging of TLR4 activation in RAW264.7 cells and TLR4-dependent interleukin-1 release from BV-2 microglia revealed that amitriptyline blocked TLR4 signaling. Lastly, tricyclics with no (carbamazepine), moderate (cyclobenzeprine), and strong (amitriptyline) TLR4 inhibition were tested intrathecally (rats) and amitriptyline tested systemically in wildtype and knockout mice (TLR4 or MyD88). While tricyclics had no effect on basal pain responsivity, they potentiated morphine analgesia in rank-order with their potency as TLR4 inhibitors. This occurred in a TLR4/MyD88-dependent manner as no potentiation of morphine analgesia by amitriptyline occurred in these knockout mice. This suggests that TLR2 and TLR4 inhibition, possibly by interactions with MD2, contributes to effects of tricyclics in vivo. These studies provide converging lines of evidence that several tricyclics or their active metabolites may exert their biological actions, in part, via modulation of TLR4 and TLR2 signaling and suggest that inhibition of TLR4 and TLR2 signaling may potentially contribute to the efficacy of tricyclics in treating chronic pain and enhancing the analgesic efficacy of opioids. 2010 IBRO. Hutchinson MR, Loram LC, Zhang Y, Shridhar M, Rezvani N, Berkelhammer D, Phipps S, Foster PS, Landgraf K, Falke JJ, Rice KC, Maier SF, Yin H, Watkins LR. Neuroscience. 2010 Jun 30;168(2): 551-563. Epub 2010 Apr 8.

Reversal of Pancreatitis-Induced Pain By an Orally Available, Small Molecule Interleukin-6 Receptor Antagonist

Pancreatic pain resulting from chronic inflammation of the pancreas is often intractable and clinically difficult to manage with available analgesics reflecting the need for more effective therapies. The mechanisms underlying pancreatitis pain are not well understood. Here, the possibility that interleukin-6 (IL-6) may promote pancreatitis pain was investigated with TB-2-081 (3-O-formyl-20R,21-epoxyresibufogenin, EBRF), a small molecule IL-6 receptor antagonist that was semi-synthetically derived from natural sources. The potential activity and mechanism of TB-2-081 were investigated following the induction of persistent pancreatitis using dibutyltin dichloride (DBTC) in rats. TB-2-081 displaces the binding of IL-6 to the human recombinant soluble IL-6 receptor with apparent high affinity and inhibits IL-6 mediated cell growth. Systemic or oral, but not intrathecal, administration of TB-2-081 reversed DBTC-induced abdominal hypersensitivity in a dose- and time-dependent manner. IL-6 levels were significantly up-regulated in the dorsal root ganglia (DRG) of rats with pancreatitis on day 6 after DBTC injection. IL-6-enhanced capsaicin-evoked release of calcitonin gene-related peptide from cultured DRG neurons was blocked by TB-2-081. These data demonstrate that TB-2-081 acts as a systemically available and orally active small molecule IL-6 receptor

antagonist. TB-2-081 effectively reduces pancreatitis-induced pain through peripheral mechanisms that are likely due to (a) increased expression of IL-6 in the DRG and (b) IL-6-mediated sensitization of nociceptive neurons. The activity of TB-2-081 implicates an important role for IL-6 in sustaining pancreatitis pain. Strategies targeting IL-6 actions through small molecule antagonists may offer novel approaches to improve the therapy of chronic pancreatitis and other chronic pain states. Vardanyan M, Melemedjian OK, Price TJ, Ossipov MH, Lai J, Roberts E, Boos TL, Deschamps JR, Jacobson AE, Rice KC, Porreca F. Pain. 2010 Jul 2. [Epub ahead of print].

Evidence for Noncompetitive Modulation of Substrate-Induced Serotonin Release

Prior work indicated that serotonin transporter (SERT) inhibitors competitively inhibit substrate-induced [3H]5-HT release, producing rightward shifts in the substrate-dose response curve and increasing the EC50 value without altering the Emax. IRP researchers hypothesized that this finding would not generalize across a number of SERT inhibitors and substrates, and that the functional dissociation constant (Ke) of a given SERT inhibitor would not be the same for all tested substrates. To test this hypothesis, the authors utilized a well-characterized [3H]5-HT release assay that measures the ability of a SERT substrate to release preloaded [3H]5-HT from rat brain synaptosomes. Dose-response curves were generated for six substrates (PAL-287 [naphthyliso propylamine], (+)-fenfluramine, (+)-norfenfluramine, mCPP [meta-chlorophenylpiperazine], (±)-MDMA, 5-HT) in the absence and presence of a fixed concentration of three SERT inhibitors (indatraline, BW723C86, EG-1-149 [4-(2-(benzhydryloxy)ethyl)-1-(4-bromobenzyl)piperidine oxalate]). Consistent with simple competitive inhibition, all SERT inhibitors increased the EC50 value of all substrates. However, in many cases a SERT inhibitor decreased the Emax value as well, indicating that in the presence of the SERT inhibitor the substrate became a partial releaser. Moreover, the Ke values of a given SERT inhibitor differed among the six SERT substrates, indicating that each inhibitor/substrate combination had a unique interaction with the transporter. Viewed collectively, these findings suggest that it may be possible to design SERT inhibitors that differentially regulate SERT function. Rothman RB, Baumann MH, Blough BE, Jacobson AE, Rice KC, Partilla JS. Synapse. 2010 April 23. [Epub ahead of print].

Antinociceptive Interactions Between Mu Opioid Receptor Agonists and the Serotonin Uptake Inhibitor Clomipramine In Rhesus Monkeys: Role Of Mu Agonist Efficacy

Mu-opioid agonists are effective analgesics but have undesirable effects such as sedation and abuse liability that limit their clinical effectiveness. Serotonergic systems also modulate nociception, and serotonin uptake inhibitors may be useful as adjuncts to enhance analgesic effects and/or attenuate undesirable effects of mu agonists. This study examined effects of the serotonin uptake inhibitor clomipramine on behavioral effects produced in rhesus monkeys by mu agonists with varying efficacy at mu receptors (nalbuphine< morphine< methadone). Clomipramine and each mu agonist were studied alone and in fixed-proportion mixtures in assays of schedule-controlled responding, thermal nociception and capsaicin-induced thermal allodynia. In the assay of schedule-controlled responding, all mu agonists dose-dependently decreased response rates. Clomipramine was inactive alone and did not alter effects of mu agonists. In the assay of thermal nociception, all mu agonists produced dose-dependent antinociception. Clomipramine was inactive alone but produced a proportion-dependent enhancement of the antinociceptive effects of nalbuphine>morphine> methadone. In the assay of capsaicin-induced allodynia, nalbuphine produced dose-dependent anti-allodynia. Clomipramine alone was inactive, but as in the assay of thermal nociception, it produced a proportion-dependent enhancement in the effects of nalbuphine. These findings suggest that serotonin uptake inhibitors can selectively enhance the antinociceptive effects of mu agonists in nonhuman

primates. These effects of serotonin uptake inhibitors may be dependent on the proportion of the serotonin uptake inhibitor and the efficacy of the mu agonist. The greatest enhancement was observed with intermediate proportions of clomipramine in combination with the low-efficacy mu agonist nalbuphine. Banks ML, Rice KC, Negus SS. J. Pharmacol. Exp. Ther. 2010 July 30. [Epub ahead of print].

In Vivo Evaluation Of [123I]-4-(2-(Bis(4-Fluorophenyl)Methoxy)Ethyl)-1-(4- Iodobenzyl) Piperidine, An Iodinated SPECT Tracer For Imaging The P-Gp Transporter

P-glyco protein (P-gp) is an energy-dependent transporter that contributes to the efflux of a wide range of xenobiotics at the blood-brain barrier playing a role in drug-resistance or therapy failure. In this study, IRP scientists evaluated [(123)I]-4-(2-(bis(4-fluorophenyl)methoxy)ethyl)-1-(4-iodobenzyl) piperidine ([(123)I]-FMIP) as a novel single photon emission computed tomography (SPECT) tracer for imaging P-gp at the brain in vivo. The tissue distribution and brain uptake as well as the metabolic profile of [(123)I]-FMIP in wild-type and mdr1a (-/-) mice after pretreatment with physiological saline or cyclosporin A (CsA) (50 mg/kg) was investigated. The influence of increasing doses CsA on brain uptake of [(123)I]-FMIP was explored. microSPECT images of mice brain after injection of 11.1 MBq [(123)I]-FMIP were obtained for different treatment strategies thereby using the Milabs U-SPECT-II. Modulation of P-gp with CsA (50 mg/kg) as well as mdr1a gene depletion resulted in significant increase in cerebral uptake of [(123)I]-FMIP with only minor effect on blood activity. [(123)I]-FMIP is relatively stable in vivo with >80% intact [(123)I]-FMIP in brain at 60 min p.i. in the different treatment regiments. A dose-dependent sigmoidal increase in brain uptake of [(123)I]-FMIP with increasing doses of CsA was observed. In vivo region of interest-based SPECT measurements correlated well with the observations of the biodistribution studies. These findings indicate that [(123)I]-FMIP can be applied to assess the efficacy of newly developed P-gp modulators. It is also suggested that [(123)I]-FMIP is a promising SPECT tracer for imaging P-gp at the blood-brain barrier. De Bruyne S, Wyffels L, Boos TL, Staelens S, Deleye S, Rice KC, De Vos F. Nucl Med Biol. 2010 May;37(4): 469-477. Epub 2010 Apr 7.

GABAB Receptor Positive Modulators: Enhancement of GABAB Receptor Agonist Effects In Vivo

In vivo effects of GABA(B) receptor positive modulators suggest them to have therapeutic potential to treat CNS disorders such as anxiety, depression, and drug abuse. Although these effects are generally thought to be mediated by positive modulation of GABA(B) receptors, such modulation has been examined primarily in vitro. The present study was aimed at further examining the in vivo positive modulatory properties of the GABA(B) receptor positive modulators, 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethylpropyl) phenol (CGP7930) and (R,S)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one (rac-BHFF). Both compounds enhanced loss of righting induced by baclofen in mice. However, CGP7930 was less effective and rac-BHFF was less potent to enhance loss of righting induced by GHB, which, like baclofen, has GABA(B) receptor agonist properties. In contrast with baclofen- and GHB-induced loss of righting, the hypothermic effects of baclofen and GHB were not enhanced by rac-BHFF, and were enhanced by CGP7930 only at doses that produced hypothermia when given alone. CGP7930-induced hypothermia was not attenuated by the GABA(B) receptor antagonist CGP35348, at doses that blocked baclofen-induced hypothermia, and was not increased by the NOS inhibitor L-NAME, at doses that increased the hypothermic effects of baclofen and GHB. The results are evidence that CGP7930 and rac-BHFF act in vivo as positive modulators at GABA(B) receptors mediating loss of righting, but not at GABA(B) receptors mediating hypothermia. Conceivably, CGP7930, but not rac-BHFF, acts as an allosteric agonist at these latter receptors. Taken together, the results are further evidence of pharmacologically distinct GABA(B) receptor subtypes, possibly allowing for a more selective therapeutic interference with the

GABA(B) system. Koek W, France CP, Cheng K, Rice KC. J Pharmacol Exp Ther. 2010 Jul 13. [Epub ahead of print].

Cellular Neurobiology Research Branch

Development and Plasticity Section, Cellular Neurobiology Research Branch

Cocaine Causes Deficits In Radial Migration and Alters the Distribution of Glutamate and GABA Neurons In The Developing Rat Cerebral Cortex
Prenatal cocaine exposure induces cytoarchitectural changes in the embryonic neocortex; however, the biological mechanisms and type of cortical neurons involved in these changes are not known. Previously IRP scientists found that neural progenitor proliferation in the neocortical ventricular zone (VZ) is inhibited by cocaine; here they examine the changes in cortical neurogenesis and migration of glutamate and GABA neurons induced by prenatal cocaine exposure. Pregnant rats received 20 mg/kg of cocaine intraperitoneally twice at an interval of 12 hr during three periods of neocortical neurogenesis. Neocortical area and distribution of developing neurons were examined by counting Tuj1+, glutamate+ or GABA+ cells in different areas of the cerebral cortex. Cocaine decreased neocortical area by reducing the size of the Tuj1+ layer, but only when administered during early periods of neocortical neurogenesis. The number of glutamatergic neurons was increased in the VZ, but was decreased in the outer cortical laminae. Although the number of GABA+ neurons in the VZ of both the neocortex and ganglionic eminences was unchanged, GABA+ cells decreased in all other neocortical laminae. Tangential migration of GABA+ cells was also disrupted by cocaine. These findings suggest that in utero cocaine exposure disturbs radial migration of neocortical neurons, possibly due to decreased radial glia guiding support through enhanced differentiation of neocortical VZ progenitors. Cocaine interrupts radial migration of both glutamatergic and GABAergic neurons within the neocortex, in addition to the tangential migration of GABAergic neurons from the subcortical telecephalon. This may result in abnormal neocortical cytoarchitecture and concomitant adverse functional effects. Lee CT, Chen J, Worden, LT, Freed WJ. Cocaine causes deficits in radial migration and alters the distribution of glutamate and GABA neurons in the developing rat cerebral cortex. Synapse. 2010 May 4. [Epub ahead of print].

Electrophysiology Research Section, Cellular Neurobiology Research Branch

Afferent-Specific AMPA Receptor Subunit Composition and Regulation of Synaptic Plasticity In Midbrain Dopamine Neurons By Abused Drugs
Ventral tegmental area (VTA) dopamine (DA) neurons play a pivotal role in processing reward-related information and are involved in drug addiction and mental illness in humans. Information is conveyed to the VTA in large part by glutamatergic afferents that arise in various brain nuclei, including the pedunculopontine nucleus (PPN). Using a unique rat brain slice preparation, IRP investigators found that PPN stimulation activates afferents targeting GluR2-containing AMPA receptors (AMPAR) on VTA DA neurons, and these afferents did not exhibit long-term depression (LTD). In contrast, activation of glutamate afferents onto the same DA neurons via stimulation within the VTA evoked EPSCs mediated by GluR2-lacking AMPARs that demonstrated LTD or EPSCs mediated by GluR2-containing AMPA receptors that did not express LTD. Twenty-four hours after single cocaine injections to rats, GluR2-lacking AMPARs were increased at both PPN and local VTA projections, and this permitted LTD expression in both pathways. Single injections with the main psychoactive ingredient of marijuana, Delta(9)-tetrahydrocannabinol (Delta(9)-THC), increased GluR2-lacking AMPA receptors and permitted LTD in only the PPN pathway, and these effects were prevented by in vivo pretreatment with the cannabinoid CB1 receptor antagonist AM251. These results demonstrate that

cocaine more globally increases GluR2-lacking AMPA receptors at all glutamate synapses on VTA dopamine neurons, whereas Delta(9)-THC selectively increased GluR2-lacking AMPA receptors at subcortical PPN synapses. This suggests that different abused drugs may exert influence over distinct sets of glutamatergic afferents to VTA DA neurons which may be associated with different reinforcing or addictive properties of these drugs. Good CH, Lupica CR. Afferent-specific AMPA receptor subunit composition and regulation of synaptic plasticity in midbrain dopamine neurons by abused drugs. J Neurosci. 2010;30(23): 7900-7909.

Delta9-Tetrahydrocannabinol Is A Full Agonist At CB1 Receptors On GABA Neuron Axon Terminals In the Hippocampus

Marijuana impairs learning and memory through actions of its psychoactive constituent, delta-9-tetrahydrocannabinol (Delta(9)-THC), in the hippocampus, through activation of cannabinoid CB1 receptors (CB1R). CB1Rs are found on glutamate and GABA neuron axon terminals in the hippocampus where they control neurotransmitter release. Previous studies suggest that Delta(9)-THC is a partial agonist of CB1Rs on glutamate axon terminals in the hippocampus, whereas its effects on GABA terminals have not been described. Using whole-cell electrophysiology in brain slices from C57BL6/J mice, IRP scientists examined Delta(9)-THC effects on synaptic GABA IPSCs and postsynaptic GABA currents elicited by laser-induced photo-uncaging (photolysis) of alpha-carboxy-2-nitrobenzyl (CNB) caged GABA. Despite robust inhibition of synaptic IPSCs in wildtype mice by the full synthetic agonist WIN55,212-2, using a Tween-80 and DMSO vehicle, Delta(9)-THC had no effects on IPSCs in this, or in a low concentration of another vehicle, randomly-methylated beta-cyclodextrin (RAMEB, 0.023%). However, IPSCs were inhibited by Delta(9)-THC in 0.1% RAMEB, but not in neurons from CB1R knockout mice. Whereas Delta(9)-THC did not affect photolysis-evoked GABA currents, these responses were prolonged by a GABA uptake inhibitor. Concentration-response curves revealed that the maximal effects of Delta(9)-THC and WIN55,212-2 were similar, indicating that Delta(9)-THC is a full agonist at CB1Rs on GABA axon terminals. These results suggest that Delta(9)-THC inhibits GABA release, but does not directly alter GABA(A) receptors or GABA uptake in the hippocampus. Furthermore, full agonist effects of Delta(9)-THC on IPSCs likely result from a much higher expression of CB1Rs on GABA versus glutamate axon terminals in the hippocampus. Laaris N, Good CH, Lupica CR. Delta9-tetrahydrocannabinol is a full agonist at CB1 receptors on GABA neuron axon terminals in the hippocampus. Neuropharmacology. 2010; 59(1-2): 121-127.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Interactions Between Intracellular Domains As Key Determinants of the Quaternary Structure and Function of Receptor Heteromers

G protein-coupled receptor (GPCR) heteromers are macromolecular complexes with unique functional properties different from those of its individual protomers. Little is known about what determines the quaternary structure of GPCR heteromers resulting in their unique functional properties. In the present study, using Resonance Energy Transfer (RET) techniques in experiments with mutated receptors, IRP researchers provide for the first time clear evidence for a key role of intracellular domains in the determination of the quaternary structure of GPCR heteromers between adenosine A2A, cannabinoid CB1 and dopamine D2 receptors. In these interactions, arginine-rich epitopes form salt bridges with phosphorylated serine or threonine residues from CK1/2 consensus sites. Each receptor (A2A, CB1 and D2) was found to include two evolutionary conserved intracellular domains to establish selective electrostatic interactions with intracellular domains of the other two receptors, indicating that these particular electrostatic interactions constitute a general mechanism for receptor heteromerization. Mutation experiments indicated that the interactions of the intracellular domains of the CB1 receptor with A2A and D2

receptors are fundamental for the correct formation of the quaternary structure needed for the function (mitogen-activated protein kinase, MAPK, signaling) of the A2A-CB1-D2 receptor heteromers. Analysis of MAPK signaling in striatal slices of CB1 receptor KO mice and wild-type littermates supported the existence of A1-CB1-D2 receptor heteromer in the brain. These findings allowed the authors to propose the first molecular model of the quaternary structure of a receptor heteromultimer. Navarro G, Ferre S, Cordomi A, Moreno E, Mallol J, Casado V, Cortes A, Hoffmann H, Ortiz J, Canela EI, Lluis C, Pardo L, Franco R, Woods AS. Interactions between intracellular domains as key determinants of the quaternary structure and function of receptor heteromers. J Biol Chem 2010. Jun 18. [Epub ahead of print].

Neuroimaging Research Branch

A Genetically Modulated, Intrinsic Cingulated Circuit Supports Human Nicotine Addiction

Genome-wide searches have yielded genetic variants tied to human nicotine dependence. One such variant, called Asp398Asn, in a gene on human chromosome 15 that encodes an alpha 5 subunit of the nicotinic acetylcholine receptor has been repeatedly linked to smoking. Hong et al recently identified a brain circuit that reflects nicotine addiction. However, the relationship between dependence, neural circuitry and genetic predisposition are poorly understood. Elliot Hong et al. used a resting state functional magnetic resonance imaging technique on smokers and non-smokers to compare the strength of a circuit linking the dorsal anterior cingulate-ventral striatum-extended amygdala, brain regions where the gene is active and that have been implicated in addiction. The authors found that Asp398Asn was linked to a greater drop in the circuit's strength in smokers than in non-smokers, and that the circuit strength predicts the severity of the dependence among smokers. The authors report that the circuit is also impaired in people with mental illnesses, who are known to be at a higher risk of smoking, irrespective of the gene variant, suggesting that the circuit might be a common link underpinning nicotine dependence in smokers and people with mental illnesses. The findings could be used to develop an assay of the circuit's function in animal models of human nicotine dependence, possibly leading to novel treatment targets for smoking cessation, according to the authors. Hong LE, Hodgkinson CA, Yang Y, Sampath H, Ross TJ, Buchholz B, Salmeron BJ, Srivastava V, Thaker GK, Goldman D, Stein EA. A genetically modulated, intrinsic cingulated circuit supports human nicotine addiction. Proceedings of the National Academy of Science USA 107(30): 13509-13514, 2010.

Medications Discovery Research Branch, Medicinal Chemistry Section

Dopamine D3 Receptor Partial Agonist CJB090 and Antagonist PG01037 Decrease Progressive Ratio Responding For Methamphetamine In Rats With Extended-Access

The development of novel compounds acting selectively at dopamine D3 receptors has opened new possibilities to explore the role of these receptors in animal models of psychostimulant dependence. Here IRP scientists investigated whether the dopamine D3 partial agonist CJB090 (1-10 mg/kg, i.v) and the D3 antagonist PG01037 (8-32 mg/kg, s.c.,) modified methamphetamine (0.05 mg/kg/injection) intravenous self-administration under fixed- (FR) and progressive- (PR) ratio schedules in rats allowed limited (short access, ShA; 1h sessions 3 days/week) or extended access (long access, LgA; 6h sessions 6 days/week). Under a FR1 schedule, the highest dose of the D3 partial agonist CJB090 selectively reduced methamphetamine self-administration in LgA but not in ShA rats, whereas the full D3 antagonist PG01037 produced no effect in any group. Under a PR schedule of reinforcement, the D3 partial agonist CJB090 reduced the maximum number of responses performed ("breakpoint")

for methamphetamine in LgA rats at the doses of 5 and 10 mg/kg and also it produced a significant reduction in the ShA group at the highest dose. However, the D3 full antagonist PG01037 only reduced PR methamphetamine self-administration in LgA rats at the highest dose of 32 mg/kg with no effect in the ShA group. The results suggest that rats might be more sensitive to pharmacological modulation of dopamine D3 receptors following extended access to methamphetamine self-administration, opening the possibility that D3 receptors play a role in excessive methamphetamine intake. Orio L, Wee S, Newman AH, Pulvirenti L, Koob GF. The dopamine D3 receptor partial agonist CJB090 and antagonist PG01037 decrease progressive ratio responding for methamphetamine in rats with extended-access. Addict Biol. 2010; 15(3): 312-323.

Dopamine D3 and D2 Receptor Mechanisms in the Abuse-Related Behavioral Effects of Cocaine

Dopamine (DA) D3 and D2 receptor mechanisms are implicated in cocaine's abuse-related behavioral effects, but the relative contribution of the two receptor subtypes is only partially characterized. This study investigated the role of D3 and D2 subtype mechanisms by determining the degree to which the D3-prefering antagonist PG01037 [N-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-trans-but-2-enyl}-4-pyridine-2-yl-benzamide HCl] and the D2-prefering antagonist L-741,626 [3-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]methyl-1H-indole] attenuated several behavioral effects of cocaine in squirrel monkeys. Quantitative observational studies established doses of each antagonist that did not produce untoward effects, which was used in subsequent comparisons. Additionally, the capacities of the D3-preferring agonist PD128907 [(R-(+)-trans-3,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano[4,3-b]-1,4-oxazin-9-ol)] and the D2-preferring agonist sumanirole to reproduce cocaine's discriminative stimulus (DS) and priming effects were compared. In monkeys trained to discriminate cocaine from vehicle, both DA antagonists attenuated and both DA agonists partially reproduced cocaine's DS effects. PG01037 also attenuated the cocaine-like DS effects of PD128907, but not sumanirole, whereas L-741,626 attenuated the cocaine-like DS effects of both agonists. In self-administration studies, L-741,626 non-selectively reduced cocaine- and food-maintained responding, whereas PG01037 was ineffective against either reinforcer. In studies involving reinstatement of extinguished cocaine-seeking, both antagonists attenuated cocaine-induced reinstatement of responding, and both agonists induced reinstatement of cocaine-seeking. L-741,626 also attenuated sumanirole- but not PD128907-induced reinstatement of responding, whereas PG01037 was ineffective against either DA agonist. The results are consistent with a role for D3 and D2 receptor mechanisms in cocaine's DS effects and cocaine-induced reinstatement of drug-seeking, but provide no evidence for a major role of D3 receptors in the direct reinforcing effects of cocaine. Achat-Mendes C, Grundt P, Cao J, Platt DM, Newman AH, Spealman RD. Dopamine D3 and D2 Receptor Mechanisms in the Abuse-Related Behavioral Effects of Cocaine: Studies with Preferential Antagonists and Agonists in Squirrel Monkeys. J Pharmacol Exp Ther e-pub May 21, 2010.

Structure-Activity Relationships at the Metabotropic Glutamate Receptor Subtype 5

The metabotropic glutamate receptor subtype 5 (mGluR5) has been implicated in numerous neuropsychiatric disorders including addiction. IRP researchers hypothesized that the rigid diaryl alkyne template, derived from the potent and selective noncompetitive mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP), can serve to guide the design of novel quinoline analogues and pharmacophore optimization has resulted in potent mGluR5 noncompetitive antagonists (EC50 range 60-100 nM) in the quinoline series. This study demonstrates that the structure-activity relationships derived from MPEP analogues can be used to direct the further investigation of novel quinoline analogues. In vivo evaluation of the lead compounds herein will

provide valuable direction toward future drug design. Zhang P, Zou M-F, Rodriguez AL, Conn PJ, Newman AH. Structure-Activity Relationships in a Novel Series of 7-Substituted-Aryl Quinolines and 5-Substituted-Aryl Benzothiazoles at the Metabotropic Glutamate Receptor Subtype 5. Bioorg Med Chem. 2010; 18(9): 3026-3035.

Postendocytic Sorting of Constitutively Internalized Dopamine Transporter in Dopaminergic Neurons

The dopamine transporter (DAT) mediates reuptake of dopamine from the synaptic cleft and is a target for psychostimulants such as cocaine and amphetamine. DAT is known to undergo marked constitutive endocytosis but little is known about the fate and sorting of the endocytosed transporter. To study sorting in heterologous cells lines IRP scientists fused the one-transmembrane segment protein Tac to DAT, thereby generating a transporter (TacDAT) with an extracellular N-terminal antibody epitope suited for trafficking studies. TacDAT was functional and endocytosed constitutively in HEK293 cells. According to an ELISA-based assay, TacDAT intracellular accumulation was increased by the lysosomal protease inhibitor leupeptin and by monensin, an inhibitor of lysosomal degradation and recycling. Monensin also reduced TacDAT surface expression consistent with partial recycling. In both HEK293 cells and in the dopaminergic cell line 1Rb3An27, constitutively internalized TacDAT displayed primary colocalization with the late endosomal marker Rab7, less with the 'short loop' recycling marker Rab4 and little colocalization with the marker of 'long loop' recycling endosomes, Rab11. Removal by mutation of N-terminal ubiquitination sites did not affect this sorting pattern. The sorting pattern was distinct from a bona fide recycling membrane protein, the §2-adrenergic receptor, colocalizing primarily with Rab11 and Rab4. Constitutively internalized wild type DAT probed with the fluorescently tagged cocaine analogue, JHC 1-64, exhibited the same co-localization pattern as TacDAT both in 1Rb3An27 cells and in cultured midbrain dopaminergic neurons. The authors conclude that independent of cell type, constitutively internalized DAT is sorted in an ubiqutination-independent manner to late endosomes/lysosomes and in part to a Rab4 positive 'short loop' recycling pathway. Ericksen J, Yoshimoto WBE, Jorgensen TN, Cha JH, Newman AH, Gether U. Postendocytic sorting of Constitutively Internalized Dopamine Transporter in Cell Lines and Dopaminergic Neurons. J Biol Chem. e-pub June 15, 2010.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

Neural and Cardiac Toxicities Associated With 3,4-Methylenedioxymethamphetamine (MDMA)

(+/-)-3,4-Methylenedioxymethamphetamine (MDMA) is a commonly abused illicit drug which affects multiple organ systems. In animals, high-dose administration of MDMA produces deficits in serotonin (5-HT) neurons (e.g., depletion of forebrain 5-HT) that have been viewed as neurotoxicity. Recent data implicate MDMA in the development of valvular heart disease (VHD). The present paper reviews several issues related to MDMA-associated neural and cardiac toxicities. The hypothesis of MDMA neurotoxicity in rats is evaluated in terms of the effects of MDMA on monoamine neurons, the use of scaling methods to extrapolate MDMA doses across species, and functional consequences of MDMA exposure. A potential treatment regimen (l-5-hydroxytryptophan plus carbidopa) for MDMA-associated neural deficits is discussed. The pathogenesis of MDMA-associated VHD is reviewed with specific reference to the role of valvular 5-HT(2B) receptors. The authors conclude that pharmacological effects of MDMA occur at the same doses in rats and humans. High doses of MDMA that produce 5-HT depletions in rats are associated with tolerance and impaired 5-HT release. Doses of MDMA that fail to deplete 5-HT in rats can cause persistent behavioral dysfunction, suggesting even moderate

doses may pose risks. Finally, the MDMA metabolite, 3,4-methylenedioxyamphetamine (MDA), is a potent 5-HT(2B) agonist which could contribute to the increased risk of VHD observed in heavy MDMA users. Baumann MH, Rothman RB. Neural and cardiac toxicities associated with 3,4-methylenedioxymethamphetamine (MDMA). Int Rev Neurobiol 2009; 88: 257-296.

Synthetic Studies of Neoclerodane Diterpenes From Salvia Divinorum: Role of the Furan In Affinity for Opioid Receptors

Further synthetic modification of the furan ring of salvinorin A (1), the major active component of Salvia divinorum, has resulted in novel neoclerodane diterpenes with opioid receptor affinity and activity. A computational study has predicted 1 to be a reproductive toxicant in mammals and is suggestive that use of 1 may be associated with adverse effects. IRP scientists report in this study that piperidine 21 and thiomorpholine 23 have been identified as selective partial agonists at kappa opioid receptors. This indicates that additional structural modifications of 1 may provide ligands with good selectivity for opioid receptors but with reduced potential for toxicity. Simpson DS, Lovell KM, Lozama A, Han N, Day VW, Dersch CM, Rothman RB, Prisinzano TE. Synthetic studies of neoclerodane diterpenes from Salvia divinorum: role of the furan in affinity for opioid receptors. Organic & Biomolecular Chemistry 2009;7(18): 3748-3756.

Serotonergic Drugs and Valvular Heart Disease

The serotonin (5-HT) releasers (+/-)-fenfluramine and (+)-fenfluramine were withdrawn from clinical use owing to increased risk of valvular heart disease. One prevailing hypothesis (i.e., the '5-HT hypothesis') suggests that fenfluramine-induced increases in plasma 5-HT underlie the disease. Here, IRP researchers critically evaluate the possible mechanisms responsible for fenfluramine-associated valve disease. Findings from in vitro and in vivo experiments performed in the authors' laboratory are reviewed. The data are integrated with existing literature to address the validity of the 5-HT hypothesis and suggest alternative explanations. The overwhelming majority of evidence refutes the 5-HT hypothesis. A more likely cause of fenfluramine-induced valvulopathy is activation of 5-HT(2B) receptors on heart valves by the metabolite norfenfluramine. Future serotonergic medications should be designed to lack 5-HT(2B) agonist activity. Rothman RB, Baumann MH. Serotonergic drugs and valvular heart disease. Expert Opin Drug Safety 2009; 8(3): 317-329.

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Program Activities

New NIDA PAs and RFAs

On April 20, 2010, NIDA issued a PAR entitled **NIDA Research Education Program for Clinical Researchers and Clinicians (R25) (PAR-10-173)**. This PAR is a reissuance of PAR-07-221. This research education program is clinically-focused, designed to foster the development of clinical researchers, and/or train clinicians to be sophisticated consumers of research to evaluate and apply research-based findings in their practice. Participants must be in a clinically focused career, which includes health services research, at the following levels of professional career development: undergraduate (see Notice NOT-DA-10-022), medical/graduate student, postdoctoral fellow, medical resident, and/or independent scientist. This mechanism may not be used for support of non-research related clinical training.

On April 27, 2010, NIDA issued a PAR entitled **NIDA Mentored Clinical Scientists Development Program Award in Drug Abuse and Addiction (K12) (PAR-10-177)**. This institutional career development award program is designed to support career development experiences for clinical investigators (scholars) leading to research independence in the area of drug abuse and addiction. Candidates selected for support as scholars must hold a clinical or research doctorate. Under this award, scholars will be supported for 3-5 years of consecutive 12-month appointments and are strongly encouraged to apply for independent research grant support during the award period.

On June 22, 2010, NIDA issued a PA entitled **NIDA Core "Center of Excellence" Grant Program (P30) (PAR-10-220)**. NIDA Core Center of Excellence Grants (P30) are intended to bring together investigators currently funded by NIH or other Federal or non-Federal sources, to enhance the effectiveness of existing research and also to extend the focus of research to drug abuse and addiction. It is expected that a Center will transform knowledge in the sciences it is studying. Incremental work should not be the focus of Center activities; rather, new and creative directions are required. A P30 should integrate and promote research in existing funded projects, to achieve new and creative directions. It is expected that individual core activities reflect a relationship to the integrating theme of the Center and the Center is expected to support the education, training, and mentoring of new investigators, and share findings, data and their resources. Letters of Intent Receipt Date(s): September 27, 2010, August 25, 2011, August 25, 2012. Application Submission Dates(s): October 27, 2010, September 25, 2011, September 25, 2012.

On July 9, 2010, NIDA issued a PA entitled **Science Education Drug Abuse Partnership Award (R25) (PAR-10-227)**. This funding opportunity announcement (FOA) encourages Science Education (R25) grant applications to fund the development and evaluation of innovative model programs and materials for enhancing knowledge and understanding of neuroscience and the neurobiological mechanisms of drug abuse and addiction among K-12 students, the general public, health care practitioners, museums, media experts, and other educational groups. The award provides support for the formation of partnerships between scientists and educators, media experts, community leaders, and other interested organizations for the development and evaluation of programs and materials that will enhance knowledge and understanding of science related to drug abuse. The intended focus is on topics not well addressed in existing efforts by educational, community, or media activities.

On August 3, 2010, NIDA issued a PA entitled **NIDA Program Project Grant**

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Applications (P01) (PAR-10-244). This FOA is to provide support for applications from institutions/organizations that propose broadly based investigative efforts with a well defined central focus or object to address critical issues in drug abuse and addiction involving neuroscience, behavior, prevention, treatment, epidemiology, etiology, health services, HIV/AIDS or other drug abuse-related research areas.

On August 20, 2010, NIDA issued a PA entitled **Neuroscience Research on Drug Abuse (R01) (PA-10-268)**. This FOA encourages Research Project Grant (R01) applications from institutions/organizations that are relevant to the understanding of the process(es) and mechanisms underlying drug abuse and addiction, including use, dependence, addiction, withdrawal, and treatment, and may be conducted using model systems, animals, and/or humans.

On August 20, 2010, NIDA issued a PA entitled **Neuroscience Research on Drug Abuse (R21) (PA-10-269)**. This FOA encourages research grant applications from institutions/ organizations that are relevant to the understanding of the process(es) and mechanisms underlying drug abuse and addiction, including use, dependence, addiction. This research may be conducted using model systems, animals, and/or humans. The Exploratory/Developmental Grant (R21) mechanism is intended to encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research.

On August 20, 2010, NIDA issued a PA entitled **Neuroscience Research on Drug Abuse (R03) (PA-10-270)**. This FOA encourages research grant R03 applications from institutions/ organizations that are relevant to the understanding of the process(es) and mechanisms underlying drug abuse and addiction. 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. Preliminary data are not required for an R03.

On August 26, 2010, NIDA issued a PA entitled **Early Career Award in Chemistry of Drug Abuse and Addiction (ECHEM)** -- NIDA (R21/R33) (PAS-10-274). Through the issuance of this program announcement, with set aside funds (PAS), NIDA invites Phased Innovation (R21/R33) grant applications from new-to-NIH investigators into basic chemistry research applied to drug abuse and addiction. NIDA invites newly independent investigators and investigators who have not had previous NIH funding to submit applications for research projects related to NIDA's mission.

On August 26, 2010, NIDA issued an RFA entitled **Pharmacological Development of Treatment Agents and Formulations for Tobacco Dependence (STTR [R41]) (RFA-DA-11-004)**. The goal of this FOA is to facilitate the development of new, more effective treatments for tobacco dependence. Opening Date: December 13, 2010; Letters of Intent Receipt Date(s): December 13, 2010; Application Due Date(s): January 13, 2011.

PAs/RFAs Issued with Other NIH Components/Agencies

On May 21, 2010, NIDA, in collaboration with numerous other NIH components issued a Program Announcement (PA) entitled **NIH Blueprint for Neuroscience Research Competitive Revisions for Studies Focused on Neuropathic Pain or Neural Plasticity to Promote Collaborative Pain Research (R01) (PAR-10-204)**. 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 (for further information, see http://neuroscienceblueprint.nih.gov/). The goal of this FOA is to facilitate the partnering of pain scientists and non-pain neuroscientists from the field of neural plasticity to capture insights and expertise from disciplines where transitions from health to disease have been extensively examined. An expected outcome of this FOA will be the formation of partnerships between pain researchers and non-pain neuroscientists to develop new collaborations focused on understanding the maladaptive neuroplastic changes that occur during the transition from acute to chronic pain. It is anticipated that these initial collaborations will lead to new applications for highly innovative projects centered on similar studies of the transition from acute to chronic pain. The purpose of this FOA is to encourage the submission of

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competitive revision applications that propose a collaborative, one year pilot study or a new specific aim associated with an active NIH grant. The parent grant may be focused on pain or on neural plasticity outside the area of pain. This FOA will utilize the Competitive Revision grant mechanism for R01 applications. Opening Date for this PA: August 28, 2010; Application Due Date(s): September 28, 2010; September 28, 2011; September 28, 2012.

On June 10, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Development of Assays for High-Throughput Screening for use in Probe and Pre-therapeutic Discovery (R01) (PA-10-213)**. This FOA encourages Research Project Grant (R01) applications from institutions/organizations that propose the development of assays for high throughput screening (HTS) relevant to processes and diseases specific to its mission with the intent of using them to screen for small molecule compounds that show desired properties as probes for use in advancing knowledge about the relevant target, identifying new targets, or serving as pre-therapeutic leads. The NIH launched a Molecular Libraries and Imaging initiative as part of the NIH Roadmap for Medical Research to establish a network of HTS screening centers which provide access to a large compound library, robotics to carry out the assays, and informatics to interpret the results. This FOA seeks to establish a stream of scientifically and technologically outstanding assays for screening by these and other academic centers. Assays may involve targets indirectly related to disease, but which might provide insight into the biology of relevant diseases. Other targets might be associated with rare and neglected diseases, an area of increasing focus for the NIH (http://www.nih.gov/news/health/may2009/nhgri-20.htm). Assays should be relevant to the scope of the research for at least one of the sponsoring NIH Institutes.

On June 18, 2010, NIDA, in collaboration with several other NIH components, issued a PA entitled **PHASE II IICOHRTA AIDS/TB Research Training Program (U2R) (PAR-10-218)**. This FOA encourages renewal and new applications in the Phase II International Implementation, Clinical, Operations and Health Services Research Training Award for AIDS and TB (IICOHRTA AIDS/TB) program. Applications must propose, in an integrated manner, a collaborative research training program that will strengthen the capacity of institutions in low-and middle-income countries (LMIC), defined by the World Bank classification system, to conduct HIV and/or tuberculosis implementation research. Opening Date: July 16, 2010; Letters of Intent Submission Date(s): July 16, 2010; July 16, 2011; July 16, 2012; Application Due Date(s): August 16, 2010; August 16, 2011; August 16, 2012.

On June 18, 2010, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **AIDS International Training and Research Program (AITRP) (D43) (PAR-10-219)**. This FOA encourages renewal and new applications in the AIDS International Training and Research Program (AITRP). The application must propose a collaborative research training program that will strengthen the capacity of institutions in low-and middle-income countries (LMIC), defined by the World Bank classification system, to conduct HIV-related research. Opening Date: July 16, 2010;Letters of Intent Submission Date(s): July 16, 2010; July 16, 2011; July 16, 2012; Application Due Date(s): August 16, 2010; August 16, 2011; August 16, 2012.

On July 1, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Advancing Novel Science in Women's Health Research (ANSWHR) (R21) (PAS-10-226)**. The purpose of this Funding Opportunity Announcement (FOA), issued by the Office of Research on Women's Health (ORWH) and co-sponsoring NIH institutes and centers (ICs), is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. ORWH is particularly interested in encouraging extramural investigators to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health; however, applications in all areas of women's health and/or sex/gender research are invited. Opening Date: September 16, 2010; Application Due Dates: October 16, 2010; October 16, 2011, October 16, 2012 for new applications; November 16, 2010; November 16, 2011; November 16, 2012 for resubmission applications.

On July 9, 2010, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Structural Biology of Membrane Proteins (R01) (PA-10-228)**. This FOA encourages grant applications from institutions/organizations that propose to develop research and methods to enhance the rate of membrane protein structure determination and to determine specific membrane protein structures.

Innovative methods for expression, oligomerization, solubilization, stabilization, purification, characterization, crystallization, isotopic labeling, and structure determination of unique and biologically significant membrane proteins by x-ray diffraction, nuclear magnetic resonance (NMR), electron microscopy, mass spectrometry, and other biophysical techniques are encouraged. Projects that will lead in the near term to determining the structures of biologically important membrane proteins are also encouraged. Responding to this FOA, rather than the regular investigator-initiated Research Project Grant (R01) FOA, will help NIH staff track interest and progress of research in this scientific area.

On July 21, 2010, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Bioengineering Research Partnerships (BRP)(R01) (PAR-10-234)**. Through this FOA, participating Institutes and Centers (ICs) of the National Institutes of Health (NIH) invite applications for R01 awards to support Bioengineering Research Partnerships (BRPs) for basic, applied, and translational multi-disciplinary research that addresses important biological, clinical or biomedical research problems. In the context of this program, a partnership is a multi-disciplinary research team, that applies an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. The partnership must operate according to a clear leadership plan and include appropriate bioengineering or allied quantitative sciences in combination with biomedical and/or clinical components. BRPs may propose, within a 12-page research strategy section, design-directed, developmental, discovery-driven, or hypothesis-driven research at universities, national laboratories, medical schools, large or small businesses, or other public and private entities or combinations of these entities, and will be evaluated against expanded review criteria. It is expected that a BRP will have a well-defined goal or deliverable that will be achieved in a 5-10 year timeframe based on objective milestones specified in the initial application.

On August 10, 2010, NIDA, in collaboration with a number of other NIH components, issued a PA entitled **Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award (NCD-LIFESPAN) (D43) (PAR-10-257)**. This FOA encourages applications for the Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award (NCD-LIFESPAN) D43 program for collaborative research training between institutions in the U.S. and low-and middle-income countries (LMIC), defined by the World Bank classification system. The proposed institutional research training program is expected to sustainably strengthen the research capacity of the LMIC institutions, and to train in-country experts to conduct research on chronic, non-communicable diseases and disorders across the lifespan, with the ultimate goal of implementing evidence-based interventions relevant to their countries. Opening Date: October 2, 2010; Letters of Intent Receipt Date(s): October 2, 2010, August 21, 2011, August 21, 2012; Application Due Date(s): November 2, 2010, September 21, 2011; September 21, 2012.

On July 9, 2010, NIDA, in collaboration with NIGMS and other NIH institutes, issued a PA entitled **Structural Biology of Membrane Proteins (R01) (PA-10-228)**. NIH invites applications proposing to enhance the availability of three dimensional structures of relevant membrane proteins by analytical and biophysical methods.

On May 18, 2010, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **U.S.-India Bilateral Collaborative Research Partnerships (CRP) on the Prevention of HIV/AIDS and Co-morbidities (R21) (RFA-AI-10-022)**. This FOA solicits Exploratory/Developmental (R21) applications from United States (U.S.)-funded institutions with an Indian-institution partner to establish Collaborative Research Partnerships (CRP) in the field of HIV/AIDS prevention or in preventing, treating, or ameliorating HIV-related co-morbidities such as malignancies, metabolic complications or opportunistic infections (OIs). The U.S.-India Bilateral CRP Program is designed to develop collaborations between scientists and institutions in the U.S. and India to conduct high quality HIV/AIDS prevention research of mutual interest and benefit to both countries while developing the basis for future institutional and individual scientific collaborations. This FOA will utilize the research capacities of the institutions and scientists in both countries to advance the field of HIV/AIDS prevention and to develop preliminary data that may support a more extensive future research proposal to test an HIV/AIDS prevention program. Opening date for this RFA: July 2, 2010; Letters of Intent Receipt Date: July 2, 2010; Application due date: August 3, 2010.

On June 10, 2010, NIDA, in collaboration with NIMH, issued an RFA entitled **Seek, Test, Treat, and Retain: Addressing HIV among Vulnerable Populations (R01)**

(RFA-DA-11-001). This FOA solicits R01 applications for both domestic and international studies that test the seek, test, treat, and retain paradigm. This paradigm predicts that expanding HIV testing and reducing viral load among HIV+ individuals through HAART therapy can be effective in reducing the HIV transmission at a population level. In particular, this FOA focuses on research on expanding HAART therapy coverage to reduce HIV transmission among high-risk, vulnerable populations. Opening Date for this RFA: October 15, 2010; Letters of Intent Receipt Date(s): October 15, 2010; Application Due Date(s): November 15, 2010.

On July 7, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Epigenomics of Human Health and Disease (R01) (RFA-ES-10-002)**. This funding opportunity announcement (FOA) invites applications proposing highly innovative research that will investigate the epigenetic basis of human diseases. These studies will discover and define epigenetic marks or features and their possible interactions in cells and tissues that are representative of various human disease states, conditions or processes. Studies may also investigate the mechanism by which epigenetic changes occur in diseased or otherwise compromised states, and how these changes result in phenotypic differences. Letters of Intent Receipt Date: August 29, 2010; Application Due Date: September 29, 2010.

On August 3, 2010, NIDA, in collaboration with numerous other NIH components issued an RFA entitled **Effects of the Social Environment on Health: Measurement, Methods and Mechanisms (R01) (RFA-DA-11-003)**. This FOA, issued as part of the NIH Basic Behavioral and Social Science Opportunity Network (OppNet), solicits Research Project Grant (R01) applications from institutions/organizations that propose to investigate structural, behavioral, sociocultural, environmental, cognitive, emotional, and/or biological mechanisms through which the social environment affects health outcomes. To address this objective, applicants should propose research studies that will: (1) deepen our understanding of which aspects of social environments affect health outcomes for women and men at different stages of the lifecourse and in different social, economic, geographic, racial and ethnic sub-populations; (2) lead to a clearer understanding of mechanisms through which social environments have such effects; or (3) improve measurement methods and/or contribute to advances in analytic methods used in the study of social environments and health. Opening Date: December 6, 2010; Letters of Intent Receipt Date(s): December 6, 2010; Application Due Date(s): January 6, 2011.

On August 5, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Sleep and Social Environment: Basic Biopsychosocial Processes (R01) (RFA-HD-11-101)**. This FOA issued by the Basic Behavioral and Social Sciences Research Opportunity Network (OppNet), National Institutes of Health, solicits Research Project Grant (R01) applications from institutions/organizations that propose to investigate the reciprocal interactions of the processes of sleep and circadian regulation and function with behavioral and social environment processes. Sleep is a complex biological phenomenon that is essential to normal behavioral and social functioning, as well as optimal health. In spite of its vital nature, the mechanisms by which social environment factors affect sleep behavior patterns have not been studied systematically, especially within the contexts of individual vulnerabilities and resilience. There is a need for greater understanding of the dynamic relationships between behavioral and social environment factors on the one hand and the basic mechanisms of sleep-wake and circadian regulation and function on the other. This FOA is not intended to support research on or development of treatments or interventions for disorders of sleep or circadian rhythms. Opening Date: September 8, 2010; Letters of Intent Receipt Date(s): September 8, 2010; Application Due Date(s): October 8, 2010.

On August 5, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Sleep and Social Environment: Basic Biopsychosocial Processes (R21) (RFA-HD-11-102)**. This FOA issued by the Basic Behavioral and Social Sciences Research Opportunity Network (OppNet), National Institutes of Health, solicits Research Project Grant (R21) applications from institutions/organizations that propose to investigate the reciprocal interactions of the processes of sleep and circadian regulation and function with behavioral and social environment processes. Sleep is a complex biological phenomenon that is essential to normal behavioral and social functioning, as well as optimal health. In spite of its vital nature, the mechanisms by which social environment factors affect sleep behavior patterns have not been studied systematically, especially within the context of individual vulnerabilities and resilience. There is a need for greater understanding of the dynamic relationships between behavioral and social environment factors on the one hand and the basic mechanisms of sleep-wake and circadian regulation and

function on the other. This FOA is not intended to support research on or development of treatments or interventions for disorders of sleep or circadian rhythms. Letters of Intent Receipt Date(s): September 8, 2010; Application Due Date(s): October 8, 2010.

On August 10, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Basic Research on Self-Regulation (R21) (RFA-AG-11-010)**. This FOA issued by the NIH Basic Behavioral and Social Sciences Opportunity Network (OppNet) solicits exploratory/developmental (R21) research applications examining basic mechanisms of self-regulation. The intent of this FOA is to advance research on basic processes and mechanisms of self-regulation, capitalizing on recent advances in methods and theory from the psychological (social, personality, developmental), economic, neuroscience, sociocultural, and other behavioral and social science literatures. The current lack of consistency and conceptual integration in how self-regulation is studied across a range of disciplines hinders our understanding of the basic mechanisms underlying many important health and developmental outcomes. Applications submitted to this FOA are expected to address one or more of the following basic behavioral and social science research (b-BSSR) challenges: (1) to precisely identify and operationally reconcile the basic processes and mechanisms involved in self-regulation of cognition, emotion, and behavior, and refine their measurement and theoretical conceptualizations, (2) to assess relations among various self-regulatory functions and their sub-components, and (3) to systematically characterize changes in self-regulatory functions over time, across different social and environmental contexts, and across the lifespan in both men and women. Proposals are expected to engage investigators working at multiple levels of analysis and across disparate literatures. Letters of Intent Receipt Date: December 6, 2010; Application Due Date: January 6, 2011.

On August 13, 2010, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Validation and Field Testing of New Tools for Characterizing the Personal Environment (R01) (RFA-ES-10-007)**. This FOA solicits applications to conduct field testing and initial validation of existing prototype tools for characterizing the personal environment including chemical exposures, diet, physical activity, psychosocial stress and the use of addictive substances. Applicants must have a functional prototype which has been validated under controlled (i.e., laboratory) conditions and partner with an ongoing human subjects research study with existing reference measures to assess the validity and usability of the prototype as well as the additional scientific impact of the exposure metric. Limited support for device refinement and expansion of the study cohort is allowable but not the focus of this FOA. Opening Date: September 21, 2010; Letters of Intent Receipt Date(s): September 21, 2010; Application Due Date(s): October 21, 2010.

On August 13, 2010, NIDA, in collaboration with NIAAA and NIEHS, issued an RFA entitled **Validation and Field Testing of Novel Biomarkers of Response to Environmental Stressors (R01) (RFA-ES-10-008)**. This FOA solicits grant applications from institutions/ organizations to conduct pilot testing of novel candidate biomarkers and technologies that measure biological responses to chemical toxicants and other environmental stressors. Through collaborations with existing human population studies, investigators will conduct a rigorous evaluation of the performance of novel biomarkers and technologies under a range of exposure levels and collection and storage conditions, to establish the potential and feasibility of applying these novel approaches to large-scale epidemiology and gene-environment studies. Applicants will be expected to describe characteristics of their candidate biomarkers or technologies (e.g., laboratory validation studies, limits of detection, and preliminary data from discovery cohort studies) that demonstrate their suitability for further pilot testing. The goal of this 2-year program is to assess the performance (including testing for sensitivity, specificity, reliability and reproducibility) of these novel approaches in independent cohorts. The emphasis of this FOA is the validation of promising biomarkers and technologies; projects to discover and develop new technology and biomarkers of response are not appropriate to this solicitation and will be returned as nonresponsive. Opening Date: September 21, 2010; Letters of Intent Receipt Date(s): September 21, 2010; Application Due Date(s): October 21, 2010.

On August 17, 2010, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) (R01) (RFA-GM-11-003)**. This FOA solicits Research Project Grant (R01) applications from institutions/organizations proposing exceptionally innovative research on novel hypotheses or difficult problems, solutions to which would have an extremely high impact on biomedical or biobehavioral research that is germane to the mission of one or more of the participating NIH

Institutes. This FOA is for support of new projects, not continuation of projects that have already been initiated. It does not support pilot projects, i.e., projects of limited scope that are designed primarily to generate data that will enable the PD/PI to seek other funding. Opening Date: September 21, 2010; Application Due Date(s): October 21, 2010.

On August 17, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Psychosocial Stress and Behavior: Integration of Behavioral and Physiological Processes (R01) (RFA-HL-11-033)**. This FOA issued by the NIH Basic Behavioral and Social Sciences Opportunity Network (OppNet) solicits Research Project Grant (R01) applications from institutions and organizations that propose to investigate the mechanistic pathways linking psychosocial stressors and behavior. This research will facilitate investigation of multiple and potentially bidirectional pathways underlying the link between psychosocial stressors and behaviors that may ultimately impact biological function, health, and disease. Applicants are encouraged to use model systems and longitudinal approaches to design innovative and integrative studies to elucidate how psychological factors, social factors, and environments impact the processes by which stressors are coupled with and influenced by various behaviors. Applications examining moderating factors such as individual demographic (age, gender/sex, ethnicity) and psychological (vulnerabilities, resilience) differences, risk factors, early exposure, and environments (including toxicants) are desirable. This research will provide a deeper understanding of the psychological, environmental, and social processes that ultimately connect psychosocial stress to behaviors, physiological processes, health, and disease. Opening Date: September 14, 2010; Letters of Intent Receipt Date(s): September 14, 2010; Application Due Date(s): October 14, 2010.

On August 17, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Development of Comprehensive and Conceptually-based Measures of Psychosocial Stress (R21) (RFA-HL-11-034)**. This FOA issued by the NIH Basic Behavioral and Social Sciences Opportunity Network (OppNet) solicits Research Project Grant (R21) applications from institutions and organizations that propose to develop and test conceptually-based and comprehensive measures of psychosocial stress that can be applied across species and across the lifespan. Applicants submitting proposals under this FOA are encouraged to incorporate variations in exposures, chronicity, environments (including toxicants and social environments), cognitions, and responses, as well as capture important factors for measuring stress in both humans and animals, in men and women, and across the lifespan. Such studies should demonstrate that the measures, coupled with appropriate bridges between laboratory and population-based designs, advance our understanding of the components of psychosocial stressors that are most relevant to disease, and provide comparability across studies. Opening Date: September 14, 2010; Letters of Intent Receipt Date(s): September 14, 2010; Application Due Date(s): October 14, 2010.

On August 17, 2010, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Basic Mechanisms Influencing Behavioral Maintenance (R01) (RFA-HL-11-035)**. This FOA issued by the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) solicits research applications examining basic mechanisms of behavioral maintenance. The intent of this FOA is to advance research on basic processes and mechanisms involved in sustaining learned behavior over time and in the context of dynamic environmental influences and changing psychological and biological states. Maintenance of health behavior change is a critical problem in applied clinical research, and innovative strategies to address this problem require a better understanding of basic processes and mechanisms involved in long-term behavior maintenance. This FOA requests applications that will improve our understanding of how newly learned, effortful, and goal-directed behaviors transition to less effortful, automatic, and essentially non-goal-directed behaviors that are more easily maintained over time. A range of possible processes and mechanisms (e.g., neurobiological, cognitive, and environmental) may be proposed for study, and applicants are encouraged to study multiple mechanisms and their potential interactions. Regardless of mechanisms or processes of interest, however, applications should test how these mechanisms and processes facilitate or impede the transition from newly learned, effortful, and goal-directed behaviors to less effortful, automatic, and essentially non-goal-directed behaviors. A wide array of research proposals are potentially appropriate under this FOA, ranging from animal neurobehavioral models to human learning studies of social and environmental influences that facilitate or impede the transition to habitually maintained behaviors. Opening Date: September 14, 2010; Letters of Intent Receipt Date(s): September 14, 2010; Application Due Date(s): October 14, 2010.

On August 27, 2010, NIDA, in collaboration with numerous other NIH components issued an RFA entitled **Scientific Meetings for Creating Interdisciplinary Research Teams in Basic Behavioral and Social Science Research (R13) (RFA-CA-10-017)**. This FOA solicits Research Conference Grant (R13) applications for scientific meetings aimed at building interdisciplinary research teams in basic behavioral and social science research (b-BSSR). Applicants must propose developmental activities (i.e., meetings/workshops) that will build the capacity of interdisciplinary teams to accelerate, expand, and/or strengthen fundamental knowledge in b-BSSR as relevant to the Nation's health and well-being. Proposed interdisciplinary teams must include at least one investigator from the basic social and/or behavioral sciences, and must include investigators from at least one additional discipline. Applicants are encouraged to either: (1) accelerate, expand, and/or strengthen the scope of investigation of a specific b-BSSR research domain through the integration of disparate approaches from b-BSSR and allied disciplines; or (2) increase the sophistication of theoretical, methodological, and analytical approaches in b-BSSR. These goals may be accomplished by fostering the development of shared scientific terminology, approaches, and methodologies across disciplines in order to address a common b-BSSR research question. Investigators may submit applications to support multiple meetings over a period of up to two years. Opening Date: November 14, 2010; Letters of Intent Receipt Date(s): November 14, 2010; Application Due Date(s): December 14, 2010.

Other Program Activities

Clinical Trials Network (CTN) Update

Protocols: A total of 45 protocols have been initiated since 2001, including multi-site clinical trials (31), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 23 ancillary studies have been supported by CTN and non-CTN funds. There are about 11,500 participants enrolled in CTN 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 0017**, HIV and HCV Intervention in Drug Treatment Settings
- **Protocol CTN 0018**, Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment
- **Protocol CTN 0019**, Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment
- **Protocol CTN 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.
- **Protocol CTN 0030**, Effects of Chronic Opioids in Subjects with a History of Opioid Use

In addition, the following protocols have submitted primary paper:

- **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)
- **Protocol CTN 0030**, Prescription Opioid Addiction Treatment Study (POATS)

The following protocols have locked data:

- **Protocol CTN 0030A1**, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR; it is in the data analysis 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. Recruitment was completed on September 30, 2009, yielding a total of 471 randomized participants across 10 sites. This total represents 21 more participants than proposed and was reached one week earlier than planned. Data lock was June 14, 2010; the study is now in the data analysis phase.
- **Protocol CTN 0031A1**, An Evaluation of Neurocognitive Function, Oxidative Damage, and Their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers. Recruitment was completed on September 30, 2009, yielding a total of 173 participants across 6 sites completing the data collection and blood draw procedures. Data lock was June 14, 2010; the study is now in the data analysis phase.
- **Protocol 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 lock was June 14, 2010; the study is now in the data analysis phase.
- **Protocol CTN 0031A3**, Organizational and Practitioner Influences on Implementation of STAGE-12. The study assesses the influence of counselor and organizational variables on fidelity of the STAGE-12 intervention during the clinical trial, tests the impact of fidelity on clinical trial participant outcomes, and explores the influence of counselor and organizational variables on sustainability of the STAGE-12 intervention following completion of the clinical trial. Study staff has already collected the organizational and counselor level data from all ten STAGE-12 sites. The baseline data obtained in this research formed the foundation for an R01 grant awarded by DESPR to Joseph Guydish, PhD, at the University

of California, San Francisco.

- **Protocol CTN 0032**, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S. This study randomized 1281 participants 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 enrollment and is currently in the data analysis phase.

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

- **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). 1,269 participants were randomized. Data collection is expected to end in June, 2010.
- **Protocol CTN 0027A1**, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies. This ancillary study consented 843 of the 1,269 subjects from the START study. Data collection is expected to end in June, 2010.
- **Protocol CTN 0030A3**, POATS Long-Term Follow Up Study (LTFU) is being conducted at all POATS sites to examine long-term outcomes for individuals who participated in CTN-0030 with opioid analgesic (OA) dependence. This study will follow POATS participants for 42 months after randomization in the POATS study.
- **Protocol CTN 0032A1**, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This 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.
- **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 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 currently enrolling:

- **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 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 0037**, Stimulant Reduction Intervention Using Dosed Exercise (STRIDE). This randomized clinical trial is testing the efficacy of the addition of exercise to treatment as usual in improving drug abuse treatment outcomes in patients abusing stimulants. As of August 5, 2010, ten participants have been enrolled at 4 sites.
- **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. As of July 22, 2010, 29 randomized participants have been enrolled from 10 sites.

- **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.

The following protocols are in the implementation/development phase:

- **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 0044A2**, Acceptability of a Web-delivered, Evidence-based, Psychosocial Intervention among Individuals with Substance Use Disorders who Identify as American Indian/Alaska Native. Results from prior research support the efficacy of a web-based version (Therapeutic Education System: TES) of the Community Reinforcement Approach (CRA) with individuals in outpatient substance abuse treatment; however, TES has yet to be tested among American Indian/Alaska Native (AI/AN) populations. The principal objective of this study is to explore the acceptability of TES among a diverse sample of AI/AN enrolled in outpatient substance abuse treatment. The study is in the pre-implementation phase.
- **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 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. Training for the two Wave 1 sites took place July 19-21, 2010 in Albuquerque, NM. Initial enrollment is expected to open later in the summer. Four additional Wave 2 sites were selected this summer and will be trained in November 2010.
- **Protocol CTN 0048**, Cocaine Use Reduction with Buprenorphine (CURB). This concept is currently being developed into a protocol. The aim of this study is to investigate the safety and efficacy of buprenorphine in the presence of naltrexone for the treatment of cocaine dependence in a sample of individuals who meet criteria for cocaine dependence and lifetime opioid dependence or cocaine dependence and past year opioid abuse.
- **Protocols CTN 0037A1, CTN-0044A1, CTN0046A1, and CTN0047A1**, Organizational and Practitioner Influences on Patient Outcomes. This series of ancillary studies will assess associations between site organizational and practitioner variables and site differences in clinical trial outcomes.

- **Protocol CTN 0049**, Project HOPE (Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users) has been approved to develop into a full protocol. The study will evaluate the effectiveness of a brief intervention, delivered to HIV-infected drug users recruited from the hospital setting, in achieving viral suppression.
- **Protocol CTN 0050**, Long Term Follow Up of START Patients. This concept has been approved for further development into a protocol. The study will follow patients from the CTN 0027 START (Starting Treatment with Agonist Replacement Therapies) study for 3-5 years to determine longer-term outcomes of Suboxone versus methadone treatment and investigate factors associated with post-START treatment access, utilization as well as providers' attitudes and knowledge regarding Suboxone and its adoption.

In addition to the primary CTN trials, there are currently five secondary analyses underway using data across several of the completed trials. Manuscripts are in progress and/or being prepared by the investigators. Posters are being presented at scientific meetings for several of the trials.

1. Gender Differences in the Prevalence and Predictors of HIV Risk Behaviors, PI: Audrey Brooks (CA/AZ Node) - paper published by Substance Use and Misuse;
2. Pattern of alcohol use and alcohol-related diagnoses among drug abusing/dependent participants, PIs: Dennis Donovan and Bryan Hartzler (Pacific Northwest Node); poster at ICTAB, paper published by Journal of Substance Abuse Treatment, Manuscript submitted to special issue of AJDAA.
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); poster at CPDD, Manuscript submitted to special issue of AJDAA.
4. The Efficacy of Motivational Enhancement Therapy for African Americans, PI: Kathleen Burlew (Ohio Valley Node); poster at CPDD, Manuscript submitted to special issue of AJDAA.
5. Substance Abuse Treatment Outcomes in Racial/Ethnic Minority Populations, PI: Carmen Masson (California-Arizona Node).

There are also approximately 45 funded studies supported by independent grants that use CTN studies as a platform.

Science Education

Two NIDA grants received administrative supplements as part of the NIH's Blueprint for Neuroscience Research supplement program for R25 science education grants. A total of only 6 supplements were awarded across all of NIH. Drs. Rochelle Schwartz-Bloom and Leslie Miller both received supplements for their outstanding Science Education Drug Abuse Partnership Award funded science education programs.

NIDA's New and Competing Continuation Grants Awarded Since May 2010

Aharonovich, Efrat -- New York State Psychiatric Institute
Healthcall: Brief Intervention to Reduce Drug Use in HIV Primary Care

Al'absi, Mustafa N. -- University of Minnesota, Twin Cities
Stress Response and Opioid Dysfunction in Nicotine Dependence

Altice, Frederick Lewis -- Yale University
Prison Interventions and HIV Prevention Collaboration

Ananthan, Subramaniam -- Southern Research Institute
Targeted Library Synthesis and Screening: Allosteric Modulators of Transporters

Back, Sudie E. -- Medical University of South Carolina
Integrated Treatment of OEF/OIF Veterans with PTSD and Substance Use Disorders

Bartlett, Selena E. -- Ernest Gallo Clinic and Research Center
Identifying Chemical Modulators of CRF-Binding Protein and CRF Receptor Complexes

Becker, Jill B. -- University of Michigan at Ann Arbor
Protective Benefits of Maternal Behavior on Susceptibility for Drug Abuse

Bickel, Warren K. -- University of Arkansas Medical Sciences, Little Rock
Inter-Temporal Trade-Offs in the Risky Decisions of Cocaine Addicts

Binswanger, Ingrid A. -- University of Colorado Denver
HIV Risk Behavior in Drug-Involved Former Inmates

Bland, Sondra T. -- University of Colorado Denver
Social Influences on Drug Reward and Monoamines

Borders, Tyrone Finley -- University of Arkansas Medical Sciences, Little Rock
Rural and Urban African American Cocaine Users' Perceived Need for Care

Boyden, Edward S. -- Massachusetts Institute of Technology
Novel Platforms for Systematic Optical Control of Complex Neural Circuits in Vivo

Brene, Stefan -- Karolinska Institute
Role of Nogo Receptor in Addiction

Brouwer, Kimberly C. -- University of California, San Diego
Evolving HIV/STI Risk Environments of FSWs on the Mexico/U.S. Border

Caldwell, Linda Lee -- Pennsylvania State University-University Park
Healthwise Dissemination: Translation to Multiple Schools

Carrico, Adam Wayne -- University of California, San Francisco
A Pilot RCT of Expressive Writing with HIV-Positive Methamphetamine Users

Carroll, Frank I. -- Research Triangle Institute
Selective Opioid Antagonists as Medications for Drug Abuse

Chang, Yu-Ping -- State University of New York at Buffalo
Prescription Psychotherapeutic Drug Use Among Older Adults

Chawarski, Marek C. -- Yale University
Behavioral Drug and HIV Risk Reduction Counseling with MMT in China

Churchwell, John Clyburn -- University of Utah
Imaging the Fronto-Limbic-Striatal Circuit in Adolescent Cannabis Users

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

Conger, Rand Donald -- University of California, Davis
Mexican Family Culture and Substance Use Risk and Resilience

Cooper, Hannah L. -- Emory University
Public Housing Relocations: Impact on HIV Risk and Drug Use

Corsi, Karen F. -- University of Colorado, Denver
Reduction of Drug Use and HIV Risk Among Out-of-Treatment Methamphetamine Users

Cullen, Bryan R. -- Duke University
HIV-1: micrORNA Interactions

Dallery, Jesse -- National Development and Research Institutes
Internet-Based Group Contingency Management to Promote Smoking Abstinence

Dore, Gregory J. -- University of New South Wales
Treatment of Recently Acquired Hepatitis C Virus Infection

Dougherty, Donald M. -- University of Texas Health Science Center, San Antonio
Consequences of Adolescent Substance Use on the Development of Impulse Control

Eitle, David -- Montana State University (Bozeman)
Understanding Racial Disparities in Teen Methamphetamine Use

France, Charles P. -- University of Texas Health Science Center, San Antonio
Delay Discounting: Effects of Drug Dependence and Withdrawal

Frank, Deborah A. -- Boston Medical Center
Prenatal Cocaine Exposure: Young Adult Follow Up

Fuller, Crystal M. -- Columbia University Health Sciences
Post Exposure Prophylaxis Among IDU Syringe Customers-Pharmacy Pilot Intervention

Garner, Bryan R. -- Chestnut Health Systems, Inc.
Impact, Predictors, and Mediators of Therapist Turnover

Gendelman, Howard E. -- University of Nebraska Medical Center
Nanoart Manufacture, Delivery and Pharmacokinetics for Optimizing Drug Adherence

Gewirtz, Abigail -- University of Minnesota Twin Cities
Effectiveness of a Web-Enhanced Parenting Program for Military Families

Gintzler, Alan R. -- SUNY Downstate Medical Center
Sex-Dependent Expression and Utilization of Spinal Mu- and Kappa-Opioid Systems

Heimer, Robert -- Yale University
Influences on HIV Prevalence and Service Access Among IDUs in Russia and Estonia

Hudson, Teresa Jo -- University of Arkansas Medical Sciences, Little Rock
Use and Abuse of Prescription Opioids Among OEF/OIF Veterans

Hulgan, Todd M. -- Vanderbilt University
Mitochondrial Genomics and Effects of Cocaine on T-Cells During HIV-Infection

Janda, Kim D. -- Scripps Research Institute
Vaccines for the Treatment of Opiate Addiction

Janda, Kim D. -- Scripps Research Institute
Immunopharmacotherapy for the Treatment of Cocaine Abuse

Jensen, John E. -- McLean Hospital (Belmont, MA)
Proton Echo-Planar Spectroscopic Imaging of GABA, Glutamate/Glutamine at 4 Tesla

Kable, Joseph W. -- University of Pennsylvania
Neural Mechanisms Underlying Changes in Preference

Kalivas, Peter W. -- Medical University of South Carolina
Cocaine, Opoids and Drug Abuse

Kennedy, Mary B. -- California Institute of Technology
CRCNS: Modeling Activation of CaMKII in Spines

Khan, Maria Rabia -- University of Maryland, College Park Campus
Relationship Disruption During Incarceration and HIV Risk in African American Men

Kiehl, Kent A. -- The Mind Research Network
Action Monitoring, Action Observation and Dopamine Genes as Predictors of Substance

Kleinfeld, David -- University of California, San Diego
CNiFERs Cell-Based Neurotransmitter Fluorescent Engineered Reporters

Kornbluth, Richard -- Multimeric Biotherapeutics, Inc.
Precision Immunization Vaccine for Nicotine and Other Drugs of Abuse

Kotelchuck, Milton -- Boston University Medical Campus
Linking State Data to Identify Unmet Need for Drug Treatment in Women Aged 15-49

Kurtz, Steven P. -- University of Delaware
A Self-Assessment Intervention for Young Adult Polydrug Users at Risk for HIV

Ladias, John A.A. -- Beth Israel Deaconess Medical Center
Structural Basis for Cannabinoid Receptor 2 Signaling

Langford, Teresa Dianne -- Temple University
Cocaine and HIV-Mediated Disruptions of Hypothalamic Signaling in Hypothyroidism

Larson, Mary Jo -- Brandeis University
First Longitudinal Study of Missed Treatment Opportunities Using DOD and VA Data

Latimer, William W. -- Johns Hopkins University
Four-Arm RCT of Brief MI vs. Couples-Based HIV/STI Prevention in South Africa

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

Lerman, Caryn -- University of Pennsylvania
Pharmacogenetics of Nicotine Addiction Treatment

Lester, Henry A. -- California Institute of Technology
Nicotinic Ligands for Smoking Cessation

Lester, Henry A. -- California Institute of Technology
Alpha4 Nicotinic Receptor in Addiction: Mouse Models

Levy, Jay A. -- University of California San Francisco
Protection from HIV Infection in Intravenous Drug Users

Li, Li -- University of California, Los Angeles
Development of a Family Intervention to Address Drug Use and HIV in Vietnam

Lipford, Grayson B. -- Selecta Biosciences, Inc.
Development of a Next Generation Vaccine for Smoking Cessation and Relapse Prevention

Liu, Philip K. -- Massachusetts General Hospital
Aptamer Imaging: A Theranostic Approach to Treat Substance Abuse

Lynch, Wendy Jean -- University of Virginia, Charlottesville
Dopaminergic and Glutamatergic Mechanisms of Cocaine Addiction: Sex Differences

Mach, Robert H. -- Washington University
PET Radiotracers for Imaging the Dopamine D3 Receptor

Mackie, Kenneth P. -- Indiana University, Bloomington
Neuronal Cannabinoids

MacPherson, Laura -- University of Maryland, College Park Campus
Behavioral Activation Intervention, Reward Processing and Youth Smoking Cessation

MacPherson, Laura -- University of Maryland, College Park Campus
Stage II Trial of Novel Behavioral Activation Intervention for Smoking Cessation

Madden, Gregory J. -- Utah State University
Experimental Manipulations of Impulsivity: Effects on Gambling and Drug Taking

Mahajan, Supriya Dinkar -- State University of New York at Buffalo
Innovative Nanotherapy for Drug Addiction.

Mandara, Jelanin -- Northwestern University
Parenting Prevention-Intervention for Mothers of African American Adolescent Males

Margolis, David M. -- University of North Carolina, Chapel Hill
HIV Latency, Epigenetics, and Therapeutics

Mason, W. Alex -- Father Flanagan's Boys' Home
Skills Training for Parents and Teens to Improve the Transition to High School

McCann, Una D. -- Johns Hopkins University
PET Studies of the SERT and DAT in Meth Users

McCarthy, Danielle Erin -- Rutgers the State University of NJ, New Brunswick
Evaluation of Learning-Theory-Based Smoking Cessation Strategies

McDonald, Patricia Helen -- Scripps Research Institute
Development of Chemical Probes to Investigate the Role of Ntsr1 in Cns Disorders

McGovern, Mark P. -- Dartmouth College
A Stage II Efficacy Study of CBT for PTSD in Community Addiction Treatment

McGovern, Mark P. -- Dartmouth College
Integrated CBT for Co-Occurring PTSD and Substance Use Disorders

Mercier, Richard W. -- Northeastern University
Ligand Assisted Protein Structure: A Novel Method for Deducing Ligand Binding Arc

Mesangeau, Christophe M. -- University of Mississippi
Non-Peptidic Neuropeptide FF Receptor Probes

Miller, Gregory M. -- Harvard University (Medical School)
Epigenetic Regulation of Serotonin: Relevance to HIV and Methamphetamine Abuse

Molina, Patricia E. -- Louisiana State University HSC, New Orleans
Cannabinoid Epigenomic and MiRNA Mechanisms Impact HIV/SIV Disease Progression

Moron-Concepcion, Jose A. -- Columbia University Health Sciences
AMPA Receptors: Common Role in Opiate Withdrawal and Pain Sensitivity

Moroz, Leonid L. -- University of Florida
Spatial Organization of the Genome in Identified Neurons of Memory Circuits

Nestler, Eric J. -- Mount Sinai School of Medicine of NYU
Neurotrophic Mechanisms in Opiate and Cocaine Action

Ohlmeyer, Michael -- Mount Sinai School of Medicine of NYU
Small Molecule Libraries Targeted to CBP and Attenuation AfosB Expression

Parsons, Jeffrey T. -- Hunter College
Intervention Targeting Substance Using Older Adults with HIV

Perry, Seth -- University of Rochester
GSK3, Endocytosis, and Enhanced HIV Infection: Abused Drugs and Novel Therapies

Posner, Michael -- University of Oregon
Reducing Addiction Through Training Brain States

Rana, Tariq M. -- Burnham Institute for Medical Research
Regulation of HIV Infection by Methamphetamine and Non-Coding RNAs

Rice, Andrew P. -- Baylor College of Medicine
Effects of Cocaine on MiRNAs That Regulate HIV-1 Replication

Riggins, Tracy -- University of Maryland, College Park Campus
Neural Correlates of Risk-Taking in Adolescents Exposed to Drugs Prenatally

Rosenblum, Andrew Bruce -- National Development and Research Institutes
Web-Based CBT for Opioid-Treated, Chronic Pain Patients with Aberrant Behavior

Rothenberg, Richard B. -- Georgia State University
Network-Directed Community Screening for HIV

Rusyniak, Daniel E. -- Indiana University-Purdue University at Indianapolis
CNS Circuitry and Receptors Mediating the Effects of MDMA

Schultz, John Albert -- Ionwerks, Inc.
Bio-Mass Spec Microanalysis Augments Optical Histology

Sevy, Serge -- Feinstein Institute for Medical Research
Improving Substance Use and Clinical Outcomes in Heavy Cannabis Users

Shacham, Enbal -- Washington University
Where to Intervene? Geospatial Variation of HIV Transmission Behaviors

Shane, Matthew -- The Mind Research Network
Using Real-Time fRMI to Facilitate Neuromodulation to Drug-Cues in Adolescent Abu

Shane, Matthew -- The Mind Research Network
Error Detection and Error Awareness in Incarcerated Cocaine Dependent Individuals

Shannon, Kate -- University of British Columbia
Social and Structural Context of HIV/STI Risk Among FSWs

Sharma, Anjali -- SUNY Downstate Medical Center
Insulin-Like Growth Factor and Bone Mineral Density in HIV-Infected Women and Men

Shin, Sunny H. -- Boston University
Childhood Interpersonal Trauma and Substance Abuse

Spirito, Anthony N. -- Brown University
Individual and Family Motivational Interviews for Substance Using Truant Teens

Strain, Eric C. -- Johns Hopkins University
Medications Development for Drug Abuse Disorders

Suchman, Nancy E. -- Yale University
Fostering Mothers' Emotionally-Responsive Parenting

Swenson, Cynthia Cupit -- Medical University of South Carolina

Family-Based Treatment for Parental Substance Abuse and Child Maltreatment

Tao, Rui -- Florida Atlantic University
Mechanisms of Sudden Onset of Malignant MDMA Neurotoxicity

Thomas, David L. -- Johns Hopkins University
HIV HCV Co-infection Antiviral Therapy and Fibrosis

Thomas, James B. -- Research Triangle Institute
Synthesis and Testing of Targeted Libraries to Identify Small-Molecule Agonists A

Tyndale, Rachel Fynvola -- Centre for Addiction and Mental Health
Reduced CYP2B6 Metabolism Influences Smoking Initiation and Treatment Response: I

Van Dorn, Richard -- University of South Florida
Longitudinal Substance Use Trajectories for Persons with Schizophrenia: An Applicatiom

Verdin, Eric J. -- David Gladstone Institutes
Epigenetic Regulation of HIV Latency

Wainberg, Milton L. -- New York State Psychiatric Institute
HIV/STI Prevention for Adolescents with Substance Use Disorder in Treatment

Walsh, Sharon L. -- University of Kentucky
Licit and Illicit Opioids: Comparative Studies in Humans

Walwyn, Wendy M. -- University of California, Los Angeles
Delta Opioid Receptor Upregulation: A New Model to Examine the Effects of Cocaine

West, Mark O. -- Rutgers the State University of NJ, New Brunswick
Cocaine-Seeking in Rats: Ultrasonic Vocalizations and Accumbens Neural Activity

Wilcox, George Latimer -- University of Minnesota, Twin Cities
Mechanisms of Opioid Receptor Interactions

Wiley, Jenny L. -- Research Triangle Institute
Endocannabinoid Discrimination

Woolverton, William L. -- University of Mississippi Medical Center
Delay Discounting and the Choice to Take a Drug

Yao, Honghong -- University of Nebraska Medical Center
Cocaine-Mediated Neuroinflammation: Role in Neuroaids

Yonkers, Kimberly A. -- Yale University
Project Start: Screening to Augment Referral to Treatment

Yonkers, Kimberly A. -- Yale University
Progesterone for Postpartum Cocaine Relapse

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1902 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 1167 applications.

OEA arranged and managed 18 grant review meetings in which 371 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA staff arranged and managed 18 contract proposal and concept review meetings.

NIDA has one standing chartered committee, NIDA-K, which reviews Career Development applications and Institutional Training Grant applications (T32). There were also 17 Special Emphasis Panels to review grant applications for a variety of reasons:

- Conflicts with the chartered committee
- Behavioral Science Track Award for Rapid Transition (B/START)
- Imaging Science Track Award for Research Transition (I/START)
- Conference Grants (R13)
- Loan Repayment Applications
- Requests for Applications (RFAs)
- Mechanism for Time-Sensitive Research Opportunities (R21)

OEA managed the following RFA reviews:

- DA10-006/007 - Cognitive Remediation Approaches to Improve Drug Abuse Treatment Outcomes (R01 & R21)
- DA10-012 - 2010 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1)
- DA10-013 - 2010 NIDA Translational Avant-Garde Award for Medication Development for Diseases of Addiction (DP1)
- DA10-014 - Systems Biology, HIV/AIDS, and Substance Abuse (R01)
- DA10-016 - Medications Development for Cannabis-Related Disorders (R01)
- DA10-018 - Medications Development for Substance Related Disorders (R01)
- DA10-019 - Deep Sequencing and Analysis of Pharmacogenomic Regions: Discovery and Analysis of Genetic Variants Contributing to Drug Abuse and Addiction (R01)

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- OD09-108 - Extramural Loan Repayment Program for Clinical Researchers (LRP-CR)
- OD09-109 - Extramural Pediatric Research Loan Repayment Program (LRP-PR)

Completed contract-related review activity from the Contracts Review Branch since the last Council includes:

R&D and non-R&D Contract Reviews

- NO1DA-11-1143 - Research Dissemination

Phase II SBIR Contract Reviews

- N44DA-10-7769 - Tool Development for New or Improved Capture Reagents
- N44DA-10-5542 - RAPID: Risk Assessment & Prevention Involving Drug & Sexual Behaviors
- N44DA-10-5543 - Substance Abuse Treatment Referral System

Phase I SBIR Contract Reviews

- N43DA-11-1206 - International Activities
- N43DA-11- 5563 - Developing Implementation Packages for Evidence-based HIV Prevention Intervention Materials for Drug Users
- N43DA-11- 5562 - Improving Measures of Addiction
- N43DA-11- 5564 - Developing, Validating, Refining Tools for Ecologic Momentary Assessment
- N43DA-11-5566 - Reintegration of Criminal Offenders into the Community
- N43DA-11-5567 - E-Technology Tools for Extending the Reach of Prevention Interventions in Rural and Remote Locations
- N43DA-11-2223 - Development of a Device for Auto-administering Naloxone to Overcome Overdose
- N43DA-11-2222 - Development of an Innovative Electronic Health Record (EHR) Translator Platform Facilitating Communication Among Different EHR Systems Used in Clinical Research and Treatment
- N43DA-11-2224 - Development of a Device to Assess Hyperalgesia at the Bed Side by the Cold Pressor Test
- N43DA-11-8897 - Development of New Methods and Approaches to Monitor Medication Compliance in Clinical Trials
- N43DA-11-8898 - New Techniques for the Large Scale Production and Purification of Antibodies or Vaccines for the Treatment of Substance Use Disorders
- N43DA-11-4413 - Real-time Activity as a Potential Diagnostic Marker for Pain or Drug-craving
- N43DA-11-4414 - Video Game Targeting Relapse Prevention in Youth with Substance use Disorders
- N43DA-11-2225 - Confirming Compliance with Experimental Pharmacotherapy Treatment of Drug Abuse

CTN Review Activities

The Data and Safety Monitoring Board met May 27, 2010 to discuss the final study report for protocol CTN 0032, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.

Certificates of Confidentiality

Between April 3, 2010 and August 4, 2010, OEA processed 103 Certificate of Confidentiality applications, including 17 amendments for either extension of expiration date or protocol change.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued to provide open forums for discussions and presentations that included: an open forum on NIH Guide Notices about Vertebrate Animals sections in grant applications; clarification of policies on application resubmission and determination of new application status; expansion of the provisions of the e-SNAP process; an update on Center grant and program project grant application and review processes; a Freedom of Information Act presentation by Susan Cornell, FOIA Officer and Chief FOIA Liaison, NIH; and an overview of the Cutting-Edge Basic Research Awards (CEBRA) program presented by Dr. Susan Volman, DBNBR.

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Congressional Affairs (Prepared September 1, 2010)

Appropriations

The President's Fiscal Year 2011 budget request includes $32.1 billion for NIH, a $1 billion (3.2%) increase over FY 2010. For NIDA, the request includes $1.094 billion, $34.6 million (3.3%) over the FY 2010 level.

The Senate Appropriations Committee has reported out its Labor, HHS, and Education bill - it would fund the NIH and NIDA at the level requested in the President's Budget. Committee action is pending in the House.

Hearings/Briefings

Congressional Briefing on Medications to Treat Addiction: On May 11, 2010, the Friends of NIDA, in conjunction with the Congressional Addiction,Treatment and Recovery Caucus, sponsored and presented a briefing on developing medications to treat drug addiction and implications for policy and practice. Nora D. Volkow, MD, Director of NIDA, and A. Thomas McLellan, PhD, Deputy Director of the Office of National Drug Control Policy (ONDCP), addressed an interested audience of congressional staff members, addiction treatment professionals, and advocates.

Dr. Volkow began by presenting new medication research supported by NIDA. Pointing out the lack of effective approved medications to treat cocaine, marijuana, and opiate addictions, Dr. Volkow described the major barriers to funding for medication research and proposed strategies to address those barriers. Major barriers to funding included the stigma of addiction, lack of pharmaceutical industry involvement, cost and length of drug discovery process, and regulatory issues surrounding controlled substances. (NIDA's Topic in Brief on this subject is available at http://www.nida.nih.gov/tib/MedicationsDev.html.)

Dr. McLellan conveyed the state of drug addiction in the U.S. and illustrated the need for an improved infrastructure to deliver medication and other forms of addiction treatment. Dr. McLellan discussed the nature and course of drug use and addiction and the necessity for treatment, including specific medications and behavioral therapies.

Following the presentations, congressional staff members were eager to learn how Congress can act to promote medication development research and addiction treatment. One major focus of the question and answer session was the role that Congress can play in incentivizing pharmaceutical companies to fund research on medications to treat addiction. Dr. Volkow's presentation is available at http://www.apa.org/about/gr/science/spin/2010/05/volkow-presentation.pdf. Dr. McLellan's presentation is available at

http://www.apa.org/index.aspx.

Congressional Hearing on Medications to Treat Addiction: On June 23, 2010, the House Committee on Oversight and Government Reform, Subcommittee on Domestic Policy, held a hearing titled "Treating Addiction as a Disease: The Promise of Medication Assisted Recovery." This hearing was scheduled as the result of interest generated by the May 11 briefing, described above. NIDA Director Dr. Nora Volkow and ONDCP Deputy Director Dr. Thomas McLellan testified as government witnesses at this hearing. Formal testimonies from this hearing, a complete witness list, and the Chairman's (Dennis Kucinich, D-OH) opening statement are available at http://oversight.house.gov/index.php

Legislation of Particular Interest

Cocaine Sentencing (S. 1789)—On August 3, the President signed the Fair Sentencing Act of 2010 into law (P.L. 111-220). The law sets an 18-to-1 ratio for crack and powder cocaine in sentencing guidelines (reduced from a 100-to-1 ratio) and eliminates the mandatory minimum prison sentence for simple possession of crack, the only drug for which possession leads to such sentences.

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. 18—On January 6, Representative Roscoe Bartlett (R-MD) introduced the "Powder-Crack Cocaine Penalty Equalization Act of 2009," to amend the Controlled Substances Act and the Controlled Substances Import and Export Act with respect to penalties for powder cocaine and crack cocaine offenses. The bill was referred to the Judiciary and Energy and Commerce Committees. [see "Cocaine Sentencing," above]

H.R. 179—On January 6, Representative Jose Serrano (D-NY) introduced the Community AIDS and Hepatitis Prevention Act, to permit the use of federal funds for syringe exchange programs for purposes of reducing the transmission of bloodborne pathogens, including HIV and viral hepatitis. The bill was referred to the House Committee on Energy and Commerce.

H.R. 265—On January 7, Representative Sheila Jackson-Lee (D-TX) introduced the Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2009, to target cocaine kingpins and address sentencing disparity between crack and powder cocaine. The bill was referred to the Judiciary and Energy and Commerce Committees. [see "Cocaine Sentencing," above]

H.R. 439—On January 9, Representative Dennis Rehberg (R-MT) introduced the Family-Based Meth Treatment Access Act of 2009, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other services. The bill was referred to the Committee on Energy and Commerce.

H.R. 554—On February 11, the House passed the National Nanotechnology Initiative Amendments (NNI) of 2009. The measure was introduced by Representative Bart Gordon (D-TN) on January 15. In general, H.R. 554 would require all agencies participating in the NNI to support the setting of standards for nanotechnology. The bill was sent to the Senate where it is pending before the Committee on Commerce, Science, and Transportation.

H.R. 756—On March 30, the House passed the National Pain Care Policy Act.

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Relevant to NIH, the bill would (1) encourage the NIH Director, through the NIH Pain Consortium, to continue and expand an aggressive pain research program, (2) require the NIH Pain Consortium to submit annual recommendations on pain research initiatives that could be paid for by the Common Fund, and (3) require the HHS Secretary to establish an Interagency Pain Research Coordinating Committee, which would include NIH membership. The bill is pending in the Senate as S. 660. (Note: many aspects of this bill were included in the new health reform law.)

H.R. 758—On January 28, Representative Diana DeGette (D-CO) introduced the Pediatric Research Consortia Establishment Act to amend Title IV of the PHS Act to provide for the establishment of pediatric research consortia. The bill was referred to the House Committee on Energy and Commerce. See S.353

H.R. 836—On February 3, Representative Earl Pomeroy (D-ND) introduced the Brewers Excise and Economic Relief (BEER) Act, which if enacted would effectively return the federal beer excise tax to its pre-1991 levels. In the House the bill has 242 cosponsors. The bill was referred to the Committee on Ways and Means. See S. 1058

H.R. 872—On February 4, Representative Diana DeGette (D-CO) introduced the Stem Cell Research Improvement Act of 2009. The bill would require the Secretary to conduct and support research that uses human embryonic stem cells, regardless of the date on which such cells were derived. The bill outlines certain ethical criteria, and would require that the Secretary, in consultation with the Director of NIH, issue guidelines to carry out the provisions of the legislation within 90 days of enactment. H.R. 872 also provides that the Secretary may issue guidelines on research involving other human stem cells, as determined to be scientifically warranted by the Director of NIH. The bill was referred to the House Committee on Energy and Commerce.

H.R. 873—On February 4, Representative Diana DeGette (D-CO) introduced H.R. 873, the Stem Cell Research Enhancement Act of 2009. Like H.R. 872, the bill would require the Secretary to conduct and support research that uses human embryonic stem cells. The bill sets out certain ethical criteria, and would require that the Secretary, in consultation with the Director of NIH, issue final guidelines to carry out the provisions of the legislation within 60 days of enactment. H.R. 873 was referred to the House Committee on Energy and Commerce. See S. 487

H.R. 877—On February 4, Representative Randy Forbes (R-VA) introduced H.R. 877, the Patients First Act of 2009. The bill would require the Secretary of HHS to conduct and support research using stem cells, including pluripotent stem cells that "have the flexibility of embryonic stem cells (whether or not such pluripotent stem cells have an embryonic source)." The Secretary, after consultation with Director of NIH, would be required to issue guidelines within 90 days that would prioritize research that has the "potential for near term clinical benefit in human patients." The bill also would add "stem cells" to the list of issues for which a summary of research activities is required as part of the NIH biennial report. H.R. 877 was referred to the House Committee on Energy and Commerce.

H.R. 1011—February 12, Representative Gene Green (D-TX) 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 Energy and Commerce Committee. See S. 1188.

H.R. 1028—On February 12, Representative Lucille Roybal-Allard (D-CA) introduced the Support 21 Act of 2009, to provide additional support for the efforts of community coalitions, health care providers, parents and others to prevent and reduce underage drinking, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 1429—On March 17 the House passed the Stop AIDS in Prison Act of 2009, to provide for an effective HIV/AIDS program in Federal prisons. The bill was transmitted to the Senate, where it is pending in the Committee on the Judiciary.

H.R. 1459—On March 12 Representative Bobby Scott (D-VA) introduced the Fairness in Cocaine Sentencing Act of 2009, to amend the Controlled Substance Act and the Controlled Substances Import and Export Act regarding penalties for cocaine offenses. The bill was reported from the Judiciary Committee and is pending in the Energy and Commerce Committee. See H.R. 3245. [see "Cocaine Sentencing," above]

H.R. 1483—On March 12 Representative Patrick Kennedy (D-RI) introduced the National Neurotechnology Initiative Act, to direct the Secretary of HHS to implement a National Neurotechnology Initiative, and for other purposes. The bill was referred to the Committee on Energy and Commerce. See S. 586

H.R. 1715—On March 25, Representative Diana DeGette (D-CO) introduced H.R. 1715, the Protection for Participants in Research Act of 2009. The bill includes several modifications to the current system for protections of human research participants. H.R. 1715 was referred to the House Committee on Energy and Commerce.

H.R. 2134—On April 28, 2009, Representative Eliot Engel (D-NY) introduced the Western Hemisphere Drug Policy Commission Act of 2009, to establish the Western Hemisphere Drug Policy Commission. The bill was passed on December 8, and is currently pending in the Senate. It has been referred to the Senate Committee on Foreign Relations.

H.R. 2138—On April 28 Representative Patrick Kennedy (D-RI) introduced the Services, Education and Rehabilitation for Veterans (SERV) Act, to provide grants to establish veterans treatment courts. The bill was referred to the Committee on the Judiciary. See S. 902

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 oversee 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. (Note: many of these provisions were adopted as part of the new health reform law.)

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. 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. 2855—On June 12, 2009, Representative Donna Edwards (D-MD) introduced the Drug Overdose Reduction Act, to reduce deaths occurring from drug overdoses. The bill was referred to the Committee on Energy and Commerce.

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 includes a new advisory commission that would coordinate research by several agencies, including NIH. 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. 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. [see "Cocaine Sentencing," above]

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 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; and (3) prohibit the Federal Coordinating Council for Comparative Effectiveness Research findings from being released in final form until after consultation 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 Substance 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. See S. 459

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.

H.R. 3939—On October 27, 2009, Representative Sam Farr (D-CA) introduced the Truth in Trials Act, to amend Title 18 of the United States Code to provide an affirmative defense for the medical use of marijuana in accordance with the laws of the various states. The bill was referred to the Committee on the

Judiciary.

H.R. 4055—On November 6, 2009, Representative Adam Schiff (D-CA) introduced the Honest Opportunity Probation with Enforcement (HOPE) Initiative Act of 2009, to authorize a national HOPE program to reduce drug use, crime, and costs of incarceration. The bill was referred to the House Judiciary Committee.

H.R. 4748—On July 27, 2010, the House passed the Northern Border Counternarcotics Strategy Act of 2010, to amend the Office of National Drug Control Policy Reauthorization Act of 2006 to require a northern border counternarcotics strategy, and for other purposes. The bill is pending in the Senate, where it was referred to the Judiciary Committee.

H.R. 5143—On July 27, 2010, the House passed the National Criminal Justice Commission Act of 2010, to undertake a comprehensive review of the criminal justice system, encompassing current Federal, State, local, and tribal criminal justice policies and practices, and make reform recommendations for the President, Congress, State, local, and tribal governments. The bill is pending in the Senate.

H.R. 5466—On May 28, 2010, Representative Patrick Kennedy (D-RI) introduced the SAMHSA Modernization Act of 2010, to amend Titles V and XIX of the Public Health Service Act to revise and extend substance use disorder and mental health programs, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 5678—On July 1, 2010, Representative Russ Carnahan (R-MO) introduced the Universal Access to Methamphetamine Treatment Act of 2010 to amend the Public Health Service Act to provide grants for treatment of methamphetamine abuse, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 5916—On July 28, 2010, Representative John Salazar (D-CO) introduced the Methamphetamine Prevention Campaign Grant Program Act of 2010, to establish a methamphetamine prevention campaign grant program. The bill was referred to the Committee on Energy and Commerce. See S. 3278.

H.R. 5925—On July 29, 2010, Representative Carol Shea-Porter (D-NH) introduced the Safe Prescription Drug Disposal and Education Act, to authorize the Attorney General to make grants to States, units of local government, Indian tribes, and other entities for prescription drug disposal units and for prescription drug abuse education. The bill was referred to the Committees on Energy and Commerce, and Judiciary.

H.R. 6090—On August 10, 2010, Representative Sheila Jackson Lee introduced the Drug Court Reauthorization Act, to reauthorize and amend the Omnibus Crime Control and Safe Streets Act of 1968 relating to drug courts. The bill was referred to the Committee on the Judiciary.

S. 77—On January 6, Senator John Kerry (D-MA) introduced the Children's Mental Health Parity Act, to amend Title XXI of the Social Security Act to provide for equal coverage of mental health services under the State Children's Health Insurance Program. The bill was referred to the Committee on Finance.

S. 114—On January 6, Senator Daniel Inouye (D-HI) introduced the National Center for Social Work Research Act, to amend the Public Health Service Act to provide for the establishment of a National Center for Social Work Research within the National Institutes of Health. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

S. 132—On January 6, Senator Diane Feinstein (D-CA) introduced the Gang Abatement and Prevention Act of 2009, to increase and enhance law

enforcement resources committed to investigation and prosecution of violent gangs, to deter and punish violent gang crime, to protect law-abiding citizens and communities from violent criminals, to revise and enhance criminal penalties for violent crimes, to expand and improve gang prevention programs, and for other purposes. Section 313 of the bill establishes a National Youth Anti-Heroin Media Campaign at the Office of National Drug Control Policy. The bill was referred to the Committee on the Judiciary.

S. 177—On January 8, Senator Russ Feingold (D-WI) introduced S. 177, the Strengthening Our Economy Through Small Business Innovation Act of 2009. The measure would extend the SBIR program through 2022 and the STTR program through 2023. Additionally, S. 177 would increase SBIR set-aside allocations to 5 percent by 2010, 7.5 percent by 2011, and 10 percent by 2012. The set-aside levels for the STTR program would also double by 2010, and then increase to 0.8 percent by 2011 and to 1.0 percent by 2012. The measure also proposes to increase the SBIR and STTR award levels for phase 1 and 2 grants to $300,000 and $2.2 million, respectively. Finally, the bill would give greater priority consideration to research areas, including those related to energy, security, transportation, and water. S. 177 currently has no co-sponsors and was referred to the Senate Committee on Small Business and Entrepreneurship.

S. 353—On January 29, Senator Sherrod Brown (D-OH) introduced the Pediatric Research Consortia Establishment Act to amend Title IV of the PHS Act to provide for the establishment of pediatric research consortia. The bill was referred to the House Committee on Energy and Commerce. See H.R. 758

S. 459—On February 24, Senator Claire McCaskill (D-MO) introduced the SUPPORT for Substance 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 Committee on Armed Services. See H.R. 3420.

S. 487—On February 26, Senator Tom Harkin (D-IA) introduced the Stem Cell Research Enhancement Act of 2009, which was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 873

S. 586—On March 12 Senator Patty Murray (D-WA) introduced the National Neurotechnology Initiative Act, to direct the Secretary of HHS to implement a National Neurotechnology Initiative, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 1483

S. 660—On March 19, Senator Orrin Hatch (R-UT), introduced S. 660, the National Pain Care Policy Act. The NIH provisions in S. 660 are identical to H.R. 756, described above. S. 660 was referred to the Senate Committee on Health, Education, Labor and Pensions.

S. 714—On March 26, Senator James Webb (D-VA) introduced the National Criminal Justice Commission Act of 2009, a bill to establish the National Criminal Justice Commission. On January 21, 2010, the bill was amended and reported favorably from the Committee on the Judiciary. The bill (as amended) passed the House; it is pending on the Senate calendar. See H.R. 5143

S. 754—On March 31, Senator Jay Rockefeller (D-WV) introduced the Methadone Treatment and Protection Act of 2009, to provide for increased federal oversight of methadone treatment. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 902—On April 27 Senator John Kerry (D-MA) introduced the Services, Education and Rehabilitation for Veterans (SERV) Act, to provide grants to establish veterans treatment courts. The bill was referred to the Committee on the Judiciary. See H.R. 2138

S. 914—On April 28, Senator Arlen Specter (D-PA) introduced S. 914, the Cures Acceleration Network and National Institutes of Health Reauthorization Act of 2009. This legislation would (1) establish the Cures Acceleration Network, an independent agency that would make awards to accelerate the development of cures and treatment of diseases, (2) elevate NCMHD to institute status, (3) increase NIH's authorization of appropriations section to $40 billion for FY 2010 and such sums as may be necessary for each of the FYs 2011 to 2012, and (4) require the Director of NIH to develop and enforce conflict of interest policies. S. 914 was referred to the Senate Committee on Health, Education, Labor and Pensions (HELP). (NOTE: many provisions of this bill were included in the new health reform law.)

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. See H.R. 2354

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. 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.

S. 3011—On February 11, 2009, Senator Kirsten Gillibrand (D-NY) introduced S. 3011, the National Black Clergy for the Elimination of HIV/AIDS Act of 2009, to address HIV/AIDS in the African-American community. Research provisions would (1) authorize the Secretary, DHHS, acting through the Director, NIH, to conduct or support culturally competent research to develop evidence-based behavioral strategies to reduce the transmission of HIV/AIDS within this community, and (2) require the Secretary to prioritize research that focuses on populations within the African-American community that are at increased risk for HIV/AIDS. Authorized to be appropriated would be $10 million for Fiscal Year (FY) 2010, and such sums as may be necessary for FYs 2011 through 2014. In addition, the Secretary, acting through the Director, NCMHD, would be authorized to make grants for studies of biological and behavioral factors that lead to increased prevalence and that are conducted by researchers with a history and tradition of service to African-American communities; and behavioral and structural network research and interventions, in collaboration with other NIH institutes and centers, faith- and community-based organizations and others. Authorized to be appropriated would be $100,000,000 for FY 2010, and such sums as may be necessary for FYs 2011 through 2014. S. 3011 was referred to the Senate Committee on Health, Education, Labor and Pensions.

S. 3031—On February 24, 2010, Senator Leahy (D-VT) introduced the Drug Free Communities Enhancement act of 2010, to authorize Drug Free Communities enhancement grants to address major emerging drug issues or local drug crises. The bill was amended and reported favorably by the Judiciary Committee, and is now pending on the Senate calendar.

S. 3278—On April 29, 2010, Senator Michael Bennet (D-CO) introduced the Methamphetamine Prevention Campaign Grant Program Act of 2010, to establish a methamphetamine prevention campaign grant program. The bill was referred to the Committee on Energy and Commerce. See H.R. 5916

S. 3397—On August 3, 2010, the Senate passed the Secure and Responsible Drug Disposal Act of 2010, to amend the Controlled Substances Act to provide for take-back disposal of controlled substances in certain instances, and for other purposes. The bill was sent to the House, where it is pending before the Committees on Energy and Commerce, and Judiciary.

S. 3575—On July 13, 2010, Senator Richard Durbin introduced the National All Schedule Prescription Electronic Reporting Reauthorization Act of 2010, to amend and reauthorize the controlled substance monitoring program under section 3990 of the Public Health Service Act and to authorize the Secretary of Veterans Affairs to share information about the use of controlled substances by veterans with State prescription monitoring programs to prevent misuse and

diversion of prescription medicines. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

On April 20, 2010, Representative Patrick Kennedy (RI), along with Representative John Sullivan (OK), Representative Mary Bono Mack (CA), and Representative Carol Shea-Porter (NH), entered an official statement into the Congressional Record recognizing and congratulating the accomplishments of the CTN on its 10th Anniversary. Excerpts from the statement include: "Ten years ago, the National Institute on Drug Abuse (NIDA)... embarked upon a bold initiative by creating the National Drug Abuse Treatment Clinical Trials Network (CTN) to accelerate the process of transforming research findings into proven treatments for use in community practice settings. The CTN focuses directly on studies that can demonstrate the effectiveness of treatments for people whose lives are affected by drug abuse in communities and neighborhoods nationwide... Madam Speaker, we congratulate the National Institute on Drug Abuse and its Clinical Trials Network on its important accomplishments over the past ten years. Their work has lessened the suffering of many, and as Co-chairs and Vice Co-chairs of the Addiction, Treatment and Recovery Caucus, we look forward to continuing to work with NIDA and even greater achievements of the CTN [in] the years to come."

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

International Activities

Tanzania and U.S. Launch Medication-Assisted Therapy Program for Drug Users Based on NIDA-Supported Research

The governments of Tanzania and the United States have begun the first medication- assisted therapy (MAT) program for drug users in sub-Saharan Africa at two sites in Dar es Salaam and one in Zanzibar. Recognizing that high-risk practices related to drug use contribute to HIV transmission, the Tanzania Drug Control Commission (DCC) has promoted and adopted novel and evidence-based interventions to facilitate improved access to services that prevent HIV among drug users. Working with colleagues from the Ministry of Health and Social Welfare and Muhimbili University of Health and Allied Sciences, former Humphrey Drug Abuse Research Fellow Dr. Amani Msami Kisanga, who leads the DCC Education, Information & Statistics Section, helped draft five documents outlining Tanzania's response to HIV among drug users, including policy guidelines, an outreach service guide for HIV prevention among drug users, healthcare facility standards for MAT programs, clinical guidelines, and a substance abuse screening and brief intervention protocol for primary care settings. The documents were based in part on research conducted in Dar es Salam by NIDA IP grantees Dr. Sheryl A. McCurdy, Dr. Michael W. Ross, and Dr. Mark L. Williams, University of Texas at Houston, and their Tanzanian partners Dr. Gad P. Kilonzo and Dr. M. T. Leshabari, Muhimbili University of Health and Allied Sciences. The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Centers for Disease Control and Prevention (CDC) supported the DCC policy development and implementation efforts.

NIDA-Funded Researcher Mixes Ethnography With Art Installation

As part of his research into preventing HIV and hepatitis C infections among injection drug users, Pedro Mateu-Gelabert, Ph.D., National Development and Research Institutes, noticed that drug dealers in New York were creating heroin brands by labeling the glassine envelopes in which they distributed the drug. Working with the Social Art Collective in New York City, Dr. Mateu-Gelabert and his colleagues interviewed drug dealers and users, as well as an artist who designs the brand images, while collecting the empty envelopes to create an art project that the New York Times said "is meant to examine the intersection of advertising and addiction and provoke questions about how society addresses dependence and disease." In addition to 150 decorated envelopes collected from city streets, the exhibit includes 12 large-scale prints of the brand designs, 1,800 empty envelopes (representing a heavy heroin user's annual consumption), and information cards describing injection drug use risks. Proceeds from the exhibit will be shared with a local needle-exchange program.

NIH-Supported Meetings

NIDA Symposium, Workshop Featured at AIDS 2010; New IAS-NIDA Fellows Announced

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Two NIDA-supported meetings featured international drug abuse research during the XVIII International AIDS Conference, which was held July 18-23, in Vienna, Austria. The **International AIDS Society (IAS)/NIDA Symposium** was organized by ARP Director Dr. Jacques Normand and featured presentations by NIDA Director Dr. Nora Volkow on the neurobiology of drug use and HIV risk behavior; U.S. Global AIDS Coordinator Dr. Eric Goosby, on PEPFAR's evolving strategy to prevent HIV among persons who inject drugs; Dr. Charles O'Brien, University of Pennsylvania, on substance abuse treatment as HIV prevention; and IAS President Dr. Julio Montaner, on HAART as prevention for injecting drug users. IAS-NIDA Postdoctoral Research Fellowships in HIV and Drug Use were announced during the symposium, supporting 18 months of training for:

- Elena Dukhoulinova, Russia, who will study with Dr. Ronald I. Swanstrom, University of North Carolina in Chapel Hill;
- Jonathan Claude Ipser, South Africa, who will work with Dr. Igor Grant, University of California, San Diego;
- Shusen Liu, China, who will train with Dr. Zunyou Wu, Chinese National Center for AIDS/STD Control and Prevention;
- Brandon Marshall, Canada, who will study with Dr. Sandro Galea, Dr. Anna Cheskis Gelman, and Dr. Murray C. Gelman at Columbia University; and
- Former NIDA INVEST Fellow Adhi Nurhidayat, Indonesia, who will work with Dr. David Metzger, University of Pennsylvania.

The **NIDA Workshop on Building International Research Capacity and Collaboration on Drug Abuse and HIV/AIDS** informed drug abuse and HIV/AIDS researchers about current and planned NIDA research funding opportunities, online networking and collaboration tools, and research training programs available to foster the development of regional research networks and collaborations. Participants had opportunities to establish new research collaborations and provide feedback to NIDA regarding research opportunities and mechanisms to establish regional research networks. Speakers included IP Director Dr. Steven W. Gust, who chaired the workshop, ARP Director Dr. Jacques Normand, and CTN Deputy Director Dr. Mary Ellen Michel. Dr. David Metzger, University of Pennsylvania, facilitated a panel discussion with Dr. Clyde B. McCoy, University of Miami, and Dr. Jeffrey Same, Boston University School of Medicine, on building effective regional research partnerships and networks.

NIDA International Forum Focuses on Research to Inform Drug Policy and Public Health

IP Director Dr. Steven W. Gust chaired the 15th NIDA International Forum, which was held June 11-15, 2010, in Scottsdale, Arizona, as a satellite to the Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD). More than 240 participants from 49 countries participated in the plenary session, workshops, and networking activities. A joint CPDD/NIDA International Forum poster session featured presentations by 140 U.S. and international researchers as well as representatives from 11 NIDA components.

IP Presents Awards of Excellence

During the 2010 NIDA International Forum, the IP presented its 2010 Awards of Excellence to honor mentors, researchers, and binational collaborative teams whose efforts support the International Program mission, including:

- Excellence in Mentoring: Dr. Walter Ling, University of California Los Angeles;
- Excellence in International Leadership: Dr. Evgeny Krupitsky, Pavlov Medical University and Bekhterev Research Psychoneurological Institute, Russia; and

Excellence in International Collaborative Research: Dr. Thomas F. Babor, University of Connecticut, and Dr. Robin Room, University of Melbourne and Turning Point Alcohol and Drug Centre, Australia.

SPR Launches International Good Behavior Game Network and Features International Networking and Poster Session

The Society for Prevention Research (SPR) 18th Annual Meeting, which was held June 1-4, 2010, in Denver, Colorado, featured the inaugural International Good Behavior Game Network meeting as well as the SPR International Networking Forum and an international poster session cosponsored by the NIDA IP and DESPR.

Fellowships

DISCA Team Examines PTSD and Substance Use Disorders

Kathleen T. Brady, M.D., Ph.D., Medical University of South Carolina (MUSC), will use her NIDA Distinguished International Scientist Collaboration Award (USDISCA) to extend her research collaboration with Maree Teesson, Ph.D., Australian National Drug and Alcohol Research Centre (NDARC), University of New South Wales. The team will collaborate on statistical analysis, interpretation, and dissemination of research findings on treatment of co-occurring post-traumatic stress disorder (PTSD) and substance use disorders in preparation for publications and a 2011 international symposium on the topic. Drs. Brady and Teesson also will explore capacity development in multisite clinical trials, translational research, and concept development. Dr. Brady directs the Clinical Neuroscience Division at MUSC, focusing on substance use disorders and co-occurring psychiatric and medical conditions, is the principal investigator of the NIDA Clinical Trials Network Southern Consortium Node, and is MUSC Associate Dean for Clinical and Translational Research.

USDISCA Team Builds HIV Prevention Effort for Young Russians

Kenneth W. Griffin, Ph.D., M.P.H., Weill Cornell Medical College, and Irina Pervova, Ph.D., St. Petersburg State University (SPSU), used Dr. Griffin's U.S. Distinguished International Scientist Collaboration Award (USDISCA) to conduct key informant interviews and focus groups on the epidemiology, etiology, and prevention activities regarding adolescent substance use in St. Petersburg; to conduct a local prevention needs assessment; and to obtain government and university approval to adapt, test, and refine evidence-based family prevention programs that address differences between the United States and Russia in culture, language, and organizational structures. The pair, who met while planning a 2006 NIDA-funded conference in St. Petersburg, has already submitted one grant application, a feasibility study for drug abuse prevention trials, and is developing two others. While he was in St. Petersburg, Dr. Griffin also presented at two SPSU conferences, met with U.S. consular officials, participated in a United Nations Office on Drugs and Crime seminar, and met with kindergarten through 12th-grade educators.

INVEST Fellow To Investigate Opioid Maintenance Treatment Adherence

Perrine Roux, Pharm.D., Ph.D., French National Institute of Health and Medical Research (Inserm), has been selected as a NIDA INVEST Drug Abuse Research Fellow. She will work with Sandra D. Comer, Ph.D., Columbia University, to better define the concept of nonadherence to opioid maintenance treatment with buprenorphine/naloxone and to validate a tool to measure nonadherence using a self-administered questionnaire. The researchers predict that identification of factors associated with nonadherence will provide important information on how to improve clinical management and outcomes in patients abusing heroin or prescription opioids, with or without chronic pain symptoms. At Inserm, Dr. Roux has participated in a longitudinal study of drug treatment for marginalized populations, a national trial of hepatitis C risk reduction interventions for prisoners, and a trial of methadone in primary care for

hepatitis C prevention.

INVEST-CTN Fellow Focuses on Family Therapy
INVEST-Clinical Trials Network (CTN) Fellow Mario Zapata, M.D., M.Sc., focused primarily on brief strategic family therapy and ended his fellowship year by submitting a grant application to fund a pilot project testing the effectiveness of the brief strategic family therapy protocol in Colombia. Working at the CTN Florida Node at the University of Miami, Dr. Zapata also helped develop protocols testing the effectiveness of rapid HIV testing and counseling; 12-step behavioral interventions; Web-based treatment delivery; and emergency room screening, brief intervention, and referral to treatment. He enrolled in academic courses about clinical trials and child and adolescent psychology, participated in scientific meetings, and presented his research to the CTN Steering Committee.

Former Humphrey Fellow Named to Top University and Research Posts
2010-2011 Humphrey Fellow Muzafar Razali received his doctoral degree from the University of Malaya in August 2010 and was appointed head of the Psychology and Counseling Department, Faculty of Education and Human Development, at Sultan Idris Education University July 1, 2010. He was also named a teaching and research Fellow at the Asian Centre for Research on Drug Abuse (ACREDA) at the Islamic Science University of Malaysia.

International Visitors

As part of the U.S. Department of State's International Visitor Leadership Program a group of visitors from Mexico came to NIDA on July 20, 2010. The purpose of the trip was to familiarize the participants with effective drug abuse prevention and treatment programs in the U.S. Meeting with the visitors from NIDA were Dale Weiss, IP, Dr. Jag Khalsa, DPMCDA, Dr. Ruben Baler, OSPC and Dr. Jacqueline Lloyd, DESPR.

On July 22, 2010 health professionals from Namibia and South Africa visited NIDA. The groups were sponsored by the U.S. Embassy in Windhoek and the U.S. Department of State's International Visitor Leadership Program. While at NIDA the visitors met with Dale Weiss, IP, Dr. Jag Khalsa, DPMCDA, Dr. Petra Jacobs, CCTN and Dr. Lula Beatty, SPO.

Other Activities

Dr. David Shurtleff, Director, DBNBR, gave a presentation entitled: "Basic Neuroscience Research at NIDA: An Update" at the Annual Meeting of The International Narcotics Research Conference. Malmš, Sweden, July, 2010.

Dr. John Satterlee, DBNBR, gave the keynote address entitled "Large Scale Epigenomics Projects" at the "Epigenetics, Environment and Health Consultation Workshop" at Niagara-on-the-Lake, Ontario on April 7, 2010. The purpose of this Canadian Institute of Health Research sponsored meeting was to develop a framework for a potential Canadian epigenetics research program.

Dr. Jonathan D. Pollock, DBNBR, attended the International Knockout Mouse Consortium Meeting and Mouse Models of Human Disease, Royal Society, London, UK, May18-21, 2010.

Dr. Ivan Montoya, DPMCDA, participated in a meeting of the European Presidency organized by the National Drug Abuse Plan of Spain. The meeting took place in Santander, Spain on June 28 and 29, 2010. Dr. Montoya presented the research collaboration between NIDA and European countries as well as a lecture on Translational Research in Drug Abuse.

Dr. Nicolette Borek, DCNBR, represented NIDA and the Pediatric HIV/AIDS

Cohort Study and the Adolescent Trials Network for HIV/AIDS Interventions at the 2nd International Workshop on HIV Pediatrics, July 16-17, 2010 in Vienna, Austria. This meeting served as a pre-conference event to the International AIDS conference.

Dr. Wilson M. Compton, Director, DESPR, presented on "Abuse of Pharmaceuticals in the USA" at an experts' meeting on prescription drug abuse, United Nations Office on Drugs and Crime, Vienna, Austria, June 22, 2010.

Dr. Meyer Glantz, DESPR, attended the 2010 World Mental Health Consortium meeting as NIDA's representative and scientific collaborator. The WHO meeting was held in Lisbon Portugal from July 6 through July 10, 2010. Dr. Glantz collaborates with the Drug Dependence, Nosology, Suicide and Global Burden of Disease analysis workgroups. The WMH Consortium is a multinational set of coordinated community psychiatric epidemiology surveys. The U.S. implementation was the National Comorbidity Survey Replication Survey.

Dr. Meyer Glantz represented NIDA at the World Psychiatric Association Epidemiology Section held in Lisbon Portugal from July 10 through July 14, 2010.

Drs. Eve Reider, Belinda Sims and Wilson Compton, DESPR, Ms. Dale Weiss, NIDA International Program, and Dr. Nicholas Ialongo, Johns Hopkins University, met with Dr. Jorge McDouall, from Mentor Colombia May 18, 2010 in Washington, DC. Mentor Colombia is a national not for profit non-government organization working as a national family member of the Mentor Foundation. Mentor seeks to undertake, identify, support and share information on proven and promising practices that effectively prevent or protect children and young people from the harm that drugs cause and which make drug misuse less likely.

Dr. Eve Reider presented on "Challenges for Application of Effective Prevention" at the meeting "International Drug Abuse Prevention: Opportunities & Challenges" that was held by the Mentor Foundation on May 18, 2010 in Washington, DC.

Dr. Eve Reider was an organizer and theme reviewer for the 3rd Annual NIDA International Poster Session, held June 1, 2010 at the 18th Annual Society for Prevention Research Annual Meeting, Denver, CO.

Drs. Kathy Etz, DESPR, NIDA, Sheila Caldwell (NCCAM) and John Lowe (Florida International University) conducted a Grant Development Workshop at the International Network of Indigenous Health, Knowledge, and Development (INIHKD) Conference on May 24, 2010 in Poulsbo, Washington.

Dr. Peter Hartsock, DESPR, served on the Scientific Committee of the Nineteenth International Conference on HIV/AIDS, Cancer and Public Health held May 22-26, 2010 in St. Petersburg, Russia.

Dr. Peter Hartsock chaired a symposium on NIDA's AIDS modeling research at the Nineteenth International Conference on HIV/AIDS, Cancer and Public Health, May 22-26, 2010 in St. Petersburg, Russia. Featured were analyses of substitution therapy and ART therapy for IDUs in Ukraine with potential applications for Russia and past and future research related to the "Seek, Test, Treat, and Retain" paradigm.

Dr. Peter Hartsock participated in a kick-off meeting on HIV "Seek, Test, Treat, and Retain" initiatives in Russia, May 27 and 28, 2010 in St. Petersburg and in the Leningrad Oblast (northwest Russia). These initiatives are a continuation of collaborative work between Dr. Hartsock's AIDS modeling research program and Russian researchers, planners, policy makers, and providers.

Dr. Peter Hartsock met with Russian scientists from St. Petersburg State

University concerned with drug abuse and child trafficking, May 29, 2010 in St. Petersburg, Russia, to discuss research on the scope and nature of the drug and child trafficking problem there, and to enlist organized crime efforts to reduce trafficking and the distribution/sales of dangerous drugs.

Dr. Peter Hartsock represented NIDA at the Center for Strategic and International Studies (CSIS) conference, "Meeting the Millennium Goals on Health: The Challenge for Africa." June 24, 2010, Washington D.C., which was also attended by health ministers from 9 African countries.

Dr. Peter Hartsock represented NIDA at the Center for Strategic and International Studies (CSIS) Statesman's Forum with Valdis Dombrovkis, Prime Minister of the Republic of Latvia, June 15, Washington, D.C. Dr. Hartsock presented on NIDA's drug abuse and HIV epidemiologic initiatives in the Baltic states—Latvia, Lithuania, and Estonia—and in adjoining Russia and Ukraine.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

Meetings/Conferences

The National Institute on Drug Abuse (NIDA) collaborated with the **American Psychiatric Association (APA) to hold a major research based track titled, *Neurobiological Circuits of Addiction: Significance for Psychiatric Practice* at the APA Annual Meeting in New Orleans, LA, May 22-26, 2010**. NIDA sponsored a number of symposia on topics unique to addiction science. This special track highlighted topics ranging from innovative technological advances, such as the use of optogenetics and epigenetic research to elucidate the basic mechanisms underlying addictive behaviors, to the translation of new knowledge into better prevention and treatments for drug use disorders. Special emphasis was given to sessions touching upon circuits in the brain that are involved in both addiction and other mental illness. In addition, symposia and lectures highlighted areas critical to psychiatric practice, including the unique issues facing military personnel and their families, the important clinical overlap of smoking with psychiatric disorders, development of medications for addiction, the commonalities between obesity and addiction, the potential therapeutic effects and abuse of cognitive enhancers, and novel approaches to stop the spread of HIV. NIDA Director, Dr. Nora Volkow gave a Frontiers of Science Lecture titled, Addiction: Conflict between Brain Circuits.

The **National Institute on Drug Abuse (NIDA) organized a program at this year's American Psychological Association (APA) Annual Meeting** in San Diego, CA, August 12-15, 2010. A number of NIDA staff throughout the Institute were involved in organizing and/or presenting on a wide range of session topics. NIDA Director, Dr. Nora Volkow, participated in a webinar plenary presentation titled, Psychotherapeutic Drug Abuse: It's Not What the Doctor Ordered. NIDA also co-sponsored an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

The first **CTN Regional Dissemination Workshop** of 2010, titled "Cutting Edge Addiction Treatment Tools from NIDA's Clinical Trials Network," was held June 3-4 in Baltimore, Maryland. The Mid-Atlantic Node of the NIDA Clinical Trials Network co-sponsored this two-day workshop in collaboration with the Central East Addiction Technology Transfer Center and the State of Maryland Alcohol and Drug Abuse Administration; 146 clinicians, program administrators, and local policy makers were registered. In plenary sessions, researchers and clinical experts presented the scientific foundation for three evidence-based practices: Medication Assisted Treatments, Motivational Incentives, and Recovery Oriented Systems of Care. During subsequent break-out workshops, the experts provided more concrete examples of these practices, the wisdom of lessons learned, and guidance for practical implementation in community settings.

Publications

Staff Highlights

Grantee Honors

CPDD: NIDA awarded 29 **Director's Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 12-17, 2010, Scottsdale, AZ. These awards are given to National Research Service Award (NRSA) trainees and fellows, and Diversity Supplement recipients to attend the CPDD meeting and the NIDA Tutorials Workshop. The Tutorials Workshop typically 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 28 **Women & Gender Junior Investigator Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 12-17, 2010 in Scottsdale, Arizona. 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/genderdifferences. The program 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 2011, and information on current NIDA funding opportunity announcements in this area. These efforts were led by Drs. Samia Noursi and Cora Lee Wetherington (DBNBR), who were assisted by Dr. Lynda Erinoff (ARP) and Dr. Joe Frascella (DCNBR).

Drs. Mimi Ghim and Ericka Boone, OSPC, coordinated the following activities at CPDD, June 12-17, 2010, in Scottsdale, AZ: [1] **NIDA Tutorials Workshop**, chaired by Dr. Ghim. Topics included: genetics, treatment of stimulant abuse, medications development, and tips for career building. [2] **NIDA/CPDD Training Networking Event**, which 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] **NIDA Grant Writing Workshop**, which provided information on NIDA research priorities, program interests and funding opportunities, review procedures, and grant writing tips. Topics were presented by Drs. Mimi Ghim, David Shurtleff, Mark Swieter, and Scott Lukas.

Dr. Karen Sirocco organized and chaired a meeting on **Developmental Neural Mechanisms of Cognitive Control: Implications for Drug Abuse Interventions** which was held May 3 - 4, 2010 in Bethesda, MD. The meeting was sponsored by NIDA Office of Science Policy and Communications (OSPC). The workshop's objectives were to highlight what we know about the neurobiological mechanisms underlying cognitive control processes and the relationship between these processes and drug abuse. The ultimate goal of this meeting will be to advance a scientific agenda that utilizes developmental cognitive neuroscience to guide the development of novel interventions to improve or ameliorate deficits in cognitive control functions and translate these strategies for the prevention and treatment of drug abuse across the human lifespan.

The Special Populations Office and the NIDA-supported American Indian/Alaska Native Work Researchers and Scholars Work Group held a workshop on **Academic Publishing for Trainees** participating in its mentoring program. The workshop was held April 21, 2010 in Albuquerque, NM in conjunction with NIDA's blending conference titled "Evidence-Based Treatment and Prevention in Diverse Populations and Settings." Workshop faculty included Drs. R. Dale Walker, Oregon Health and Science University; Clyde McCoy, University of

Miami; and Joe Gone, University of Michigan.

The Special Populations Office and the NIDA-supported Asian American/Pacific Islander Work Group held the conference **Advancing API Drug Abuse/Mental Health Prevention Sciences and Treatment: Transdisciplinary Frameworks** on June 2-3, 2010 in Alexandria, VA. This conference was convened to discuss drug abuse and addiction research and treatment issues among Asian Americans and Pacific Islanders.

The Special Populations Office and the NIDA-supported African American Researchers and Scholars Work Group convened the **Addiction Research Training Institute (ARTI)**, a four-day training for new investigators interested in pursuing careers in drug addiction research and a day-long **Mini Medical School** for the public, which was centered on public health challenges of women in the correctional system. These sessions took place at Morehouse School of Medicine in Atlanta, Georgia, July 19-23, 2010. Pamela Goodlow and Flair Lindsey of the Special Populations Office presented an overview of NIDA and the NIH, research activities supported through the Special Populations Office and NIDA/NIH funding opportunities.

The Special Populations Office coordinated the 14th annual **Summer Research with NIDA Program**, which commenced on June 1, 2010. Seventy-five high school and undergraduate students engaged in drug abuse research at various NIDA-supported research institutions for 8-10 weeks. Participants received certificates of completion signed by Dr. Nora Volkow and the site's principal investigator.

On Thursday, July 8, 2010, the Special Population Office (SPO) met with visiting summer interns participating in the Summer Research with NIDA program at the Morehouse School of Medicine in Atlanta, Georgia. The meeting provided students with information on NIDA and an overview substance abuse/addiction research. Additionally, students learned about research training opportunities at NIDA/NIIH.

On May 17-18, 2010, the Special Populations Office hosted a two-day **Special Populations Research Development Seminar Series workshop** in Bethesda, Maryland. Chaired by Pamela Goodlow, this workshop convened new investigators and NIDA-supported faculty mentors in an intensive grants-development workshop setting, and culminated in a mock review of research grant applications submitted by seminar participants.

The **National Hispanic Science Network (NHSN)** held its annual Summer Training Institute at the University of Texas in Houston, June 2 -13, 2010.

Dr. Timothy P. Condon, Deputy Director, NIDA, delivered the keynote presentation, "The Neurobiology of Addiction: NIDA Research Advances and Implications for Treatment," at the 2010 Chief Resident Immersion Training (CRIT) Program on May 3, 2010, in Cape Cod, Massachusetts.

Dr. Timothy P. Condon discussed NIDA's recent scientific advances, CJ-DATS activities, and Blending Initiative with local leaders and TASC representatives on May 6, 2010, in Chicago, Illinois.

Dr. Timothy P. Condon was a moderator at the National Association of Drug Court Professionals Annual Conference (NADCP) discussing "Medically Assisted Treatment: Clearing the Air," on June 5, 2010, in Boston, Massachusetts.

Dr. Cindy Miner, Deputy Director, OSPC, participated as a Judge for the Addiction Sciences Award at the Intel International Science and Engineering Fair held May 10-14, 2010, in San Jose, California.

Dr. Cindy Miner presented "The Promise of Science: Blending Research and

Practice" on June 2, 2010, and sponsored and chaired a NIDA/CSAT/NASADAD Joint Meeting with State Directors and State Leadership at the NASADAD/NPN/NTN Annual Meeting: "Fostering Success in an Evolving Health Care Environment" on June 3, 2010, in Norfolk. Virginia.

Dr. Cindy Miner participated in a Grantwriting Workshop at the 71st Annual College on Problems of Drug Dependence (CPDD) Conference on June 15, 2010, in Scottsdale, Arizona.

Dr. Cindy Miner delivered the Opening Plenary and presented on National Drug Facts Week to the National Youth Leadership at CADCA's 9th Annual Mid Year Training Institute on July 26-29, 2010, in Phoenix, Arizona.

Dr. Cathrine Sasek, OSPC, presented "Small Business Innovation Research (SBIR) and Technology Transfer (STTR) Programs" at NIDA's Digital Media & Communication Technologies in Adolescent Drug Abuse Treatment conference on April 26, 2010.

Dr. Cathrine Sasek presented NIDA's grant funding opportunities at the "Peek into NIH - NIDA Special Programs and Resources" as part of the 12th Annual NIH SBIR/STTR Conference on June 3, 2010.

On July 14, 2010, Dr. Ruben Baler, Science Policy Branch, OSPC, introduced, discussed, and answered questions about the movie "Candy" in the context of the "Science in the Cinema" Program, a month-long, free event sponsored by the NIH Office of the Director, and designed to promote public understanding of science, health, and medicine.

Dr. Lula Beatty, Director, Special Populations Office (SPO), participated in a workshop on academic publishing sponsored by NIDA's American Indian/Alaska Native Researchers and Scholars Work Group. The workshop was held on April 21, 2010 in Albuquerque, NM in conjunction with NIDA's Blending Conference ("Evidence-Based Treatment and Prevention in Diverse Populations and Settings").

Dr. Lula Beatty served on the Fellows Committee and the Sue Rosenberg Zalk Award Committee of the Society for the Psychology of Women, American Psychological Association.

Dr. Lula Beatty served on the planning committee and as faculty of the Leadership Institute for Women in Psychology (LIWP), American Psychological Association. Twenty-five mid-career faculty in academic and academic medicine universities from across the country participated in the institute, which included sessions on leadership, mentoring, negotiation, and goal setting. The LIWP was held August 10 -11, 2010 in San Diego CA.

Dr. Lula Beatty participated in a SAMHSA sponsored meeting titled "Integrating Evidence and Practice to Reduce Disparities: Developing an Inclusive Framework for Mental Health Interventions" on May 11-12, 2010 in Washington, DC.

Dr. Lula Beatty participated in the panel on NIH Research Opportunities for AAPI Behavioral and Social Scientists at the Asian American/Pacific Islander Researchers and Scholars Work Group 2010 conference "Advancing API Drug Abuse/Mental Health Prevention Sciences and Treatment: Transdisciplinary Frameworks" on June 2 -3, 2010 in Alexandria, VA.

Dr. Lula Beatty participated in the programs of the underrepresented populations committee and presented a talk on NIDA/NIH Resources to Increase Diversity in Drug Abuse Research in a workshop at CPDD, June 13, 2010 in Scottsdale, AZ.

Dr. Lula Beatty served on the planning committee and participated in the 5th

annual African American Healthy Marriage Initiative Research to Practice Conference titled "Preparing Resilient Families for the New Decade" sponsored by the Administration for Children and Families on June 22-24, 2010 in Hampton, VA.

Dr. Lula Beatty presented a talk titled "The National Institute on Drug Abuse: Overview of Programs and Opportunities" at the NIH orientation program for Hispanic Association of Colleges and University (HACU) participants on July 19, 2010 in Bethesda, MD.

Dr. Lula Beatty participated in the following activities at the American Psychological Association's annual convention held August 12 - 15, 2010 in San Diego, CA: Chaired symposium on Working with Special Population Youths and Substance Use Disorders: Discussant on symposium, Innovations in Research on Drug Use and Sexual Orientation: Chaired symposium, Beyond Me - Reducing Disparities in Drug Abuse Through Structural Interventions; Pursuing Research, Suite program for the Section on the Psychology of Black Women, Society for the Psychology of Women.

Ana Anders, M.S.W., SPO, participated in the Asian American/Pacific Islander Researchers and Scholars Work Group 2010 conference "Advancing API Drug Abuse/Mental Health Prevention Sciences and Treatment: Transdisciplinary Frameworks" on June 2 -3, 2010 in Alexandria, VA.

Flair Lindsey, SPO, participated in the National Training Conference of Blacks in Government on August 16-20, 2010 in Kansas City, Missouri. The conference was centered on training opportunities to enhance the performance of federal government employees.

Dr. Jerry McLaughlin, OEA, served as a reviewer for new and ongoing grants and contracts for the Army Research Institute's biology research program, July 29-30, 2010.

Dr. Jerry McLaughlin Served as a reviewer for proposals for the NIST TIP Competition in Manufacturing and Biomanufacturing, August 21-22, 2010.

Dr. Minna Liang, OEA, was selected to serve on the trans-NIH EPMC/AMC R & D Contract Policy and Procedure Committee. This R&D Contract working group aims to develop guidance for the receipt of electronic proposals, identifying data fields captured in electronic proposals, and the development of end to end IT solutions for contract reports.

Dr. Eliane Lazar-Wesley, OEA, was appointed as the NIDA representative to the Human Subject Protection Liaison Committee, starting June 2010.

Dr. Mark Swieter, OEA, presented information at the Grant Writing Workshop at the CPDD meeting, Scottsdale, AZ, June 2010.

Dr. Mark Swieter participated in presentations at the "What's New at NIDA and NIH" workshop at the CPDD meeting, Scottsdale, AZ, June 2010.

Dr. Mark Swieter participated in the "Career Development Workshop" at the CPDD meeting, Scottsdale, AZ, June 2010.

Dr. Meena Hiremath, OEA, chaired a panel entitled "The NEW NIH-Everything You Need to Know to Write Competitive Grants in 2010 and Beyond" for the 2010 NIDA Asian American & Pacific Islander Workgroup Conference on June 2-3, 2010 in Alexandria, VA.

Dr. Meena Hiremath gave a talk entitled "Current Peer Review System—Overview of Enhancement" on June 3, 2010 at the 2010 NIDA Asian American & Pacific Islander Workgroup Conference in Alexandria, VA.

Dr. Teri Levitin, Director, OEA, is serving on the newly formed working group of

the Extramural Program Management Committee (EPMC) that will examine current NIH policy concerning appeals of the initial peer review process.

Dr. Levitin attended the Society for Prevention Research in May in Denver where she met with a number of new investigators to explain the review process and changes to peer review.

Dr. Levitin co-organized and co-taught a grant writing workshop "Unlock the Mysteries of NIH Research Funding: Improve Your Grant Application and Improve Your Chance of Success", a four hour workshop at the American Psychological Association's annual meeting in August 2010 in San Diego CA.

Dr. Meena Hiremath participated as the SRO in a mock review at the 2010 NIDA Asian American & Pacific Islander Workgroup Conference in Alexandria, VA.

Dr. Kristen Huntley, OEA, co-organized and co-taught a grant writing workshop "Unlock the Mysteries of NIH Research Funding: Improve Your Grant Application and Improve Your Chance of Success" at the American Psychological Association 118th Annual Meeting, August 12-15, 2010, San Diego, CA.

Dr. Kristen Huntley organized and chaired a symposium titled "Cutting Edge Science for Clinicians: Where is Addiction Treatment Going?" at the American Psychological Association 118th Annual Meeting, August 12-15, 2010, San Diego, CA.

Dr. Meena Hiremath participated in a panel about science career paths at the Colorado State University Research Experience for Undergraduates on August 4, 2010 at Ft. Collins, CO.

Dr. Jerry McLaughlin co-organized and introduced the "Career Development: A Perspective from Junior and Senior Researchers" workshop at the annual CPDD meeting, June 13, 2010, in Scottsdale, Arizona.

Dr. Jerry McLaughlin participated in the Annual Paul F. Glenn Symposium on Aging meeting, June 21, 2010 at the Harvard Medical School, Boston, MA, and the Annual Ellison Foundation Colloquium on the Biology of Aging, August 11-13, Woods Hole MA.

Dr. Jerry McLaughlin served as President of the Scientific Program and Review Interest Group (SPRIG), the first extramural Interest Group at NIH which examines science administration issues, revised infrastructure, and he co-organized expert panel presentations.

Dr. Mark Green, OEA, was the Chair of the "What's New at NIDA and NIH" workshop at the CPDD meeting, Scottsdale, AZ, June 2010.

Dr. Jose Ruiz, OEA, co-organized the Career Development Workshop that took place June 13, 2010 at the annual CPDD meeting, in Scottsdale, Arizona.

Dr. Scott Chen, OEA, participated as the SRO for a "Mock Review", that was part of the NIDA Special Populations Research Development Seminar Series May 17, 2010, in Bethesda, Maryland.

Dr. Scott Chen is a NIDA coordinator for the workshop: "What Makes a Cigarette a Cigarette", in partnership with the FDA Center for Tobacco Products and NCI.

The 31st Annual Meeting of the Society for Clinical Trials took place May 16-19, 2010, in Baltimore, Maryland. Carmen Rosa organized a workshop titled "Considerations in the Design of Clinical Trials for Comparative Effectiveness Research".

Quandra Scudder, CCTN, and other NIDA staff (Drs. Augusto Diana, Kristopher Bough, Elena Koustova, Cathrine Sasek, Kristin Huntley, Jonathan Pollock, Brian O'Laughlin), participated in the 12th Annual NIH Small Business Innovation Research/Technology Transfer (SBIR/STTR) Conference, June 2-3, 2010, in Raleigh, North Carolina.

The College on Problems of Drug Dependence (CPDD) held its 72nd annual meeting June 12-17, 2010, in Scottsdale, Arizona. CTN members and CCTN staff presented a total of twenty posters, one symposium, and two oral presentations. The following are presentations from staff: Drs. Udi Ghitza, Steven Sparenborg, David Liu, and Betty Tai presented a poster titled "NIDA's Clinical Trials Network Can Facilitate Comparative Effectiveness Research on Addiction Treatments."; Drs. Lian Hu, Michelle Leff, Betty Tai, Steven Sparenborg, and other CTN members presented a poster titled, "The safety of prazosin in drug-abusing populations."; Drs. Steven Sparenborg, Lian Hu, and Betty Tai presented a poster titled, "Agonist replacement therapy for marijuana dependence."; Dr. Petra Jacobs co-chaired a mini-symposium titled, "The Multi-Site NIDA Clinical Trials Network Prescription Opioid Addiction Treatment Study: Outcomes and Implications."; Dr. Raul Mandler participated in the oral communications session titled, "HIV/AIDS Infection and Drug Abuse Intersection." The presentation was titled, "Never HIV tested: Results of screening data from 12 drug treatment programs in the CTN 0032 HIV Rapid Testing and Counseling Study."

Carmen Rosa, CCTN, participated in the 22nd Annual Native Health Research Conference on Promoting Participatory Research among Native Communities. The conference was held July 27-30, 2010 in Rapid City, South Dakota. She gave a presentation in the Community Based Participatory Research Workshop session titled, "Substance Use/Non-use in Native Communities: A Tribal Participatory Research Initiative."

The 2010 CALDAR Summer Institute on Longitudinal Research & CTN Dissemination Conference titled "Longitudinal Perspectives on Recovery from Drug Dependence" was held August 9-11 in Marina del Ray, CA. Dr. Betty Tai gave a presentation titled, "Bridging the Gap from Research to Practice" on day one of the conference. This three-day conference was a joint effort of the Center for Advancing Longitudinal Drug Abuse Research at UCLA and the CTN Pacific Node.

CCTN staff participated in the following events at the 118th Annual Convention of the American Psychological Association held August 12-15, 2010 in San Diego, California: On August 11, Dr. Harold Perl taught a half-day pre-convention workshop (with Drs. Teri Levitin and Kristen Huntley of OSA) titled, "Unlock the Mysteries of NIH Funding: Improve Your Application and Improve Your Chances at Success; On August 12, Dr. Perl presented a talk at the convention titled, "Putting Science-Based Treatments to Use in Real-World Practice," as part of a symposium session titled, "Cutting Edge Science for Clinicians—Where is Addiction Treatment Going?"

On June 24, 2010, Dr. Kenzie Preston, gave a presentation entitled, "Real-Time Self-Report of Drug Use and Craving." Dr. Preston is an independent investigator overseeing research in the 60-patient-outpatient substance abuse treatment research program at the National Institute on Drug Abuse Intramural Research Program (NIDA IRP). She presented studies in which Ecological Momentary Assessment (EMA) is used to study craving, drug use and relapse in heroin/cocaine users in outpatient treatment. She also presented work on adding real-time location data collection to EMA to investigate environmental influences on drug use.

Dr. Laurence Stanford and Dr. Joseph Frascella, DCNBR, presented a workshop entitled "NIH Grant-writing Process: Tips. Tricks and Strategies at the Interdisciplinary Research Training Institute on Hispanic Drug Abuse in

Houston, Texas on June 20, 2010.

Dr. Laurence Stanford served as the chair of a mock study section meeting as a part of the NIDA Research Development Seminar Series in Bethesda, Maryland on May 17, 2010.

Dr. Joseph Frascella gave a presentation entitled "Disorders of Desire: "Dirty Deeds" of a Highly Evolved Brain" within a symposium Craving, Compulsion and Consumption: Evolved Neurobiology in Disorders of Desire held at the annual meeting of the Society of Biological Psychiatry, New Orleans, Louisiana, May 20, 2010.

Dr. Joseph Frascella and Dr. Nora Volkow co-chaired a symposium entitled Neurobiology of Obesity: Why We Can Get Too Motivated to Eat at the annual meeting of the American Psychiatric Association in New Orleans, Louisiana, May 22, 2010.

Dr. James Bjork, DCNBR, with the sponsorship of the Telemedicine and Advanced Technology Research Center (TATRC) of the U.S. Army, presented a research synopsis on the acute and chronic effects of drugs of abuse on brain white matter architecture at a workshop on Diffusion MRI for Mild TBI in Chicago, IL, May 2010.

Drs. James Bjork and Susan Volman, DBNBR, co-chaired a symposium entitled Reward Neurocircuitry in Substance Dependence and other Psychiatric Disorders: What Does Brain Research Tell Us? at the American Psychiatric Association annual meeting, May 25th, 2010 in New Orleans.

Drs. Steven Grant, DCNBR, and Roger Sorenson, DBNBR, co-chaired a symposium entitled How Dysfunction of Learning and Memory Circuits Contribute to Substance Abuse and Other Psychiatric Disorders at the American Psychiatric Association annual meeting, May 26th, 2010 in New Orleans.

Drs. Mary Kautz, Woody Lin, DCNBR and Minda Lynch, DBNBR, organized a symposium entitled Executive Function as a Brain System for Self-Control: The Neurocircuitry of Psychiatric Disorders and Addiction which was held at the American Psychiatric Association Annual Meeting on May 22, 2010 in New Orleans, LA.

Dr. Yu (Woody) Lin, DCNBR, participated in a symposium entitled Moving Towards Personalized Pain Management sponsored by the NIH Pain Consortium Symposium held at NIH on May 5, 2010. The symposium highlighted several areas of interest: 1) Developing Tools for Individualized Pain Management; 2) Emerging Therapies for Individualized Pain Management; and 3) Translating Research into Tailored Clinical Practice.

Dr. Yu (Woody) Lin co-organized, together with the VA Program on Pain and Analgesia, NIA and NIDCR, a NIH-VA joint workshop to identify potential areas of common research interest between VA and NIH. The workshop was held in Baltimore during the American Pain Society annual conference on May 7, 2010. It explored the possibility of interactive collaborations between the VA intramural program and the NIH extramural programs in pain research and management.

Dr. Yu (Woody) Lin of DCNBR moderated the CCTN-DCNBR/NIDA joint seminar entitled Acupuncture: Analgesic or Placebo? -- The Science Behind the Answer that was held at NIDA on May 12, 2010. Several recent fMRI studies were presented that revealed different brain regions activated by real and shame acupuncture, indicating different mechanisms mediated in those two interventions.

Dr. Cheryl Anne Boyce and Dr. Joseph Frascella, DCNBR, co-chaired a symposium entitled, "Adolescent Potential: Exploring the Developing Brain and

Understanding Pathways of Addiction" at the 2010 annual American Psychiatric Association convention on May 25, 2010. Drs. Jay Giedd (NIMH), Linda Spear, Susan Tapert and Beatriz Luna served as presenters for this session that was part of NIDA's special programming.

Dr. Cheryl Anne Boyce served as a participant in the Robert Wood Johnson Foundation (RWJF) Meta Network for PhD Diversity meeting on May 26-28, 2010 in Princeton, NJ. The Meta Network was designed to create formal connectivity among programs that support minority students at various stages of the pipeline from high school to faculty development programs.

Dr. Nicolette Borek, DCNBR, was a member of the national organizing committee and participated in the meeting Substance Exposed Newborns: Collaborative Approaches to Complex Issues held June 23-24, 2010 in Alexandria, VA. The meeting was hosted by the National Abandoned Infants Association Resource Center and co-sponsored by NIDA, the Administration for Children and Families (ACF), and the National Center on Substance Abuse and Child Welfare, SAMHSA.

Dr. Cheryl Anne Boyce participated in a funding opportunities panel discussion at the 16th Annual National Black Graduate Psychology Conference sponsored by the University of Maryland Baltimore County (UMBC) on July 10, 2010. The conference provided a forum for research presentations, professional development experiences, and networking toward the goal of building successful research careers among underrepresented scholars.

Dr. Cheryl Anne Boyce participated in a discussion panel on the infrastructure of family research at the Institute of Medicine (IOM) Science of Family Research Workshop co-sponsored by NIDA CAWG, NICHD, OBSSR, and ACF and on July 13-14, 2010 in Washington, DC.

Dr. Cheryl Anne Boyce presented as part of the faculty for the 8th Annual Minority Fellowship Program Psychology Summer Institute (MFP PSI) in Washington, DC on July 19, 2010. This summer institute includes mentoring, educational and professional development experiences to pre-doctoral and early career researchers, thereby advancing them toward the development of a grant proposal.

On May 13, 2010, Dr. Lisa Onken, DCNBR, participated in a meeting to provide feedback and recommendations on two new Treatment Improvement Protocol (TIP) publications that the Center for Substance Abuse Treatment (CSAT) is currently developing: 1) "Building Health and Wellness in Substance Abuse Recovery" and 2) "Managing Anxiety Symptoms and Stress in Substance Abuse Treatment and Recovery".

Dr. Cecelia Spitznas, DCNBR, participated in organizing a meeting with Drs. William Riley of NHLBI, Wendy Neilsen of OBSSR and Audie Atienza from the NIH OD entitled "Reducing Barriers to Mobile Technology Usage in Behavioral and Social Sciences Research" which was held on June 7 & 8, 2010 in Bethesda MD. A major purpose was to identify and address barriers experienced by m-Health researchers including issues related to human subjects protection, data safety, regulatory rules, and to attempt to raise awareness regarding practical concerns related to hardware, software and mobile plans with stakeholders in research, industry and the government.

Dr. Cecelia Spitznas gave three presentations at the NIH Regional Seminar on Program Funding and Grants Administration in Portland Oregon on June 24th & 25th, 2010. The purpose of this meeting was to educate potential applicants and grants management staff at Northwestern Institutions interested in applying for funding from NIH about how to successfully negotiate the NIH funding process and update them on the latest happenings at NIH related to extramural grants.

Dr. Will M. Aklin, DCNBR, and Dr. Richard Denisco, DESPR, co-chaired a symposium in May 2010 at the 163rd American Psychiatry Association Annual Meeting entitled, "Treating Chronic Pain and Co-occurring Addiction in Substance Abuse Patients." A major purpose was to examine the advantages and disadvantages of buprenorphine and methadone used to treat acute pain and addiction concurrently. In addition to these pharmacological approaches, the meeting delineated the common features of integrated treatments for both chronic pain and opioid addiction.

Dr. Will M. Aklin co-chaired a meeting at the 118th American Psychological Association Annual Convention entitled, "Cognitive Remediation as a Mechanism to Improve Substance Abuse Treatment." The goal of the meeting was to provide an overview of the current evidence-based cognitive remediation strategies that improve drug abuse treatment outcomes, explore the relationships between executive function as it pertains to drug abuse, and describe novel approaches to improve executive functioning in drug dependent individuals.

Dr. James Bjork, DCNBR, participated in and gave a talk entitled "Decisions Decisions: Neuroeconomics Research and NIDA" at an NICHD workshop for grantees of the SEED (Science and Ecology of Early Development) program. This workshop was devoted to exploring potential developmental research with behavioral economics, and was held on the main NIH campus, August 9-10, 2010.

At the 118th American Psychological Association Annual Convention, Dr. Lisa Onken was a Discussant for a symposium entitled, "Cutting Edge Science for Clinicians - Where is Addiction Treatment Going?" chaired by Dr. Kristen Huntley. Presenters included Brenda Wiederhold, Ph.D. ("Virtual is the New Reality"), Michele Ybarra, Ph.D. ("Cell Phone Text Messaging: Connecting Clients with Treatment Support Services"), Kathleen Carroll, Ph.D. ("Using Computer/Video Treatment Protocols to Enhance and Extend Care"), and Harold Perl, Ph.D. ("Putting Science-Based Treatments to Use in Real-World Practice").

Dr. Lisa Onken, in collaboration with Dr. Patty Mabry from OBSSR, organized and chaired a Roadmap symposium for NIH staff entitled, "Behavioral intervention optimization: Capitalizing on engineering, computer science, and technology." Speakers at the meeting included Linda Collins, Ph.D. ("The multiphase optimization strategy for engineering optimized behavioral interventions"), Susan Murphy, Ph.D. ("Computer science, adaptive treatment, and sequential multiple assignment randomized trials."), Daniel Rivera, Ph.D. ("Applying ideas from control systems engineering to behavioral interventions") and Edward Boyer, Ph.D., M.D. ("Adaptive behavioral interventions using computer science, technology, and real-time feedback").

Dr. Roger Sorensen, DBNBR, represented NIDA and the NIH at the 2010 NIH Regional Seminars on Program Funding and Grants Administration held on June 24 - 25, 2010 in Portland, OR, co-hosted by the Oregon Health Sciences University. The Regional Seminar program provides institution administrators and scientific investigators with an inside look at processes and policies at the NIH. He gave four presentations; "Grant Writing for Success", and "Early Stage Investigators", "After the Award is Made, Then What ...", and "Primetime With Program: RPGs", as well as providing insight into the NIH grants process.

Dr. David Thomas, DBNBR, delivered a presentation entitled: "Virtual Reality and Pain Treatment" at the Joint Task Force Substance Misuse Conference held at Uniformed Services University of the Health Sciences, Bethesda, MD, May 19, 2010.

Dr. David Thomas delivered a talk entitled: "Virtual Reality and Pain Control" on May 6, 2010 at the 29th Annual Scientific Meeting of the American Pain

Society.

Dr. David Thomas delivered a presentation entitled, "Paths to Translation" at the NIDA Asian American and Pacific Islander Workgroup Conference on June 2, 2010 in Alexandria, Virginia.

Drs. Cora Lee Wetherington and Samia Noursi, DBNBR, were invited by the Office of Research on Women's Health at NIH (ORWH) to participate in a meeting of external experts, including ORWH current and former Advisory Committee members, to review and discuss the draft goals and objectives that were collected from the five ORWH regional meetings held by across the US during the previous 14 months. The goal of the meeting, held on April 14, 2010, was to develop the core of the strategic research directions for women's health research at the NIH for the coming decade.

Dr. Cora Lee Wetherington gave an invited presentation, "Observations from the IOM Workshop, Sex Differences and Implications for Translational Neuroscience Research," at the annual meeting the Organization for the Study of Sex Differences, Ann Arbor, MI, June 3-5, 2010.

Dr. Cora Lee Wetherington co-organized and co-chaired (with Helen Scharfman, Nathan Kline Institute and New York University) the symposium, "Sex Differences in Neuroplasticity and Mental Health," at the annual meeting of the Organization for the Study of Sex Differences, Ann Arbor, MI, June 3-5, 2010. The speakers were Dolores Malaspina (New York University), Neil J. MacLusk (University ofGuelph), Helen Scharfman (Nathan Kline Institute and New York University), and Cynthia Kuhn (Duke University).

Dr. Cora Lee Wetherington co-chaired (with Colleen Hanlon, Wake Forest University School of Medicine, organizer) the symposium, "Gender Differences in Response to Social Stress: Parallels from Cocaine and Alcohol Research in Human and Non-Human Primates," at the annual meeting of the College on Problems of Drug Dependence, Scottsdale, AZ, June 12-17, 2010. The speakers were Paul Czoty (Wake Forest University School of Medicine), Kathleen Grant (Oregon Health Sciences University), Colleen Hanlon (Wake Forest University School of Medicine), Helen Fox (Yale University School of Medicine), and Mary Jeanne Kreek (Rockefeller University).

Dr. Cora Lee Wetherington co-organized and co-chaired (with Shelly F. Greenfield, Harvard Medical School) the symposium, "Sex and Gender Considerations in Laboratory and Treatment Outcome Studies in Addiction," at the annual meeting of the American Psychological Association, San Diego, CA, August 12-15, 2010. The speakers were Kathleen T. Brady (Medical University of South Carolina), Rajita Sinha (Yale University School of Medicine), Shelly F. Greenfield (Harvard Medical School), Denise A. Hien (Columbia University), and Theresa Winhusen, Ph.D. (University of Cincinnati College of Medicine).

Dr. Cora Lee Wetherington organized and co-chaired (with Sudie Back, Medical University of South Carolina) the symposium, "Social Stress and Drug Addiction - Sex and Gender Matter, at the annual meeting of the American Psychological Association, San Diego, CA, August 12-15, 2010. The speakers were Michael Nader (Wake Forest University School of Medicine), Sari Izenwasser (University of Miami), Colleen Hanlon (Wake Forest University School of Medicine), Sudie Back Medical University of South Carolina), and Rajita Sinha (Yale University School of Medicine).

Dr. Cora Lee Wetherington co-chaired (with Dionne Jones, NIDA, organizer) the symposium, "Valuing Gender Sensitive Health Care and Treatment Services for Abused Women," at the annual meeting of the American Psychological Association, San Diego, CA, August 12-15, 2010. The speakers were Christine Grella (UCLA), Nena Messina (UCLA), Lisa Najavits (Harvard Medical School), and Stephanie Covington (Institute for Relational Development).

Dr. Cora Lee Wetherington co-organized and co-chaired (with Shelly F. Greenfield, Harvard Medical School) the symposium, "Sex/Gender Differences and Women-Specific Issues in Drug Abuse: Predicting and Improving Treatment Outcomes," at the annual meeting of the American Psychiatric Association, New Orleans, LA, May 22-27, 2010. The speakers were Kathleen T. Brady (Medical University of South Carolina), Rajita Sinha (Yale University School of Medicine), Shelly F. Greenfield (Harvard Medical School), Denise A. Hien (Columbia University), and Theresa Winhusen, Ph.D. (University of Cincinnati College of Medicine).

Drs. Mary Kautz, Woody Lin, DCNBR, and Minda Lynch, DBNBR, organized a symposium entitled "Executive Function as a Brain System for Self-Control: The Neurocircuitry of Psychiatric Disorders and Addiction" held at the American Psychiatric Association Annual Meeting on May 22, 2010 in New Orleans, LA.

Drs. James Bjork, DCNBR, and Susan Volman, DBNBR, organized a symposium entitled "Reward Neurocircuitry in Substance Dependence and Other Psychiatric Disorders: What Does Brain Research Tell Us?" This symposium was held at the American Psychiatric Association Annual Meeting on May 25, 2010 in New Orleans, LA.

Dr. James Bjork, DCNBR, gave a talk entitled "Alcohol and the Brain" to advanced science students at Wootten High School (Bethesda, MD) for the NIH LifeWorks Speakers Bureau, on May 19, 2010.

Dr. Mary Kautz, DCNBR, gave a presentation entitled Nicotine Abuse in the Joint Task Force National Capital Region, Medical (JTF CAPMED) CE activity Substance Misuse Symposium on May 18-19, 2010 at the Uniformed Services University in Bethesda, MD.

Dr. Minda Lynch, DBNBR, with Dr. David Shurtleff, DBNBR, as Co-chair, organized a half-day NIDA-sponsored satellite symposium at CPDD in June, Scottsdale, AZ. This session, on "Genetics Approaches in Drug Abuse and Addiction Research", included presentations to highlight recent findings from mouse mutagenesis, human pharmacogenetics, QTL studies and techniques to study micro-RNAs in paradigms relevant for understanding addiction. Seventy-five CPDD attendees participated in the satellite, representing drug abuse researchers from clinical and basic science arenas.

Dr. Samia Noursi, DBNBR, Deputy Coordinator, Women and Sex/Gender Differences Research organized and chaired a seminar entitled "Women-Focused HIV Prevention for Women Who Use Drugs: Domestic and Global Perspectives" April 20th, 2010 in Bethesda, MD. Speakers were Drs. Claire Sterk (Emory University), Nabila El-Bassel (Columbia University), and Wendee Wechsberg (RTI International).

Dr. Samia Noursi participated in the Executive Committee meeting of the National Partnership to End Interpersonal Violence (NPEIV), September 10, 2010, San Diego, CA.

Dr. Samia Noursi participated in the annual Think Tank Meeting of the National Partnership to End Interpersonal Violence (NPEIV), September 11, 2010, San Diego, CA.

Dr. Samia Noursi chaired a keynote entitle "Providing Gender-Specific Trauma-Informed Substance Abuse Treatment" at the 15th International Conference on Violence Abuse & Trauma, September 12-15, 2010, San Diego, CA.

Dr. Samia Noursi and Dr. Dionne Jones, DESPR, chaired an invited panel entitled "Adolescent Substance Abuse & Its Consequences" at the 15th International Conference on Violence Abuse & Trauma, September 12-15, 2010, San Diego, CA. Dr. Wendee Wechsberg (RTI International) will present on "The Allure of Gangs, Violence and Victimization Experienced by Drug-using

Teens in Cape Town, South Africa" and Dr. Jamila Stockman (University of California Los Angeles) will present on "Continuums of Sexual Coercion among Adolescents: Pathways to Substance Abuse".

Drs. Samia Noursi and Cora Lee Wetherington presented a poster at NIDA's International Forum at the College on Problems of Drug Dependence (CPDD), June 12-17, 2010 in Scottsdale, Arizona. The poster described NIDA's Women and Sex/Gender Differences Research Program: program history, goals, and research interests.

Drs. Joni Rutter, DBNBR and Linda Porrino, Wake Forest University, co-organized and co-chaired a session on "Translating the Genetics and Neurochemistry of Nicotine Dependence To Drug Development "at the College on Problems of Drug Dependence (CPDD), June 13, 2010 in Scottsdale, Arizona.

Dr. David Shurtleff, Director, DBNBR, gave an invited presentation at the Louisiana State University Medical School, Department of Physiology, New Orleans, LA on "What You Need to Know About NIH Early Career Funding Opportunities and Beyond," May 2010.

Drs. Rao Rapaka, David Shurtleff, Paul Schnur, Minda Lynch, DBNBR and Joseph Frascella, DCNBR, co-chaired a NIDA sponsored workshop on "Nutrition and Addiction" that was co-oranginized with Dr. Daniele Piomelli, UIC, June 2010 in Rockville, MD.

Dr. David Shurtleff gave a presentation entitled: "Research Funding Opportunities: the Role of NIDA Program" at the Annual Meeting of the College on Drug Dependence. Scottsdale, AZ in June 2010.

Drs. John Satterlee and David Shurtleff, DBNBR, co-organized and co-chaired a session on "Epigenetic Factors in Brain and Behavior Function and Dysfunction" at the American Psychological Association (APA) in San Diego CA, August, 2010.

Dr. David Shurtleff co-organized and co-chaired a session on "The Role of the Hypocretin/Orexin System in Addiction: Current Status and Rationale as a Drug Discovery Target" at the College on Problems of Drug Dependence (CPDD), June, 2010 in Scottsdale, Arizona.

Dr. John Satterlee gave a presentation "The International Human Epigenome Consortium" at the Steering Committee for the NIH Roadmap Reference Epigenome Centers, in La Jolla, CA, May 21, 2010.

Dr. John Satterlee presented "The Roadmap Epigenomics Program" at a National Institute of Aging sponsored meeting entitled: "An Integrated Epigenetic-Genetic Approach to Alzheimer's Disease" in Bethesda, MD, June 7-8, 2010.

Dr. John Satterlee chaired a session "New Pathways to Future Addiction Therapy" at CPDD, Scottsdale, Arizona, June 15, 2010.

Dr. Jonathan D. Pollock, DBNBR, attended the 4th International Conference on Genomics, Seattle Art Museum, Seattle, WA, April 13-16, 2010.

Dr. Elena Koustova and Dr. Jonathan D. Pollock, DBNBR, attended the 12th Annual NIH SBIR/STTR Conference, Raleigh, NC, June 2-3, 2010.

Dr. Elena Koustova, briefed, the Tobacco Control Staff at NCI on NIDA's proposed Public Private Partnership for the development of new medications for smoking cessation "Medications Initiative for Tobacco Dependence," May 3, 2010.

Dr. Elena Koustova briefed the Acting Director of NHLBI, Dr. Susan Surin on

NIDA's proposed Public Private Partnership for the development of new medications for smoking cessation, entitled, "Medications Initiative for Tobacco Dependence," June 4, 2010.

Dr. Elena Koustova and Dr. Jonathan D. Pollock briefed Dr. Kathy Hudson, the NIH Chief of Staff on NIDA's proposed Public Private Partnership for the development of new medications for smoking cessation, entitled, "Medications Initiative for Tobacco Dependence," Bethesda, MD. May 12, 2010 and June 24, 2010.

Dr. Steve Oversby, DPMCDA, organized and chaired a symposium titled: Bridging Gaps in Current Medication Treatment Research for Pregnant Women and In Utero Substance Exposed Neonates: Ethics, Advances and Future Directions that was held on June 23, 2010 as a part of the National Abandoned Infants Assistance (AIA) annual conference entitled Substance Exposed Newborns Collaborative Approaches to a Complex Issue held in Alexandria Virginia. The symposium featured presentations by Drs. Hendree Jones and Lauren Jansson.

Dr. Kristopher Bough, DPMCDA, in conjunction with Dr. Cathrine Sasek, Mark Fleming, Ananth Charya, and Aaron Martinek (all from the NIDA/OD) helped put together a new Small Business webpage for NIDA. (http://www.nida.nih.gov/funding/smallbusiness/)

Dr. Jag Khalsa participated in the Annual Meeting of ACTHIV in Denver, Colorado, May 2010.

Dr. Ivan Montoya, DPMCDA, co-chaired with Dr. Hendree Jones a workshop during CPDD in Scottsdale AZ to provide the neonatal and maternal outcomes of the NIDA-funded Maternal Opioid Treatment: Human Experimental Research (MOTHER) project. MOTHER is an international, eight-site, double-blind, double-dummy, flexible-dosing, parallel-group randomized clinical trial that examined the comparative safety and efficacy of methadone and buprenorphine for the treatment of opioid dependence among pregnant women and their neonates. Dr. Hendrée Jones presented the main study findings of primary neonatal outcomes [e.g., incidence and severity of neonatal abstinence syndrome (NAS) and physical birth parameters] and key maternal outcomes (e.g., maternal treatment retention, average doses received, obstetrical and delivery outcomes). Dr. Susan Stine presented results that indicate how the MOTHER sample is representative of the larger pool of opioid-dependent pregnant women. Dr. Gabriele Fischer presented comparisons between the treatment and patient characteristics of US and European women screened for the study. Dr. Peter Martin presented results of the prevalence and management of co-occurring psychiatric disorders and medication interactions in pregnant opioid dependent women. Dr. Karol Kaltenbach was the discussant and placed these seminal results in historical context, detailed their clinical relevance, and outlined their implications for affirming and changing clinical practice.

Dr. Ivan Montoya presented a poster describing the Division of Pharmacotherapies and Medical Consequences of Drug Abuse at the NIDA International Satellite Conference before CPDD in Scottsdale, AZ.

Dr. Ivan Montoya served as mentor at the Latino Mental Health Conference in New Brunswick, NJ in June 2010.

Dr. Ivan Montoya participated in the annual meeting of the American Psychiatric Association in New Orleans. He co-chaired with Wilson Compton of DESPR a symposium titled "Integrated treatment of substance use and psychiatric disorders," and co-chaired with Dr. Herb Kleber of Columbia University a workshop titled "Opiate dependence maintenance treatment: terminable or interminable".

Dr. David McCann, DPMCDA, and Dr. Nora Volkow chaired a symposium at the annual meeting of the American Psychiatric Association. The title of the symposium was "Update on Medications Development: Promising New Treatments for Drug Addiction." It included presentations by Dr. Charles O'Brien (University of Pennsylvania), Dr. Kathleen Brady (Medical University of South Carolina), Dr. David McCann (NIDA), Dr. Frances Levin (Columbia University) and Dr. Raafat Fahim (Nabi). The discussant was Dr. Herbert Kleber. The meeting was held in New Orleans, LA during May, 2010.

Dr. David McCann chaired a mini-symposium at the annual meeting of the College on Problems of Drug Dependence. The symposium was entitled "Medications Development for the Treatment of Substance Dependence: Status of Advanced Projects." Dr. Charles Gorodetzky (Catalyst) presented on the development of vigabatrin for stimulant dependence, Dr. Frances Levin (Columbia U) presented on dronabinol for cannabis dependence, and Dr. David McCann (NIDA) presented on bupropion for methamphetamine dependence.

Dr. Wilson M. Compton, Director, DESPR, continues to participate in the DSM-V Task Force and DSM-V Substance Use Disorders Workgroup meetings on a continuing basis.

Dr. Wilson M. Compton presented on "Research on Addiction Recovery" at the CALDAR Summer Institute, Los Angeles, California, August 9, 2010.

Dr. Wilson M. Compton presented in a federal panel on "Methadone Mortality—A Reassessment", Washington, District of Columbia, July 30, 2010.

Dr. Wilson M. Compton presented on "Mainstreaming Addictions in Medicine" in a plenary at the 2010 SAAS National Conference and NIATx Summit, Cincinatti, Ohio July 13, 2010.

Dr. Wilson M. Compton participated in the NIAAA APISII: Expert Panel Meeting, Bethesda, Maryland, July 6, 2010.

Dr. Wilson M. Compton served as discussant for a panel on "Novel Methods To Assess Societal-Level Causes Across Time and Place" at the annual meeting of the Research Society on Alcoholism, San Antonio, Texas, June 26, 2010.

Dr. Wilson M. Compton presented at the SAMHSA-sponsored satellite session and Chaired a workshop on DSM-5 and presented on "The Terminology of DSM-5 Substance Disorders" at the annual meeting of the College on Problems of Drug Dependence, Scottsdale, Arizona, June 15, 2010.

Dr. Wilson M. Compton presented at the meeting of the Community Epidemiology Work Group, Boston, Massachusetts, June 9, 2010.

Dr. Wilson M. Compton chaired a panel on "Community Randomized Prevention Trials" at the annual meeting of the Society for Prevention Research, Denver, Colorado, June 2, 2010.

Dr. Wilson M. Compton participated in several panels and sessions including presentations on "Progress in Addiction Research" and on "The Terminology of DSM-5 Substance Disorders" at the annual meeting of the American Psychiatric Association, May 22-25, 2010.

Dr. Wilson M. Compton presented on "Linking Public Health Drug Abuse Research to Neuroscience" at Grand Rounds, Department of Psychiatry, University of Nevada, Reno, Nevada, May 19, 2010 and at Grand Rounds, Department of Epidemioogy and Public Health, Miller School of Public Health, University of Miami, Miami, Florida, May 6, 2010.

Dr. Wilson M. Compton presented on "Drug Abuse Epidemiology" at the Mentor Foundation, Forum on International Drug Prevention, House of Sweden, Washington, District of Columbia, May 18, 2010.

Dr. Wilson M. Compton presented on "Linking Public Health Drug Abuse Research to Neuroscience" at Grand Rounds, Department of Psychiatry, University of Nevada, Reno, Nevada, May 19, 2010.

Dr. Kevin Conway, Deputy Director, DESPR, presented "Prescription Opiate Abuse: Update from the Community Epidemiology Work Group & Monitoring the Future Studies" at the Food and Drug Administration Center for Drug Evaluation and Research Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee & Drug Safety and Risk Management Advisory Committee, at the University of Maryland, on July 22, 2010.

Dr. Elizabeth Robertson, DESPR, was the Invited plenary speaker at the PROSPER Regional meeting in State College, PA on May 11, 2010. The title of her presentation was 'The History of the PROSPER Project from the NIDA Perspective.'

Dr. Redonna Chandler, DESPR, co-chaired a symposium entitled Addressing the intersection of addiction and HIV in criminal justice involved populations at the annual meeting of the College on the Problems of Drug Dependence held in Scottsdale, AZ in June 2010.

Dr. Elizabeth Robertson spoke at the Mentor International Foundation forum on international drug prevention. The title of the forum was International Drug Abuse Prevention: Opportunities and Challenges, the title of her presentation was "The Way Forward." The Meeting took place at the House of Sweden in Georgetown on May 18, 2010.

Drs. Elizabeth Robertson and Eve Reider, DESPR, co-chaired a Research Roundtable titled "Type 2 Translation Research: A Move Toward Clarity," at the June 1-4, 2010, annual meeting of the Society for Prevention Research, in Denver, CO. The Discussants were Dr. Mark Greenberg, Dr. Melinda Pankratz, Dr. Jeanne Poduska, Dr. Louanne Rohrbach, and Dr. Belinda Sims, DESPR.

Dr. Eve Reider, PRB, DESPR, was an invited discussant for a panel "Building Resilience and Violence Prevention in Children Traumatized by War, Trauma and Displacement." This panel was part of the meeting "Children & Armed Conflict: Risk, Resilience & Mental Health" that was held on December 7, 2009 at National Academy of Sciences-Institute of Medicine, Washington, D.C.

Dr. Eve Reider represented NIDA at a University of Southern California Military Family Workshop held May 4, 2010 in Washington D.C. The purpose of the workshop was to discuss emerging critical issues in military family research, and to begin to build partnerships between USC faculty - who are interested in pursuing military family research - and experienced military family researchers from other universities. Attendees included USC faculty members, faculty from other universities, and representatives from federal agencies that fund military family research or that develop programs for military families.

Dr. Eve Reider continues to represent NIDA on the Research Subcommittee of the DoD/VA Deployment Health Working Group.

Dr. Eve Reider continues to represent NIDA on the Office of National Drug Control Policy (ONDCP) Inter-agency Workgroup for Military, Veterans and their Families.

Dr. Eve Reider was a member of the program planning committee for the 18th Annual Society for Prevention Research Annual Meeting that was held June 2-4, 2010 in Denver, CO.

Dr. Aleta Meyer participated in a meeting titled "Developing and Implementing Community Prevention Systems in Indian Country: Opportunities, Challenges, and Future Directions" in Seattle, WA, May 5-6, 2010 at the University of

Washington.

Drs. Aleta Meyer and Jacqueline Lloyd, DESPR, served as Co-Chairs for a scientific dialogue titled "Facilitating Research to Understand the Impact of Widely Implemented but Untested Prevention Programs: Case Examples from Screening and Brief Interventions (SBIs) and Positive Youth Development" at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. Roundtable participants included Dr. Evelyn Yang of CADCA, Ms. Anne Jordon from the Medical College of Virginia at Virginia Commonwealth University, Mr. Brian Barhaugh from Project VOYCE in Denver, Dr. Emilie Smith from the Pennsylvania State University, and Dr. Barbara Gerbert from the University of California-San Francisco.

Dr. Aleta Meyer served as Co-Chair along with Dr. Marcia Scott, NIAAA, for a paper symposium titled "The Intersection between Substance Use Prevention and Work Settings: Research to Inform Work-focused Prevention for Adolescents and Emerging Adults" at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. The symposium discussant was Dr. Joel Bennett from Organizational Wellness & Learning Systems. The presenters were Dr. Michael Pergamit from the Urban Institute, Dr. Robert Kaestner from the University of Illinois-Chicago, and Dr. Samuel Bacharach from the Smithers Institute for Alcohol-Related Workplace Studies, Cornell University.

Dr. Aleta Meyer presented a paper titled "Overview of NIDA's Interest in Physical Activity and Prevention" as part of an invited paper symposium titled "Active Living: Societal Approaches to Prevention Across Multiple Behaviors" at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. The symposium discussant was Dr. Richard Catalano from the University of Washington. The other presenters were Dr. Kevin Patrick from the University of California-San Diego, and Dr. Frank Perna of NCI.

Dr. Aleta Meyer participated as a member of a scientific dialogue titled "Actively Building Community-Researcher Partnerships: The Road to True Community-Based Participatory Research"at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. This session was chaired by Dr. Jane Callahan of CADCA; other participants were Dr. Ralph Hingson of NIAAA, Dr. Mark Wolfson from Wake Forest University, and Ms. Shereen Khatapoush from Youth Services System at Santa Barbara Fighting Back, and Dr. Evelyn Yang, CADCA.

Dr. Aleta Meyer served as moderator for a paper symposium titled "Reducing Youth Substance Use and Other Negative Behaviors through Innovative Prevention Program Strategies" at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. Paper presenters were Dr. Judith Andrews from the Oregon Research Institute, Dr. Tanya Nieri from the University of California-Riverside, and Dr. F. Marsiglia from Arizona State University.

Dr. Elizabeth Ginexi, DESPR, moderated a session at the NIDA meeting Developmental Neural Mechanisms of Cognitive Control: Implications for Drug Abuse held at NIDA, NSC, Rockville, MD on May 3-4, 2010.

Drs. Elizabeth Ginexi and Patty Mabry, NIH, OBSSR, and Linda Collins, Pennsylvania State University organized a preconference workshop at the Society for Prevention Research meeting on June 1, 2010, Denver, CO titled "Systems Science Methodologies for Prevention Research." The purpose of this interactive full-day workshop was to introduce prevention scientists to the utility of systems science methodologies for addressing some of the challenging research questions in their field and to familiarize them with four selected methodologies: system dynamics modeling, agent-based modeling, network analysis, and engineering control methods for optimizing intervention design.

Dr. Elizabeth Ginexi served as Chair for an invited Paper Symposium at the annual meeting for the Society for Prevention Research in Denver, CO on June 2, 2010 titled "The Application of System Sciences Methodologies to Prevention Research." Papers were presented by Drs. Thomas Valente of the University of Southern California, Kristen Hassmiller Lich of the University of North Carolina, and Edward J. Wegman of George Mason University. Dr. Patty Mabry, NIH, OBSSR served as Discussant.

Dr. Elizabeth Ginexi organized and participated in a Roundtable Discussion/Scientific Dialogue session at the annual meeting for the Society for Prevention Research in Denver, CO on June 2, 2010 titled "Using genetic and other neurobiological markers to identify children and adolescents at risk: Forging new prevention science frontiers or walking on thin ice?" Panelist discussants included Michael T. Bardo, Director of the Center for Drug Abuse Research Translation at the University of Kentucky, Diana H. Fishbein Senior Fellow, Behavioral Neuroscience at RTI International, Thomas J. Dishion, Director of Research at the Child and Family Center and Professor of Clinical Psychology at the University of Oregon, Celia B. Fisher, Director of the Fordham University Center For Ethics Education, and Ezemenari M. Obasi, Assistant Professor, University of Georgia, Department of Counseling and Human Development Services.

Dr. Elizabeth Ginexi served as Discussant an Organized Paper Symposium at the annual meeting for the Society for Prevention Research in Denver, CO on June 4, 2010 titled "Cells to Society: Filling the Gap Between Neural and Prevention Sciences." Dr. Michael Bardo of the University of Kentucky Chaired the session, and papers were presented by Dr. Susan Young of the Institute for Behavioral Genetics at the University of Colorado at Boulder, Dr. Thomas Crowley of the University of Colorado in Denver, and Dr. Jane Joseph of University of Kentucky.

Drs. Elizabeth Ginexi, Michael Spittel (NICHD), and Gregory Bloss, NIAAA participated in the NIH Funders Panel as part of the Institute on Systems Science and Health (ISSH) at the Columbia University Mailman School of Public Health at Columbia University on June 16, 2010. The Institute on Systems Science and Health is a week-long, immersive learning opportunity designed to introduce the general principles of systems science and foster a deeper understanding of selected methodologies that may be used to engage the behavioral and social drivers of population health.

Dr. Jacqueline Lloyd, DESPR, served as one of the coordinators of the 2010 Early Career Social Work Scholars Program, which took place during the NIDA Blending Conference in Albuquerque, New Mexico on April 22 - 23, 2010.

Dr. Jacqueline Lloyd chaired a session titled "HIV Prevention Interventions for At-Risk and Vulnerable Youth" at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. Papers were presented by Dr. Laurie Bauman, Dr. Mary McKay and Dr. Norweeta Milburn, and Dr. Mary Jane Rotheram-Borus served as the session discussant.

Dr. Jacqueline Lloyd and Susannah Allison, NIMH served as co-chairs for a session titled "The Promises and Pitfalls of Using Technology in HIV Prevention Interventions with Youth" at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. Paper presenters were Dr. Marguerita Lightfoot, Dr. Brian Mustanski, and Dr. Edward Smith.

Dr. Jacqueline Lloyd chaired a session titled "Delivery of Mental Health and Drug Abuse Prevention Services in Communities: Findings from the SAMHSA State Incentive Grant Programs" at the Society for Prevention Research Annual Meeting in Denver, CO, June 2-4, 2010. The presenters were Phillip W. Graham, Dr. Ann Landy, and Dr. Jennifer Schroeder.

Drs. Aria Crump and Belinda Sims, DESPR, co-chaired a Discussion Session titled "Obtaining Your First NIH R01: Recent New Investigators Answer Your Questions," during the June 1-4, 2010 annual meeting of the Society for Prevention Research, in Denver, CO.

Drs. Aria Crump and Belinda Sims co-chaired a Symposium, titled "Frontiers in Parenting Intervention Research for Drug Abuse Prevention" at the June 1-4, 2010, annual meeting of the Society for Prevention Research, in Denver, CO. The presenters were Dr. Betsy Davis, Drs. Guillermo Prado and Hilda Pantin, and Dr. Lew Bank. The Discussant was Dr. Emilie Smith.

Dr. Aria Crump presented on a panel titled "U.S. Department of Health and Human Services Grant Options for Early Career Prevention Scientists," at the June 1-4, 2010, annual meeting of the Society for Prevention Research, in Denver, CO.

Dr. Belinda Sims moderated a symposium titled "Implementation of Sustainable District and State-Level Prevention Infrastructure," at the June 1-4, 2010, annual meeting of the Society for Prevention Research, in Denver, CO. The presenters were Dr. Kris Bosworth, Dr. Michael Stoolmiller, and Mr. Brian Bumbarger.

Dr. Belinda Sims presented on Mentored K Awards at a panel on Mentored Research at the June 1-4, 2010 annual meeting of the Society for Prevention Research, in Denver, CO.

Dr. Richard Denisco chaired an APA session entitled: Neurobiological Circuits of Addiction: Significance for Psychiatric Practice on May 23, 2010.

Drs. Kathy Etz, Carmen Rosa, Aria Crump and Denise Pintello conducted an American Indian/Alaska Native Mentoring and Networking Program at the Blending Addiction Science and Practice: Evidence-Based Treatment and Prevention in Diverse Populations and Settings Conference in Albuquerque, New Mexico April 21-23, 2010. Fourteen American Indian/Alaska Native Scholars were selected to participate in the program. The program offered the opportunity to meet with Dr. Nora Volkow as well as many senior investigators in drug abuse treatment and prevention research, and a grand development session.

Drs. Kathy Etz, DESPR, and Richard Moser (NCI) co-chaired a pre-conference workshop entitled "Everything You Ever Wanted to Know about Secondary Data Analysis, But Were Afraid to Ask" at the Society for Prevention Meeting in Denver, Colorado on June 1, 2010.

Dr. Kathy Etz participated in the Bemijdi-Area HHS Regional Tribal Consultation session in Minneapolis, MN on April 20, 2010.

Dr. Bethany Deeds and Wilson Compton, DESPR, organized a symposium entitled Place & Substance Use: Linking Environments to Health to highlight NIDA's spatial epidemiology research for the American Association of Geographers Annual Meeting at the Marriott Wardman Park Hotel in Washington, DC on April 14, 2010.

Dr. Peter Hartsock, DESPR, represented NIDA at the Center for Strategic and International Studies (CSIS) conference on "HIV Prevention among Injection Drug Users: Strengthening U.S. Support for Core Interventions," with a focus on the emerging challenge of injecting drug use in East Africa, June 10, Washington D.C. Dr. Hartsock reported on NIDA's drug abuse and HIV epidemiologic research in Tanzania, Kenya, and South Africa.

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Media and Education Activities

Media Support of Events & Meetings

NIDA's eighth **Blending Conference** April 22-23, 2010 in Albuquerque NM received significant national, local and trade media coverage. Stories about the meeting ran on several outlets, including CNN, UPI, KOAT-TV, HealthDay, Medical News Today, and others. Of particular interest to reporters was the ongoing development of NIDA-sponsored vaccines to treat addiction to nicotine and cocaine. To capitalize on the growing importance of social media, an interview was scheduled during the meeting with Dr. Volkow and three influential addiction and health bloggers: Addiction Inbox, Psychology Today's "All About Addiction" and About.com: Addictions. In addition, Dr. Cindy Miner "tweeted" throughout the two-day conference on the @NIDAnews Twitter account. In total, 34 tweets were posted; of these, 30 were "retweeted" by NIDAnews followers, reaching more than 5,000 people. The @NIDAnews Twitter stream now has 281 followers, with re-tweets reaching up to 250,000 readers.

NIDA also promoted its participation in the annual **American Psychiatric Association** meeting May 22-26, 2010, in New Orleans which received national, local and trade media coverage, including Associated Press, Alcohol and Drug Abuse Weekly and APA Daily Bulletin. Of particular interest to reporters was NIDA's latest research track highlighting a wide range of topics, including how disruptions in brain circuitry are linked to mental illness and addiction, what overeating and obesity have in common with drug addiction, promising treatments for addiction to marijuana, cocaine, nicotine and methamphetamines and how a web-based video doctor approach may help soldiers and their families deal with drug abuse related to combat stress.

NIDA once again co-sponsored an addiction science award at the **2010 Intel International Science and Engineering Fair** (Intel ISEF) held May 9-14, 2010, in San Jose, CA. Intel ISEF is the world's largest international pre-college science competition for students in grades 9-12. Over 1,500 high school students from over 50 countries, regions, and territories showcased their independent research at the annual event. NIDA staff and grantees served as judges for the addiction science award, and Friends of NIDA provided funding. The three winners came to NIDA Headquarters in August 2010 to present their projects and were given a tour of the NIH campus. NIDA continues to nurture the careers of the ISEF Addiction Science winters. 2009 winner Jada Nicole Dalley, who won first place for her project on third hand smoke and recently graduated from Keystone School in San Antonio, spent five weeks as an intern in NIDA's Office of Science Policy & Communications before attending Elon University in North Carolina. Ethan Garrett Guinn, whose project on video games addiction won a second place Addiction Science Award in 2008, spent the summer of 2010 at Boston Children's Hospital working with Dr. Michael

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Rich and Dr. David Bickham to complete his data analysis and prepare for publication of his research.

Dr. Volkow, NIDA AIDS Program Director Jacques Normand, and a team of NIDA scientists traveled to Vienna, Austria, July 18-23, 2010, for the **XVIII International AIDS Conference**. Dr. Volkow sat on the stage while former President Bill Clinton spoke about how far we have come in the fight against AIDS. The Vienna location represented a gateway to the east — as the conference theme "Rights Here, Right Now," represented a fight against the stigma of addiction. A compelling body of evidence was presented at the conference demonstrating that Highly Active Antiretroviral Therapy (HAART) is not only highly effective at preventing HIV-related morbidity and mortality, but also dramatically decreases HIV transmission from all routes. Dr. Volkow was interviewed by the New York Times and Voice of America (Russia) during the conference, and NIDA grantees were interviewed about their research for short video segments that will be posted on NIDA's website. NIDA's communications chief Carol Krause was at the conference to coordinate the video project.

NIDA Wins Plain Language Awards

Three NIDA products, including the Sara Bellum blog, the NIDAMED initiative, and NIDA's video series for teens, received **NIH Plain Language Awards** at a ceremony held on May 26, 2010. The annual NIH Plain Language Award ceremony honors outstanding NIH communication products, including websites, fact sheets, multi-media presentations, and other materials. Check out these excellent products at www.drugabuse.gov.

Upcoming Events

Partnerships have been secured with the Discovery Channel, MTV, and the MusiCares/Grammy Foundation for **National Drug Facts Week (NDFW)**, to be held November 8-14, 2010. The event is an extension of NIDA's annual Drug Facts Chat Day, during which thousands of teens ask questions about drugs via a Web chat. NIDA developed NDFW to encourage teens, schools and community groups all over America to hold their own "Q and A" events, with local experts. Throughout the week, teens will participate in a variety of NDFW activities such as hosting movie nights and book club meetings, contacting their members of congress, holding school assemblies and sponsoring music and art contests. NIDA will hold its annual Drug Facts Chat Day during the week, on November 9, 2010. The NDFW web site can be accessed directly from the NIDA home page.

Press Releases, Media Advisories & Notes to Reporters

Press Releases & Media Advisories

April 15, 2010 — A media advisory about NIDA's Blending Conference titled "From Theory into Practice: NIDA's Blending Conference Highlights the Latest in Drug Abuse Treatment" was distributed, which highlighted research to be discussed during the conference.

April 22, 2010 — A press release titled "NIDA Blending Conference Launches New Training Approach for Young Adults Addicted to Opioids" was distributed regarding NIDA's Blending Conference in Albuquerque. This eighth meeting in the series brought together researchers and clinicians so their latest findings could be immediately applied to the needs of patients and their families dealing with addictive disorders.

May 14, 2010 — A press release titled "Computer Modeling to Identify New Medications for Nicotine Addiction Wins First Place NIDA Addiction Science

Award at 2010 Intel ISEF" was distributed announcing the 2010 INTEL ISEF awards winners. INTEL ISEF is the world's largest science competition for high school students.

May 20, 2010 — A media advisory titled "Neurobiological Circuits of Addiction: Significance for Psychiatric Practice" was distributed announcing the highlights of NIDA's Special Research Track at the American Psychiatric Association's Annual Conference.

July 7, 2010 — A press release titled "NIH-Supported Finding on Cocaine Addiction: Tiny Molecule, Big Promise" was distributed highlighting NIDA-funded research on cocaine addiction.

July 18, 2010 — A press release titled "HIV/AIDS Treatment Curbs Spread of HIV Among Drug Users, According to NIH Supported Study" was distributed highlighting how NIDA-funded research about highly active antiretroviral therapy (HAART), currently known for its therapeutic benefits against HIV, also reduced the spread of the virus among people with a history of injection drug use.

Notes to Reporters:

April 12, 2010 — A note was sent to reporters announcing NIDA's launch of its Twitter account, *NIDAnews*. Tweets from *NIDAnews* announce important new studies, link to comments by NIDA scientists discussing drug-related topics in the news, and provide the latest facts about drug use and its consequences.

April 27, 2010 — A note alerted media about a NIDA-funded study in the journal *Circulation: Heart Failure*. The article titled "Long Term Anabolic-Androgenic Steroid Use is Associated with Left Ventricular Dysfunction" by Baggish, et al. summarized research from the Massachusetts General Hospital in Boston that looked at the risks of long-term anabolic steroid use on the heart.

May 18, 2010 — A note to reporters was distributed regarding a NIDA-funded study in the journal *Brain*. The article titled "Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/ [11C] DASB and structural brain imaging study" by Kish, et al. discussed the effects of chronic ecstasy abuse and found that ecstasy users have low levels of serotonin transporters.

May 23, 2010 — Reporters were notified about a NIDA-funded study in the journal *Nature Neuroscience*. The article titled "Cortical DNA methylation maintains remote memory" by Miller, et al. discussed a mechanism that makes memories last, such as those underlying PTSD or the cravings that drive drug addiction.

May 30, 2010 — A note to reporters was sent out announcing the May issue of NIDA NewsScan, a monthly newsletter sent to trade press that highlighted NIDA research on a variety of issues affecting drug addiction/abuse.

June 10, 2010 — A note informed reporters about highlights of NIDA's presentations at the 72nd Annual Meeting of the College on Problems of Drug Dependence (CPDD) in Scottsdale, Arizona.

July 9, 2010 — A note to reporters was distributed highlighting a NIDA-funded study published in the Archives of Internal Medicine that examined a single-question screener for use in primary care settings to identify drug use and drug use disorders.

Research News

Full NewsScans can be seen at

http://www.nida.nih.gov/NIDANews.html#newsscan.

May 2010 - NIDA NewsScan #66 - Research News

- Potential viability of HIV medications for HIV prevention in high-risk populations, but not for standard use
- Understanding more about the needs and expectations of patients seeking outpatient substance abuse treatment
- Individuals with substance addiction, bipolar disorder share overlapping genetic profiles
- Low dose naltrexone + methadone during detox eases withdrawal symptoms, reduces cravings
- Predicting risk and resilience in children of opiate-dependent parents
- Key receptors, brain areas in nicotine withdrawal identified
- Drug prevention programs during adolescence may have long-term benefits against risky sexual behavior
- Consistent behavioral outcomes and neural activity shown in real and hypothetical discounting

July 2010 - NIDA NewsScan #67 - Special AIDS Issue Research News

- A Note from NIDA's AIDS Research Program Director
- Rapid HIV Testing May Be Useful in Jails with Frequent Turnover, But More Research Needed
- Buprenorphine - Promising Treatment for Preventing Relapse in HIV-Positive Released Prisoners
- Community Plasma HIV-1 RNA Concentrations are Predictive of HIV Incidence Among Injection Drug Users
- Methadone Maintenance Therapy Promotes Use of Antiretroviral Therapy Among HIV-Infected Injection Drug Users
- Substantial Global Health Crisis—High Prevalence of HIV-infected Injecting Drug Users Worldwide
- Global Coverage of HIV Services for Injecting Drug Users Inadequate to Prevent HIV Transmission
- HIV-infected Injecting Drug Users Benefit from Highly Active Antiretroviral Therapies

Highlights of Interviews: April - July, 2010

Discovery Magazine — Dr. Nora Volkow was interviewed about nicotine and cocaine vaccine research.

CNET.com — Dr. David Epstein was interviewed about GPS/digital devices tracking.

Family Practice News — Dr. Geetha Subramaniam was interviewed about her presentation at the Blending Conference on a young adult opioid treatment program.

Prevention — Dr. Joseph Frascella was interviewed about research that has linked overeating to other addictive behaviors, such as drug abuse.

Washington Post — Dr. Marilyn Huestis was interviewed about K2/Spice or fake marijuana.

NPR — Dr. Steven Grant was interviewed about mephedrone.

Web MD — Dr. Kevin Conway was interviewed about inhalant abuse.

Washington Post — Dr. Nicolette Borek was interviewed about children born to crack addicted women.

Reuters — Dr. Nora Volkow was interviewed about anabolic steroids.

Pittsburgh Tribune-Review — Dr. Wilson Compton was interviewed about overdose from prescription drug abuse.

Good Morning America — Dr. Nora Volkow was interviewed about digital devices and addiction.

Reader's Digest — Dr. Nora Volkow was interviewed about teens and prescription drug abuse.

The New York Times — Dr. Nora Volkow was interviewed about research in Tanzania on the link between drug abuse/HIV.

Parent Magazine - Dr. Liz Robertson was interviewed about talking to kids about drug use.

Voice of America — Dr. Nora Volkow was interviewed about the link between HIV and drug addiction.

Detroit Free Press — Dr. Eve Reider was interviewed about drug abuse and the military.

Wired Magazine - Dr. Steven Grant was interviewed on the topic of brain changes after treatment for substance abuse.

Recent and Upcoming Conferences/Exhibits

National Conference on Addiction Disorders (NAADAC: the Association for Addiction Professionals Annual Conference)
September 9-11, 2010 -- Arlington, VA

15th Annual Latino Behavioral Health Institute Conference (LBHI)
September 22-24, 2010 -- Los Angeles, CA

American College of Emergency Physicians Scientific Assembly 2010
September 28 - October 1, 2010 -- Las Vegas, NV

American Academy of Family Physicians (AAFP) Scientific Assembly
September 29 - October 2, 2010 -- Denver, CO

American Association for the Treatment of Opioid Dependence (AATOD) National Conference
October 23-27, 2010 -- Chicago, IL

American Academy of Child and Adolescent Psychiatry (AACAP)
October 26-31, 2010 -- New York, NY

National Middle School Association (NMSA) Annual Conference
November 4-6, 2010 -- Baltimore, MD

American Public Health Association Annual Meeting and Exposition
November 6-10, 2010 -- Denver, CO

Society for Neuroscience Annual Meeting (SfN)
November 13-17, 2010 -- San Diego, CA

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Planned Meetings

Planning is currently underway for the first **National USA Science & Engineering Festival** to be held on the National Mall and at Freedom Plaza in Washington, D.C., on October 23 & 24, 2010. As one of the key NIH organizers for this event, NIDA is involved in planning and organizing NIH's large exhibits. These exhibits will cover a broad range of health and research areas and will be both interactive and engaging to children and their parents. Currently there are over 400 organizations in addition to NIH who have signed up to host an exhibit.

Drs. Steven Grant, DCNBR, organized and will chair a panel entitled **Role of the Habenula in Addiction and Depression: Worse than Expected** which will be part of the American College of Neuropsychopharmacology (ACNP) annual meeting to be held December 5-9, 2010 in Miami, FL.

Dr. Ruben, Baler, OSPC, will co-chair with Dr. Danny Weinberger, a session at the ACNP annual meeting on December 8, 2010 in Miami Beach, FL titled **"Neuregulin 1: A Gene at the Crossroads of Synaptic Plasticity, Psychiatric Disorders, and the Self Medication Theory of Smoking."**

Drs. Thomas Aigner, DBNBR and Susan Weiss, OSPC will co-chair a session at the ACNP annual meeting, titled: **"Emerging Nanotechnology-Based Drug Delivery Methods and their Applications to Addiction Research."**

Dr James Bjork, DCNBR, organized and will chair a session entitled **Connectivity of the Human Brain and its Disruption by Drugs of Abuse** at the NIDA Frontiers in Addiction Research mini-convention prior to the annual meeting of the Society for Neuroscience on November 12, 2010 in San Diego, CA.

Dr. Samia Noursi, DBNBR and Deputy Coordinator, Women and Sex/Gender Differences Research, and Dr. Thomas Brady, DESPR, will chair a panel entitled "Gender Differences in ADHD, Substance Use, and Other Comorbid Psychiatric Disorders: Implications for Treatment of Adolescent and Young Adult Females" at the 57th Annual Meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) in New York, NY, October 26-31, 2010. Presenters will be Drs. Bill Latimer (Johns Hopkins Bloomberg School of Public Health), Timothy Wilens (Massachusetts General Hospital), Amori Yee Mikami (University of Virginia), and Ken Winters (University of Minnesota Medical School). The presentations will be discussed by Dr. Frances Levin (Columbia University's Department of Psychiatry).

Dr. Samia Noursi DBNBR and Deputy Coordinator, Women and Sex/Gender Differences Research and Dr. Thomas Brady, DESPR, will chair a panel entitled "Substance Use Disorders, Comorbid Mental Disorders, and HIV/AIDS Risk Behaviors: A Longitudinal Study of Delinquent Females" at the 2010 Joint

Meeting on Adolescent Treatment Effectiveness (JMATE) in Baltimore, MD, December 14-16, 2010. Presenters will be Drs. Linda A. Teplin (Northwestern University), Sarah J. Schmiege (University of Colorado-Denver), and Patricia W. Chamberlain (Oregon Social Learning Center).

The next **National CTN Steering Committee Meetings** will be held September 21-23, 2010 in Bethesda, Maryland. In the spring, the Steering Committee Meetings will be held March 15-17, 2011 in Bethesda, Maryland.

The **NIDA CCTN** will hold a face-to-face meeting on September 24, 2010 in the Bethesda, Maryland area to bring together relevant stakeholders to develop a consensus on common core data elements relevant to drug addiction treatment that could be incorporated into harmonized electronic health record systems either locally or nationwide. To that end, the CTN Data and Statistics Center (EMMES) has collected and collated treatment-form-related information from CTN-affiliated drug abuse specialty treatment providers, Kaiser Permanente, the VA, Harvard, and the Italian Health System. The purpose was to look across community treatment practices and identify common data that are obtained as a part of standard treatment and care in real-world settings.

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NIDA Publications

Drugs, Brains, and Behavior: The Science of Addiction (Revised) (in press)
NIH Pub. No. 10-5605
The Science of Addiction explains in layman's terms how science has revolutionized our understanding of drug addiction as a brain disease that affects behavior. It uses simple language, diagrams, and graphics to help people understand how drugs change the brain in structure and in function. The booklet explains some of the reasons that people take drugs, helps explain why some people become addicted while others do not, and demonstrates how addiction, like other chronic diseases, may be prevented and treated.

Drugs: Shatter the Myths (in press)
NIH Pub. No.: 10-7589
New! Q&A booklet answers teens' most frequently asked questions about drugs and drug abuse. Written and designed specifically for teens, with teen input, this must-have resource provides scientific facts with engaging images and design to help teens shatter the myths about drugs and drug abuse.

Strategic Plan - National Institute on Drug Abuse (in press)
NIH Pub. No.: 10-6119
NIDA's Strategic Plan lays out the Institute's strategic priorities for the next five years, focusing on prevention, treatment, HIV/AIDS, and cross cutting-issues. A multipronged approach is described to confront the most pressing research needs in the area of drug abuse and addiction, capitalizing on research programs in the basic and clinical neurosciences, medication and behavioral therapies, and health services and prevention. NIDA's Strategic Plan was informed by input from NIDA's Director, NIDA staff, the National Advisory Council on Drug Abuse, and various outside constituencies. It provides a framework for exploring exciting future directions while continuing to apply what we know to best prevent and treat drug abuse and addiction and lessen their devastating consequences to individuals and to society as a whole.

Heads Up Real News About Drugs and Your Body - Student Compilation (in press)
NIH Pub. No.: 10-7647
This booklet is a collection of articles originally published and distributed nationwide in Scholastic Inc magazines. Designed to teach youth in grades 6-12 about the science and health consequences of drug abuse and addiction, this year's compilation contains articles that highlight the questions about drug abuse and addiction that teens' most want answers to and provides helpful hints for how teens can use that information to navigate peer pressure situations. Articles include "Real Questions, Real Answers" — providing answers

from NIDA scientists to real teen questions on drugs and drug abuse; "Teen Science Investigations" — profiling the winners of the 2009 Intel ISEF Addiction Science Awards; and "Facts into Action" —featuring tips for teens on how to make smart moves when it comes to drugs. As an added bonus this year's compilation includes an article previously only available on the web that contains scavenger hunt questions highlighting drug facts from the three articles.

Heads Up Real News About Drugs and Your Body - Teacher Compilation (in press)
NIH Pub. No.: 10-7648
This booklet provides skills building extension activities, individual lesson plans, and worksheet reproducibles, as well as other resources to those contained in the companion student compilation for 2000-2010. The compilation of teacher editions were originally published and distributed nationwide in Scholastic Inc magazines. Designed to assist teachers of 6th-12th graders with lesson plans that incorporate the reading and comprehension of the companion student articles on the science and health consequences of drug abuse and addiction, this year's compilation contains articles that highlight the questions about drug abuse and addiction that teens' most want answers to and provides helpful hints for how teens can use that information to navigate peer pressure situations. Lessons in this compilation, including role play exercises, pertain to the articles: "Real Questions, Real Answers," "Teen Science Investigations," and "Facts into Action."

Marijuana: Facts for Teens (Revised) (in press)
NIH Pub. No.: 10-4037
The booklet explains current knowledge about marijuana and the latest scientific information on its effects. It provides teens with questions about marijuana, including what it is, who uses it, and how it affects a person physically and mentally after short- and long-term use.

Marijuana: What Parents Need to Know (Revised) (in press)
NIH Pub. No.: 10-4036
The booklet provides valuable information from research on the dangers of marijuana. It gives parents explanations of the latest scientific information about the drug and suggestions on how to talk to teenagers about the drug.

Research Report Series: Marijuana Abuse (Revised) (in press)
NIH Pub. No.: 10-3859
This Research Report summarizes what the science tells us about marijuana abuse in the United States and its effects on the brain and body. It includes an extensive review of the latest research literature presented for a general audience interested in learning more about marijuana's consequences for physical, mental, and emotional health.

Research Report Series: Cocaine Abuse (Revised) (in press)
NIH Pub. No.: 10-4166
This updated version contains scientific information on crack and cocaine. Facts based on the latest technology are used to describe the different effects of this drug as well as the pathways in the brain that it affects; the medical consequences of use; and some behavioral treatments for cocaine abuse. NIDA also reports on several pharmacological compounds currently being tested for their potential use in treating cocaine addiction.

Research Report Series: Comorbidity Addiction and Other Mental Illnesses (Revised) (in press)
NIH Pub. No.: 10-5771
When two disorders or illnesses occur simultaneously in the same person, they are called comorbid. This research report addresses the comorbidity of drug abuse and addiction and other mental disorders. It explores the complex ways in which genetic, developmental, and environmental factors appear to interact

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to predispose individuals to develop both diseases or to have a greater risk of the second disorder after the first appears. The report describes the prevalence of comorbidity as well as the diagnostic and treatment challenges posed by comorbid conditions that involve drug abuse, addiction, and other mental disorders.

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The lead story of this issue features animal research that demonstrates the potential of two medications to reduce relapse to cocaine and heroin abuse. The issue also presents neuroimaging data suggesting that flashy public service announcements are not as effective as low-key ads at stimulating those parts of the brain most likely to help smokers abstain. Another feature reports that crack cocaine users who are infected with HIV experience an accelerated decline in immune function regardless of their success in adhering to therapy, and that cocaine and methamphetamine increase both the ease with which the HIV virus enters immune cells and its replication rate once inside. The issue also reports that cocaine-induced proliferation of microscopic structures called dendritic spines in a brain region involved in reward and motivation may represent an adaptation that limits the drug's harmful effects. The issue also includes a story about a school-centered program for social and emotional development, called Positive Action, which was credited with a sharp reduction in rates of substance abuse, violent behavior, and voluntary sexual activity among primary school children in Hawaii. Finally, in the Director's Perspective column, NIDA Director Dr. Nora D. Volkow shares her insights on new tools and strategies to bolster anti-drug abuse behavioral therapies—from medications that act as cognitive enhancers to computer programs that increase the reach of behavioral therapies.

Addiction Science & Clinical Practice Vol. 5, No. 2
NIH Pub. No.: 10-7418

This issue presents an article by Dr. Thomas J. Gould that reviews current knowledge on the cognitive effects of drugs and the neurological underpinnings for those effects. In addition, Margaret Mroziewicz and Dr. Rachel F. Tyndale introduce the field of pharmacogenetics and provide examples demonstrating the impact of genetic variation on drug effects and drug dependence. Dr. Steve Martino reviews the empirical basis of evidence-based treatments for addiction and describes strategies for training counselors in using them. Drs. Jody L. Sindelar and Samuel A. Ball examine cost considerations of adopting evidence-based treatments and analyze, as an example, whether adopting contingency management is the best use of a certain program's resources. Dr. Michael S. Robbins and colleagues present challenges encountered and solutions developed during a scientifically rigorous trial of Brief Strategic Family Therapy implemented in a community setting.

CTN-Related Publications

CTN Brochure - Bridging the Gap Between Research and Practice -- National Drug Abuse Treatment Clinical Trials Network: The First Decade. This new 12-page brochure provides an overview of the first decade of research in the National Drug Abuse Treatment Clinical Trials Network. It highlights several of the most successful protocols (buprenorphine, motivational incentives, etc.) and describes both the NIDA/SAMHSA Blending Initiative and the CTN Dissemination Library. It can be downloaded from the dissemination library: http://ctndisseminationlibrary.org/display/513.htm or from the CTN website: http://www.drugabuse.gov/about-nida/organization/cctn/ctn

Seven editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 22 CTN studies are now available on the CTN Data Sharing Web Site http://www.nida.nih.gov/CTN/Data.html. 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. The CTN Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

International Program Publications

NIDA International Program 2009 Annual Report
The 2009 Annual Report demonstrates how the NIDA International Program has promoted new research initiatives, disseminated knowledge, and engaged partners in diverse settings to build a network of international and regional organizations that share the common goal of finding evidence-based solutions to the public health problems of drug abuse, addiction, and drug-related HIV/AIDS.

NIDA International Forum Abstract Database
Research abstracts accepted for poster presentation at NIDA International Forums from 2003 through 2010 are now available in a searchable online database at http://www.international.drugabuse.gov/information/abstracts/. Users may look for abstracts by author, title/subject, year, research category (basic science, epidemiology, prevention, or treatment), country, or geographic region.

Other Publications

Dr. David Thomas, DBNBR, published a Guest Editorial on Virtual Reality and Pain Research in Cybertherapy and Rehabilitation (1) 2010.

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Eriksen J,Yoshimoto WB, Jorgensen TN, Newman AH, Gether U. Postendocytic Sorting of Constitutively Internalized Dopamine Transporter in Cell Lines and Dopaminergic Neurons. J Biol Chem 2010; e-pub June 15, 2010.

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Staff Honors and Awards

The Society for Prevention Research (SPR) presented its 2010 International Collaborative Prevention Research Award to NIDA International Program Director **Dr. Steven W. Gust** at its 18th Annual Meeting, which was held June 1-4, 2010, in Denver, Colorado. The award recognized Dr. Gust's contributions to advancing the field of prevention science globally during his decade of leading the International Program.

Dr. Cora Lee Wetherington, DBNRB and NIDA's Women & Sex/Gender Differences Research Coodinator, received the J. Michael Morrison Award presented by the College on Problems of Drug Dependence (CPDD) "to recognize her outstanding contributions in the area of scientific administration related to drugs of abuse." The award was presented June 13, 2010 at the plenary session of the College's seventy-second annual meeting held in Scottsdale, AZ.

Dr. Wilson M. Compton, DESPR, received the Paul Hoch Award from the American Psychopathological Association and presented on "Criminal Justice Settings: Intersecting Risks of Mental Health, Substance Abuse and High Risk Behaviors, New York, New York, March 4, 2010.

Drs. Lisa Onken and Cecelia Spitznas along with members of the NIDAMED development committee received an NIH Plain Language award for work on the NIDAMED website and provider training tools.

Dr. Redonna Chandler, DESPR, was awarded the 2010 NIH Plain Language and Clear Communication Award: NIDA Med electronic platform to facilitate screening and treatment of addiction in healthcare settings.

Dr. Redonna Chandler was awarded the 2010 NIH Plain Language and Clear Communication Award: YouTube Video on dangers of smoking.

Dr. Teri Levitin, Director, OEA, received an NIH Director's Group Award for her participation in the NIH volunteer program for teaching English to maintenance and other workers who want to improve their English proficiency.

Flair Lindsey, Program Analyst, Special Populations Office, was presented with an Exemplary Leadership award from the African American Researchers and Scholars Work Group on July 19, 2010 in Atlanta, GA for her leadership in the Special Populations Research Development Seminar Series and Summer Research with NIDA programs.

Dr. Richard Rothman, IRP, was listed as a co-inventor for U.S. Patent 7,728,001 'Opioid Receptor Ligands and Methods for Their Preparation' and is

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also a co-inventor on provisional patent application No, 61/169,586 entitled 'Phenylmorpholines and Analogues Thereof', filed April 15, 2009.

Dr. Amy Newman, IRP, received a NIDA Directors Award of Merit in June 2010 for her contributions as chair of the committee that created the new NIDA IRP webpage.

Dr. Ashwini Banala, IRP, was selected as a 2010 NIH FARE award winner and has been invited to present a poster at the NIH Research Festival in October.

NIDA Director's Awards

Division of Basic Neuroscience and Behavioral Research
Mark Caulder

PDP Medications Initiative for Tobacco Dependence (MITD) Task Force (NIDA-Wide)
Elena Koustova, Jane Acri, Kristopher Bough, Redonna Chandler, Udi Ghitza, Steve Heishman, Allison Hoffman, Kristen Huntley, Amrat Patel, Vishnudutt Purohit, Steven Sparenborg, Geetha Subramaniam

Division of Clinical Neuroscience & Behavioral Research
Woody Lin

Division of Epidemiology, Services and Prevention Research
Eve Reider

The NIDA-CSAP SPF-SIG Collaboration Team
Elizabeth Robertson, Augusto Diana, Jacqueline Lloyd

Intramural Research Program
Eliot Gardner

NIDA IRP Webpage Committee
Amy Newman, Mark Fleming, Andras Frenyo, Susan Harrelson, Aaron Martinek, Mary Pfeiffer, Brad Smoley, Elliot Stein

NIDA IRP Science for the Non-Scientist Seminar Program
Mary Pfeiffer , Kandi Culbertson

NIDA Office of the Director
American Indian and Alaska Native Coordinating Committee
Ana Anders, Lula Beatty, Nicolette Borek, Ananth Charya, Aria Crump, JC Comolli, Kathleen Etz, Joseph Frascella, Meena Hiremath, Dionne Jones, Cecelia McNamara-Spitznas, Carmen Rosa

Office of Extramural Affairs
Kristen Huntley

NIDA eContract Reiew Development Team
Minna Liang, Kristen Huntley, Nadine Rogers

Office of Management
James Quinn

Grants Management Branch
Azeezat Abu, Carol Alderson, Debra Battle-Dudley, Maryellen Connell, Edith Davis, Suzette Epps, Pamela Fleming, Diana Haikalis, Christine Kidd, Catherine Mills, Cheryl Nathaniel, Ericka Wells, Deborah Wertz, Heidi Young

Office of Science Policy and Communications
Ruben Baler

NIDA Representative on the ONDCP Inter-Agency Working Groups

Timothy Condon, Wilson Compton, Lucinda Miner, Redonna Chandler, Marsha Lopez, Elizabeth Robertson, Susan Weiss, Aria Crump, Augie Diana, Gayathri Dowling, Jennifer Elcano, Elizabeth Ginexi, Jacqueline Lloyd, Aleta Meyer, Moira O'Brien, Eve Reider, Belinda Sims, Anna Staton

NIDA Director's Award for EEO, Divsrsity and Quality of Worklife

NIDA IRP Morale Committee
Patty Ballerstadt, LT Tracey Coleman-Rawlinson, Janis Diven, Josephine Jones, Cathleen Lyons, Cassandra Matthews, Katrina Maynard, Rolanda Morris, Mary Pfeiffer, Rochelle Randolph, Mitchele Williams

NIDA Director's Innovator Award

Elena Koustova

30 Years of Government Service Awards
Garveyette Brown, Debra Grossman, Harriette Jordan, Steven Goldberg

40 Years of Government Service Award
Kenner Rice, Nancy Soulen

Staff Changes

Deputy Press Officer **Stephanie Older** has been promoted to Press Officer. Ms. Older has been an outstanding member of the NIDA press team for more than two years, contributing to multiple top level press initiatives. Her prior communications experience includes media work for both corporate and non-profit organizations, most notably as the media liaison for the National Breast Cancer Coalition. Ms. Older holds a law degree from the University of Baltimore as well as a B.A. in communication from the University of Pennsylvania. Prior to joining NIDA, she served as Attorney-Advisor to an Associate Chief Judge at the U.S. Department of Labor.

Director's Report to the National Advisory Council on Drug Abuse - September, 2010

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CTN Florida Node

Dr. Lisa Metsch, Florida Node Co-PI, has been appointed as the Chair of the NIH/CSR study section, Behavioral and Social Science Approaches to Preventing HIV/AIDS Study Section (BSPH). The BSPH Study Section reviews studies of risk factors and antecedents of HIV infection as well as basic behavioral, epidemiologic, and social science studies of mechanisms and factors at the individual and community levels.

CTN Southern Consortium Node

The Medical University of South Carolina (MUSC) Board of Trustees chose **Dr. Kathleen Brady** as a recipient of the 2010 MUSC Foundation Distinguished Faculty Service Award. Dr. Brady was chosen for her exceptional and sustained service and numerous contributions in teaching, leadership, research, health care, and public service to the University and the citizens of South Carolina.

Dr. Louise Haynes, the Community Treatment Program Director for the Southern Consortium Node, received the "James A. Neal Award for Outstanding Contributions to the South Carolina School of Alcohol and Other Drug Studies." Dr. Haynes is the second recipient of this award. The James A. Neal Award is presented annually to an individual who has demonstrated a commitment to the School that goes "above and beyond the call." She was chosen based on her support of the South Carolina School during her tenure as a Department of Alcohol and Other Drug Abuse Services employee and her recent active participation on the School Planning Committee, especially her efforts to organize the "physicians track," secure national presenters through the NIDA Clinical Trials Network, and serve as a faculty member herself.

CTN New York Node

Lawrence S. Brown, Jr., MD, MPH, FASAM, Executive Senior Vice President of the Division of Medical Services, Research and Information Technology at Addiction Research and Treatment Corporation was nominated by New York State Governor David Paterson and confirmed by the State Senate for a two-year term as a member of the New York State Advisory Council on Alcoholism and Substance Abuse Services.

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