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

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

Research Findings - Basic Neuroscience Research

Activation of the Kappa Opioid Receptor in the Dorsal Raphe Nucleus, and Involving Serotonergic but not Dopaminergic Transmission, Mediates the Aversive Effects of Stress and Reinstates Drug Seeking

Although stress has profound effects on motivated behavior including drug seeking, the underlying mechanisms responsible are incompletely understood. Previous studies have supported a role for the dynorphin/kappa opioid receptor (KOR) system in mediating the pro-addictive effects of stress-induced relapse. However, the brain region(s) and circuitry underlying KOR action are unresolved. This study elucidates a functional neural pathway in mouse brain that encodes the aversive effects of stress and mediates stress-induced reinstatement of cocaine conditioned place preference (CPP). Activation of the dynorphin/kappa opioid receptor (KOR) system by either repeated stress or agonist produces conditioned place aversion (CPA). Because KOR inhibition of dopamine release in the mesolimbic pathway has been proposed to mediate the dysphoria underlying this response, Dr. Chavkin and his colleagues tested dopamine-deficient mice in this study and found that KOR agonist in these mice still produced CPA. However, inactivation of serotonergic KORs by injection of the KOR antagonist norBNI into the dorsal raphe nucleus (DRN), blocked aversive responses to the KOR agonist U50,488 and blocked stress-induced reinstatement of CPP. Additionally, KOR knockout (KO) mice did not develop CPA to U50,488; however, lentiviral re-expression of KOR in the DRN of KOR KO mice restored place aversion. DRN serotonergic neurons project broadly throughout the brain, but the inactivation of KOR in the nucleus accumbens (NAc) coupled with viral re-expression of KOR in the DRN of KOR KO mice demonstrated that aversion was encoded by a DRN to NAc projection. These results suggest that the adverse effects of stress may converge on the serotonergic system and offers an approach to controlling stress-induced dysphoria and relapse. Land BB, Bruchas MR, Schattauer S, et al. Activation of the kappa opioid receptor in the dorsal raphe nucleus mediates the aversive effects of stress and reinstates drug seeking. Proc Natl Acad Sci U S A. 2009 Nov 10;106(45):19168-19173.

Dopamine Enables In Vivo Synaptic Plasticity Associated with the Addictive Drug Nicotine

Addictive drugs induce a dopamine signal that contributes to the initiation of addiction, and the dopamine signal influences drug-associated memories that perpetuate drug use. The addiction process shares many commonalities with the synaptic plasticity mechanisms normally attributed to learning and memory. Environmental stimuli repeatedly linked to addictive drugs motivate continued drug use. This paper, employing in vivo recording techniques, shows

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for the first time that in freely moving and behaving mice, physiologically relevant concentrations of the addictive drug, nicotine, directly cause in vivo hippocampal synaptic potentiation of the kind that underlies learning and memory. This nicotine-induced long-term synaptic plasticity required a local hippocampal dopamine signal. Disrupting general dopamine signaling prevented the nicotine-induced synaptic plasticity and conditioned place preference. These results suggest that dopaminergic signaling serves as a functional label of salient events by enabling and scaling synaptic plasticity that underlies drug-induced associative memory. Tang J, Dani JA. Dopamine enables in vivo synaptic plasticity associated with the addictive drug nicotine. Neuron. 2009 Sep 10;63(5):673-682.

Selective Blockade of the Hydrolysis of the Endocannabinoid, 2-AG, but not of Anandamide (AEA), Enhances Retrograde Endocannabinoid Signaling and the Duration of Endocannabinoid-mediated Synaptic Transmission

Endocannabinoid (eCB) signaling mediates depolarization-induced suppression of excitation (DSE) and inhibition (DSI), two prominent forms of retrograde synaptic transmission (synaptic depression). N-Arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), two known eCBs, are degraded by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. Selective blockade of FAAH and MAGL is critical for determining the roles of the eCBs in DSE/DSI and understanding how their action is regulated. 4-Nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate (JZL184) is a recently developed, highly selective, and potent MAGL inhibitor that increases 2-AG but not AEA concentrations in mouse brain. Here, NIDA supported investigators report that JZL184 prolongs DSE in Purkinje neurons in cerebellar slices and DSI in CA1 pyramidal neurons in hippocampal slices. In contrast, neither the selective FAAH inhibitor cyclohexylcarbamic acid 3'-carbomoylbiphenyl-3-yl ester (URB597) nor FAAH knockout has a significant effect on DSE/DSI. These results indicate that the degradation of 2-AG by MAGL is the rate-limiting step that determines the time course of DSE/DSI and that JZL184 is a useful tool for the study of 2-AG-mediated signaling. Pan B, Wang W, Long JZ, Sun D, Hillard CJ, Cravatt BF, Liu QS. Blockade of 2-arachidonoylglycerol hydrolysis by selective monoacylglycerol lipase inhibitor 4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate (JZL184) enhances retrograde endocannabinoid signaling. J Pharmacol Exp Ther. 2009 Nov;331(2):591-597.

Persistent Changes in Brain Function after Repeated Ketamine

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine is a pediatric and veterinary anesthetic that is also abused at lower doses (as "Special K," etc.). Ketamine elicits and exacerbates psychotic symptoms resembling schizophrenia, including auditory hallucinations, blunted affect, and withdrawal. In some cases, past ketamine abuse is associated with a persisting psychosis, and it is not possible to determine whether a pre-existing psychosis was made florid by the drug, or the drug caused a new psychotic illness. Steven Siegel and his colleagues assessed the effects of chronic administration of a sub-anesthetic dose of ketamine on contextual fear conditioning, detection of pitch deviants, and auditory gating, in mice; deficits in these tests serve as models of schizophrenia. After four weeks of daily ketamine injections, mice exhibited decreased freezing in the fear conditioning paradigm (48 hr after cessation of treatment, which was the final test). Gating of the P80 component of auditory evoked potentials was significantly altered, as the four weeks of daily ketamine caused a significant decrease in S1 amplitude (3 and 5 weeks (last test) after cessation of treatment). S1 P20 latency was significantly increased as a result of ketamine treatment (3 and 5 weeks after cessation of treatment). Although

there was no effect of ketamine on detection of pitch deviants, these results indicate that repeated ketamine impairs fear memory and has lasting effects on encoding of sensory stimuli. Such persisting effects add support to the belief that repeated ketamine abuse could have long-term effects on brain function and information processing, similar to schizophrenia. Though NMDA antagonists have been shown to kill neurons in animal models, the neural bases of these latest observations remain to be determined, and are presently being investigated. Amann LC, Halene TB, Ehrlichman RS, Luminais SN, Ma N, Abel T, Siegel SJ. Chronic ketamine impairs fear conditioning and produces long-lasting reductions in auditory evoked potentials. Neurobiol Dis. 2009 August;35(2):311-317.

D-Cycloserine Facilitates Extinction of Naloxone-Induced Conditioned Place Aversion in Morphine-Dependent Rats

The well-documented observation that cues paired with drug administration trigger relapse to drug seeking by inducing conditioned drug craving and withdrawal was extended to examine whether cues were also operative in conditioned morphine-withdrawal aversion. As drug cues hinder abstinence in addicts, therapies that reduce responsiveness to drug cues might facilitate rehabilita-tion. Drs. Myers and Carlezon used morphine-dependent rats and trained them to associate an environ-ment with naloxone-precipitated withdrawal. Subsequently, they received extinction training in which they were confined in the previously naloxone-paired environment in the absence of acute withdrawal. Some rats were given the N-methyl-D-aspartate (NMDA) receptor partial agonist D-cycloserine (DCS) before extinction training. Previously, this treatment has been shown to facilitate the extinction of conditioned fear responses and cocaine-conditioned place preferences. They found that morphine withdrawal-induced conditioned place aversion persisted in the absence of extinction training and that the administration of DCS before extinction training facilitated its extinction. Thus, D-cycloserine facilitated extinction of morphine withdrawal-associated place aversion, in a manner similar to the effect of DCS on extinction of conditioned fear, raising the possibility of common neural mechanisms. This work extends our understanding of drug cue responsivity and provides a rationale for the development of extinction-based treatments for addiction. Myers KM, Carlezon WA, Jr. D-cycloserine facilitates extinction of naloxone-induced conditioned place aversion in morphine-dependent rats. Biol Psychiatry 2010; Jan 1; 67(1):85-87.

Calcium Signaling Cascade Links Dopamine D1-D2 Receptor Heteromer to Striatal BDNF Production and Neuronal Growth

Although the perturbation of either the dopaminergic system or brain-derived neurotrophic factor (BDNF) levels has been linked to important neurological and neuropsychiatric disorders, there is no known signaling pathway linking these two major players. Dr. Susan George and her research team at the University of Toronto and the Centre for Addiction and Mental Health, Toronto, ON, Canada reported that the exclusive stimulation of the dopamine D1-D2 receptor heteromer, which they identified in striatal neurons and adult rat brain by using confocal FRET, led to the activation of a signaling cascade that links dopamine signaling to BDNF production and neuronal growth through a cascade of four steps: (i) mobilization of intracellular calcium through Gq, phospholipase C, and inositol trisphosphate, (ii) rapid activation of cytosolic and nuclear calcium/calmodulin-dependent kinase IIalpha, (iii) increased BDNF expression, and (iv) accelerated morphological maturation and differentiation of striatal neurons, marked by increased microtubule-associated protein 2 production. These effects, although robust in striatal neurons from D5(-/-) mice, were absent in neurons from D1(-/-) mice. They also demonstrated that this signaling cascade was activated in adult rat brain, although with regional

specificity, being largely limited to the nucleus accumbens. This dopaminergic pathway regulating neuronal growth and maturation through BDNF may have considerable significance in disorders such as drug addiction, schizophrenia, and depression. Hasbi A, Fan T, Alijaniaram M, et al. Proc Natl Acad Sci U S A. 2009 Dec 15;106(50):21377-82. Epub 2009 Nov 30.

Homeostatic Synapse-Driven Membrane Plasticity in Nucleus Accumbens Neurons

Stable brain function relies on homeostatic maintenance of the functional output of individual neurons. In general, neurons function by converting synaptic input to output as action potential firing. To determine homeostatic mechanisms that balance this input-output/synapse-membrane interaction, Dr. Yan Dong of Washington State University focused on nucleus accumbens (NAc) neurons and demonstrated a novel form of synapse-to-membrane homeostatic regulation, homeostatic synapse-driven membrane plasticity (hSMP). Through hSMP, NAc neurons adjusted their membrane excitability to functionally compensate for basal shifts in excitatory synaptic input. Furthermore, hSMP was triggered by synaptic NMDA receptors (NMDARs) and expressed by the modification of SK-type Ca(2+)-activated potassium channels. Moreover, hSMP in NAc neurons was abolished in rats during a short- (2 d) or long- (21 d) term withdrawal from repeated intraperitoneal injections of cocaine. These results suggest that hSMP is a novel form of synapse-to-membrane homeostatic plasticity and dysregulation of hSMP may contribute to cocaine-induced cellular alterations in the NAc. Ishikawa M, Mu P, Moyer JT, et al. Homeostatic synapse-driven membrane plasticity in nucleus accumbens neurons. J Neurosci. 2009 May 6;29(18):5820-5831.

A Mechanisms by Which HIV-1 Evades the Immune System

HIV evades the defenses of the immune system leading eventually to the destruction of CD4+ T cells. Consequently, the host becomes susceptible to opportunistic infections. A paper in the October 2009 issue of the Journal of Virology by Professor Michael Gale and his colleagues at the University of Washington now provides an answer on how HIV evades destruction by the immune system of the host. Professor Gale and his colleagues show that HIV suppresses innate antiviral signaling and immune defenses within infected cells. Innate immunity differs from cellular immunity. In innate immunity signals within the cell fight infection; in cellular and adaptive immunity white cells such T cells, B cells, macrophages, neutrophils attack the foreign invader. Pathogen recognition receptors located on the cell surface of the host recognize viral proteins to trigger an intracellular messenger cascade that induces interferons and interferon induced pro-inflammatory cytokines. Induction of interferons is dependent upon the activation of IRF-3, IRF-7, and IRF-9. Professor Gale and his colleagues show that CD4+ T cells in vitro that normally clear paramyxovirus fail to clear paramyxovirus or HIV when infected with HIV. The inability to clear paramyxovirus or HIV infection is associated with depletion of the IRF-3 protein. Ectopic over expression of IRF-3 suppressed HIV infection. The depletion of IRF-3 is dependent on HIV replication and appears to be mediated by the Vpr protein of HIV. In vivo, Professor Gale and his colleagues show that IRF-3 levels are reduced in CD4+ T cells of patients with acute HIV-1 infection but not in long-term nonprogressors. These results suggest that suppression of IRF-3 is an important mechanism by which HIV-1 evades host defenses and suggest how the host might be more susceptible to viral coinfections such as hepatitis C. Progression of liver diseases occurs much more rapidly in HCV/HIV coinfected individuals. It is of interest to note that a gene variant in IRF-3/IL-28 is associated with inability to clear HCV infection. Thus, understanding how these two pathogens evades IRF-3 and innate immune system is central to understanding the pathogenesis of these diseases. Doehle BP, Hladik F, McNevin JP, McElrath MJ, Gale M Jr. Human

immunodeficiency virus type 1 mediates global disruption of innate antiviral signaling and immune defenses within infected cells. J Virol. 2009 Oct;83(20):10395-10405.

Differential Inheritance of Mother Centrioles Determines Fates of Daughter Radial Glia

Abnormal cortical development underlies many pathological conditions seen in mental disorders or mental retardation. Microcephaly, a cortical developmental disorder associated with maternal alcoholism, is characterized by a small head with small brain and may be caused by a disturbance in the rapid growing of neural cells during cortical development, when a large number of neural cells are generated by the progenitor cells of radial glia at the ventricular zone (VZ). It has been known that asymmetric divisions of radial glia progenitors produce self-renewing radial glia and differentiating cells simultaneously in the VZ. Whereas differentiating cells leave the VZ to constitute the future neocortex, renewing radial glia progenitors stay in the VZ for subsequent divisions. The differential behavior of progenitors and their differentiating progeny is essential for neocortical development; however, the mechanisms that ensure these behavioural differences are unclear. A group of NIDA funded researchers, led by Song-Hai Shi, at Memorial Sloan Kettering Cancer Centre show that asymmetric centrosome inheritance regulates the differential behavior of renewing progenitors and their differentiating progeny in the embryonic mouse neocortex. Centrosome duplication in dividing radial glia progenitors generates a pair of centrosomes with differently aged mother centrioles. During peak phases of neurogenesis, the centrosome retaining the old mother centriole stays in the VZ and is preferentially inherited by radial glia progenitors, whereas the centrosome containing the new mother centriole mostly leaves the VZ and is largely associated with differentiating cells. Removal of ninein, a mature centriole-specific protein, disrupts the asymmetric segregation and inheritance of the centrosome and causes premature depletion of progenitors from the VZ. These results indicate that preferential inheritance of the centrosome with the mature older mother centriole is required for maintaining radial glia progenitors in the developing mammalian neocortex. Irregular gene expression or mutations of genes that encode centrosomal components, or disturbances in the expression and regulation of such genes in substance abuse, may therefore play roles in abnormal cortical development. Wang X, Tsai JW, Imai JH, Lian WN, Vallee RB, Shi SH. Asymmetric centrosome inheritance maintains neural progenitors in the neocortex. Nature. 2009; 461: 947-955.

EphA and Ephrin-A: Signaling Pair Teams Up Functional Cortical Columns

The Eph proteins play essential roles in many aspects of brain development, from neuronal differentiation, axonal branching, pathfinding, to establishing columnar maps. The cerebral cortex is a laminated sheet of neurons composed of the arrays of intersecting radial columns. During development, excitatory projection neurons originating from the proliferative units at the ventricular surface of the embryonic cerebral vesicles migrate along elongated radial glial fibers to form a cellular infrastructure of radial (vertical) ontogenetic columns in the overlaying cortical plate. However, a subpopulation of these clonally related neurons also undergoes a short lateral shift and transfers from their parental to the neighboring radial glial fibres, and intermixes with neurons originating from neighboring proliferative units. This columnar organization acts as the primary information processing unit in the cortex. The molecular mechanisms, role and significance of this lateral dispersion for cortical development are not understood. Two groups of NIDA researchers, one led by Pat Levitt of University of Southern California, and the other led by Pasko Rakic at Yale University, jointly show that an Eph receptor A (EphA) and ephrin A

(Efna) signalling-dependent shift in the allocation of clonally related neurons is essential for the proper assembly of cortical columns. As has been seen in the ocular dominance columns, these researchers found that EphA receptors and Efna exhibit highly regulated, stereotypic spatial and temporal expression pattern in the neocortex. In addition, in contrast to the relatively uniform labeling of the developing cortical plate by various molecular markers and retrograde tracers in wild-type mice, they found alternating labeling of columnar compartments in Efna knockout mice that are caused by impaired lateral dispersion of migrating neurons rather than by altered cell production or death. Furthermore, in utero electroporation of EphA- and Efna-expressing plasmid showed that lateral dispersion depends on the expression levels of EphAs and Efnas during neuronal migration. This mechanism seems to be essential for the proper intermixing of neuronal types in the cortical columns, which, when disrupted, may contribute to neuropsychiatric disorders associated with abnormal columnar organization. Torii M, Hashimoto-Torii K, Levitt P, Rakic P. Integration of neuronal clones in the radial cortical columns by EphA and ephrin-A signaling. Nature. 2009;461:524-528.

Retinoic Acid from the Surface to the Cortex: How Meninges Regulate Brain Development

The factors that control the timing and continued progression of cortical neurogenesis have remained largely obscure. Samuel Pleasure and his colleagues at UCSF, present evidence that all-trans retinoic acid (atRA) released from the meninges is involved in the decision of neuroepithelial cells to generate IPCs and neurons. His group demonstrates that the dorsal forebrain meninges communicate with the adjacent radial glial endfeet and influence cortical development. Using Foxc1 mutant mice with defects in forebrain meningeal formation, they show that Foxc1 dosage and loss of meninges correlated with a dramatic reduction in both neuron and intermediate progenitor production and elongation of the neuroepithelium. They further demonstrate that retinoic acid (RA) is the key component of this secreted activity. In addition, Rdh10- and Raldh2- expressing cells in the dorsal meninges were either reduced or absent in the Foxc1 mutants, and Rdh10 mutants had a cortical phenotype similar to the Foxc1 null mutants. Lastly, in utero RA treatment rescued the cortical phenotype in Foxc1 mutants. These results establish RA as a potent, meningeal derived cue required for successful corticogenesis. Since Vitamin A derivative signaling plays essential roles during brain development and in mesolimbic dopaminergic pathway formation and plasticity, this newly discovered role of RA provides important insights for addiction research. Siegenthaler JA, Ashique AM, Zarbalis K, Patterson KP, Hecht JH, Kane MA, Folias AE, Choe Y, May SR, Kume T, Napoli JL, Peterson AS, Pleasure SJ. Cell. 2009;139:597-609.

CHRNA5 Nonsynonymous Polymorphism Associated with Nicotine Dependence in African-Americans

Genome-wide association studies of nicotine dependence have consistently shown a top association signal on chromosome 15q24-25, and include a nonsynonymous single nucleotide polymorphism (SNP) at rs16969968 within exon 5 of the alpha5 cholinergic nicotinic receptor subunit gene. The risk allele causes a functional amino acid change from aspartic acid at position 398 to asparagine. Additionally, this risk allele has been associated with lung cancer, chronic pulmonary obstructive disorder, and peripheral artery disease in European-descent samples. Dr. Saccone and her colleagues have studied this region in African descent to confirm its role in this population, and to leverage the contrasting genetic architecture of these two populations to help pin-point the functional source(s) of the disease associations. They report that the most significant SNP in the African-American sample is rs16969968 (P=0.0147; OR, 2.04; 1.15-3.62). They also confirm that the most significant SNP of the 76

tested in the chr 15q24-25 region in the combined African-American and European-American sample was rs16969968 (P=4.49 x 10-8; OR, 1.42; 95% CI, 1.25-1.61). This replication in African-Americans provides crucial information because of the different linkage disequilibrium structure and population history from the European-American samples. The rs16969968 SNP is rare in African-Americans, with a frequency of ~5% compared with a frequency of ~35% in European-Americans. Additionally, another SNP (rs555018) in the region is associated with brain mRNA levels of CHRNA5 in European-descent samples, but this result is not significant. When a rs16969668 is included as a covariate in the analysis with rs555018, a protective effect is seen in European-Americans, but not in African-Americans. These data suggest that mRNA levels of CHRNA5 may be influenced by additional variants in the region, and that these two SNPs may be responsible for two biological mechanisms affecting nicotine dependence risk. Saccone NL, Wang JC, Breslau N, et al. The CHRNA5-CHRNA3-CHRNB4 Nicotinic Receptor Subunit Gene Cluster Affects Risk for Nicotine Dependence in African-Americans and European-Americans. Cancer Res. 2009 Sept 69:6848-6856.

Humphrey Bogart and Betty Davis: Identification of Nicotine Response Genes in Zebrafish

Human genetic studies have recently been used with great success to identify genes associated with nicotine dependence. Animal genetic studies are an important complement to human studies since they can be used to 1) perform unbiased screens to identify genes and pathways associated with responses to drugs of abuse and 2) functionally characterize genes/variants identified in human or animal studies. Dr. Ekker and colleagues developed a nicotine behavioral response assay that allowed the identification of mutant zebrafish with altered behavioral responses to nicotine. Two independent mutant strains were identified and named Betty Davis and Humphrey Bogart (after celebrities that suffered from tobacco-related disease). The mutant animals were generated using a gene break transposon strategy which facilitated identification of the mutated genes responsible for the behavioral phenotypes. The Betty Davis mutant had a defect in the cct8 (chaperonin containing protein 8) gene. The human genome encodes an analogous version of cct8, so now the human cct8 gene can be tested for a possible role in human nicotine responses. The Humphrey Bogart mutant had a defect in the zebrafish GABA(B) receptor which binds to the neurotransmitter GABA. Interestingly, human gene variants in GABA(B) had previously been associated with nicotine dependence. This zebrafish work provides unbiased genetic confirmation of a role for the GABA(B) receptor in nicotine responses and suggests that at least a part of the nicotine behavioral response pathway is evolutionarily conserved. Furthermore the identification of the Humphrey Bogart and Betty Davis mutants in the genetically tractable zebrafish system will allow functional assessment of the role of these genes (and potentially the human variants of these genes) in nicotine responses. The development of nicotine behavioral response assays in zebrafish also could enable future inexpensive pharmacological screens to identify small molecules that could serve as the foundation for future nicotine dependence therapeutics. Petzold AM, Balciunas D, Sivasubbu S, et al. Nicotine response genetics in the zebrafish. Proc Natl Acad Sci U S A. 2009 Nov 3;106(44):18662-18667. Epub 2009 Oct 26.

Stress-Induced Potentiation of Cocaine Reward: A Role for CRF R1 and CREB

Studies in humans and animal models indicate that stress increases vulnerability to develop addiction, and potentiates drug taking and relapse in addicted individuals. Understanding the molecular mechanisms of this interaction could aid in the development of addiction treatment options. Exposure to both stress or drugs of abuse results in long-term adaptations in

the brain that involve persistent alterations in gene expression or activation of transcription factors, such as the cAMP Response Element Binding (CREB) protein. Potential CREB target genes such as corticotropin-releasing factor (CRF), Brain derived neurotrophic factor (BDNF), and dynorphin are associated with initiation or reinstatement of drug reward and are also altered following stress. Dr. Blendy has shown that a single exposure to forced swim (FS) reinstates extinguished conditioned place preference (CPP) to cocaine and that CREB is necessary for this response. Chronic exposure to FS in advance of conditioning enhances cocaine CPP in wild-type mice, but this is blocked in CREB-deficient mice. As CREB can be activated by corticotropin releasing factor (CRF) receptor type 1 (CRF(R1)) binding, which mediates neuroendocrine and behavioral responses to stress as well as to drugs of abuse, contribution of CREB and CRF(R1) to the changes in cocaine reward elicited by previous exposure to stress was investigated. Pretreatment with the CRF(R1) antagonist, antalarmin, before FS exposure, blocks the stress-induced enhancement of cocaine CPP. Furthermore, FS-induced increase in phosphorylated CREB (pCREB), specifically in the lateral septum (LS) and nucleus accumbens (NAc) is also blocked by antalarmin. Thus, both CREB and CRF(R1) activation are necessary for stress-induced potentiation of drug reward. Kreibich AS, Briand L, Cleck JN, Ecke L, Rice KC, Blendy JA. Stress-induced potentiation of cocaine reward: a role for CRF R1 and CREB. Neuropsycho-pharmacogy. 2009 Nov;34(12):2609-2617.

Crystal Structure of FAAH with an Inhibitor Reveals Enzymatic Inactivation Mechanisms

Ben Cravatt and his collaborators recently reported the cocrystal X-ray structures of two isomeric R-ketooxazole inhibitors (1 (OL-135) and 2) bound to fatty acid amide hydrolase (FAAH), a key enzymatic regulator of endocannabinoid signaling. The active site catalytic Ser241 is covalently bound to the inhibitors' electrophilic carbonyl groups, providing the first structures of FAAH bound to an inhibitor as a deprotonated hemiketal mimicking the enzymatic tetrahedral intermediate. The work also offers a detailed view of the oxyanion hole and an exceptional "in-action" depiction of the unusual Ser-Ser-Lys catalytic triad. These structures capture the first picture of inhibitors that span the active site into the cytosolic port providing new insights that help to explain FAAH's interaction with substrate leaving groups and their role in modulating inhibitor potency and selectivity. The role for the activating central heterocycle is clearly defined and distinguished from that observed in prior applications with serine proteases, reconciling the large electronic effect of attached substituents found unique to this class of inhibitors with FAAH. Additional striking active site flexibility is seen upon binding of the inhibitors, providing insights into the existence of a now well-defined membrane access channel with the disappearance of a spatially independent portion of the acyl chain-binding pocket. Finally, comparison of the structures of OL-135 (1) and its isomer 2 indicates that they bind identically to FAAH, albeit with reversed orientations of the central activating heterocycle, revealing that the terminal 2-pyridyl substituent and the acyl chain phenyl group provide key anchoring interactions and confirming the distinguishing role of the activating oxazole. Mileni M, Garfunkle J, DeMartino JK, Cravatt BF, Boger DL, Stevens RC. Binding and inactivation mechanism of a humanized fatty acid amide hydrolase by α-Ketoheterocycle inhibitors revealed from cocrystal structures. J Am Chem Soc 2009 Jul 8;131(30):10497-10506.

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

N-arachidonoyl dopamine (NADA) is an endogenous ligand that activates the cannabinoid type 1 receptor and the transient receptor potential vanilloid type

1 channel. Two potential biosynthetic pathways for NADA have been proposed, though no conclusive evidence exists for either. The first is the direct conjugation of arachidonic acid with dopamine and the other is via metabolism of a putative N-arachidonoyl tyrosine (NA-tyrosine). In the present study, Walker and colleagues investigated these biosynthetic mechanisms and report that NADA synthesis requires TH in dopaminergic terminals; however, NA-tyrosine, which is identified here as an endogenous lipid, is not an intermediate. The investigators show that NADA biosynthesis primarily occurs through an enzyme-mediated conjugation of arachidonic acid with dopamine. While this conjugation likely involves a complex of enzymes, their data suggests a direct involvement of fatty acid amide hydrolase in NADA biosynthesis either as a rate-limiting enzyme that liberates arachidonic acid from AEA, or as a conjugation enzyme, or both. Hu SS, Bradshaw HB, Benton VM, et al. The biosynthesis of N-arachidonoyl dopamine (NADA), a putative endocannabinoid and endovanilloid, via conjugation of arachidonic acid with dopamine. Prostaglandins Leukot Essent Fatty Acids, 2009 Oct; 81(4):291-301.

Inhibitors of Endocannabinoid Metabolizing Enzymes Reduce Precipitated Withdrawal Responses in THC Depenedent Mice

Abstinence symptoms in cannabis-dependent individuals are believed to contribute to the maintenance of regular marijuana use. However, there are currently no medications approved by the FDA to treat cannabis related disorders. The only treatment currently shown consistently to alleviate cannabinoid withdrawal in both animals and humans is substitution therapy, using the psychoactive constituent of marijuana, δ9-tetrahydrocannabinol (THC). However new genetic and pharmacological tools are available to increase endocannabinoid levels by targeting fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL), the enzymes responsible for the degradation of the endogenous cannabinoids ligands anandamide (AEA) and 2-arachidonylglycerol (2-AG), respectively. In the present study the authors have investigated whether increasing endogenous cannabinoids levels through the use of FAAH (-/-) mice as well as the FAAH inhibitor URB597 or the MAGL inhibitor JZL184 significantly attenuated rimonabant precipitated withdrawal signs in the THC dependent mice. By contrast, FAAH (-/-) mice showed identical withdrawal responses as wild type mice under a variety of conditions, suggesting that the absence of this enzyme across the development of dependence and during rimonabant challenge does not affect withdrawal responses. Of importance, subchronic administration of URB 597 did not lead to cannabinoid dependence, and neither URB597 nor JZL184 impaired rotarod motor coordination. These results support the concept of targeting endocannabinoid metabolizing enzymes as a promising treatment for cannabis withdrawal. Schlosburg JE, Carlson BLA, Ramesh D, Long JZ, Cravatt BF, Lichtman AH, Abdullah RA. Inhibitors of endocannabinoid metabolizing enzymes reduce precipitated withdrawal responses in THC dependent mice. The AAPS Journal, 2009 Jun;11(2):342-352.

MOR Antagonist Design

Mu opioid receptor (MOR) antagonists are of pharmacological interest in the field of analgesia, and are utilized in drug addiction research. Important objectives in the design of such antagonists include reversible rather than irreversible binding to the MOR, metabolic stability, a non-peptide structure for cell permeability, and relative selectivity toward the MOR versus the other opioid receptors. A recent report from Dr. Yan Zhang and colleagues at the Virginia Commonwealth University demonstrates the use of receptor modeling and message/address concepts to target a ligand to the opioid receptors (the message), while varying individual ligand substituents to improve selectivity (the address). Homology models of the three opioid receptors (MOR, DOR, KOR) were generated based on the 3-D structure of bovine rhodopsin,

including both transmembrane helical and loop regions. The receptor models were included in a phospholipid bilayer environment, and structures were optimized using molecular dynamics. Naltrexone was used as a model antagonist, and was docked into the transmembrane binding pocket of each receptor, using an electrostatic distance constraint between the positively charged protonated nitrogen of naltrexone and the negative charge of an aspartate (position 147 in the MOR) in helix three of each receptor. The receptor-ligand complexes were subjected to molecular dynamics to yield the conformation of lowest energy in each case. The major difference found between the MOR model versus the DOR or KOR was the proximity of extracellular loop aromatic amino acid residues (tyrosine 210, phenylalanine 221, tryptophan 318) near the naltrexone carbonyl at the C(6) position. This suggested that suitable modification of the ligand naltrexone in terms of hydrogen bond formation would enhance the selectivity of binding toward the MOR. A series of naltrexamine amides were then synthesized with these findings in mind. One series of compounds introduced a pyridyl group to interact with the aromatic binding region of the MOR, and in the second case, introduced an isoquinoline group for the same purpose. These series also provided a pyridine nitrogen atom to act as a possible hydrogen bond acceptor with the hydroxyl of Tyr 210 (extracellular loop 2) or isoquioline nitrogen with the hydroxyl of Tyr 318 (extracellular loop 3). From these series, two particular compounds were reported to be selective toward the MOR versus the DOR or KOR, and showed partial agonism in the GTPgammaS functional assay. They were reported to be competitive and full antagonists of morphine response in-vivo, using the tail immersion test in mice, with AD50 values of .45 mg/kg or 4.5 mg/kg, and with no agonism effects seen up to 100 mg/kg. This work illustrates the application of homology modeling to design antagonists emphasizing or maximizing receptor-selective interactions. Li G, Aschenbach LC, Chen J, et al. Design, synthesis, and biological evaluation of 6-alpha and 6-beta-N-heterocyclic substituted naltrexamine derivatives as mu opioid receptor selective antagonists. J Med Chem. 2009 Mar 12; 52(5):1416-1427.

An Ultra-Short Dopamine Pathway Regulates Basal Ganglia Output

Substantia nigra pars reticulata (SNr) is a key basal ganglia output nucleus critical for movement control. Its GABA-containing projection neurons intermingle with nigral dopamine (DA) neuron dendrites. Here the authors show that SNr GABA neurons coexpress dopamine D(1) and D(5) receptor mRNAs and also mRNA for TRPC3 channels. Dopamine induced an inward current in these neurons and increased their firing frequency. These effects were mimicked by D(1)-like agonists, blocked by a D(1)-like antagonist. D(1)-like receptor blockade reduced SNr GABA neuron firing frequency and increased their firing irregularity. These D(1)-like effects were absent in D(1) or D(5) receptor knock-out mice and inhibited by intracellularly applied D(1) or D(5) receptor antibody. These D(1)-like effects were also inhibited when the tonically active TRPC3 channels were inhibited by intracellularly applied TRPC3 channel antibody. Furthermore, stimulation of DA neurons induced a direct inward current in SNr GABA neurons that was sensitive to D(1)-like blockade. Manipulation of DA neuron activity and DA release and inhibition of dopamine reuptake affected SNr GABA neuron activity in a D(1)-like receptor-dependent manner. Together, these findings indicate that dendritically released dopamine tonically excites SNr GABA neurons via D(1)-D(5) receptor coactivation that enhances constitutively active TRPC3 channels, forming an ultra-short substantia nigra pars compacta --> SNr dopamine pathway that regulates the firing intensity and pattern of these basal ganglia output neurons. Zhou FW, Jin Y, Matta SG, Xu M, Zhou FM. An ultra-short dopamine pathway regulates basal ganglia output. J. Neurosci. 2009 Aug 19;29(33):10424-10435.

Visualization of Chemokine Receptor Activation in Transgenic Mice

Reveals Peripheral Activation of CCR2 Receptors in States of Neuropathic Pain

CCR2 chemokine receptor signaling has been implicated in the generation of diverse types of neuropathology, including neuropathic pain. For example, CCR2 knock-out mice are resistant to the establishment of neuropathic pain, and mice overexpressing its ligand, monocyte chemoattractant protein-1 (MCP1; also known as CCL2), show enhanced pain sensitivity. However, whether CCR2 receptor activation occurs in the central or peripheral nervous system in states of neuropathic pain has not been clear. NIDA supported investigators developed a novel method for visualizing CCR2 receptor activation in vivo by generating bitransgenic reporter mice in which the chemokine receptor CCR2 and its ligand MCP1 were labeled by the fluorescent proteins enhanced green fluorescent protein and monomeric red fluorescent protein-1, respectively. CCR2 receptor activation under conditions such as acute inflammation and experimental autoimmune encephalomyelitis could be faithfully visualized by using these mice. The investigators examined the status of CCR2 receptor activation in a demyelination injury model of neuropathic pain and found that MCP1-induced CCR2 receptor activation mainly occurred in the peripheral nervous system, including the injured peripheral nerve and dorsal root ganglia. These data explain the rapid antinociceptive effects of peripherally administered CCR2 antagonists under these circumstances, suggesting that CCR2 antagonists may ameliorate pain by inhibiting CCR2 receptor activation in the periphery. The method developed here for visualizing CCR2 receptor activation in vivo may be extended to G-protein-coupled receptors (GPCRs) in general and will be valuable for studying intercellular GPCR-mediated communication in vivo. Jung H, Bhangoo S, Banisadr G, Freitag C, Ren D, White FA, Miller RJ. Visualization of chemokine receptor activation in transgenic mice reveals peripheral activation of CCR2 receptors in states of neuropathic pain. J Neurosci. 2009 Jun 24;29(25):8051-8062.

Association of Nicotine Metabolite Ratio and CYP2A6 Genotype with Smoking Cessation Treatment in African-American Light Smokers

Cytochrome P450 2A6 (CYP2A6) is the main nicotine (NIC)-metabolizing enzyme in humans. Rachel Tyndale, Neal Benowitz and their collaborators investigated the relationships between CYP2A6 genotype, baseline plasma trans- 3'-hydroxycotinine/ cotinine (3HC/COT) (a phenotypic marker of CYP2A6 activity), and smoking behavior in African-American light smokers. Cigarette consumption, age of initiation, and dependence scores did not differ among 3HC/COT quartiles or CYP2A6 genotype groups. Slow metabolizers (SMs; both genetic and phenotypic) had significantly higher plasma NIC levels, suggesting that cigarette consumption was not reduced to adjust for slower rates of NIC metabolism. Individuals in the slowest 3HC/COT quartile had higher quitting rates with both placebo and NIC gum treatments (odds ratio 1.85, 95% confidence interval (CI) 1.08-3.16, P = 0.03). Similarly, the slowest CYP2A6 genotype group had higher quitting rates, although this trend did not reach significance (odds ratio 1.61, 95% CI 0.95-2.72, P = 0.08). The determination of the 3HC/COT ratio, and possibly CYP2A6 genotype, may be useful in the future for personalizing the choice of smoking cessation treatment in African-American light smokers. Ho MK, Mwenifumbo JC, Al Koudsi N, Okuyemi KS, Ahluwalia JS, Benowitz NL, Tyndale RF. Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. Clin Pharmacol Ther. 2009 Jun;85:635-643.

Greater Impulsivity Leads to Escalation of Cocaine Self-Administration in Rats

Impulsivity has emerged as a major risk factor in the vulnerability to several aspects of drug abuse. The relationship between impulsivity and stimulant abuse is especially robust. Stimulant abusers exhibit higher levels of impulsivity, relative to non-drug-using controls as assessed by self-report and behavioral laboratory measures. Impulsivity, as measured by the delay-discounting task, predicts the acquisition of cocaine self-administration and reinstatement of cocaine seeking in rats. This study extended the current literature to the escalation phase of drug self-administration. Female rats were initially screened for high or low impulsivity for food reinforcement using a delay-discounting procedure. They were training to self-administer cocaine and exposed to progressive ratio and fixed ratio testing as well as an extended access paradigm. The results indicated that high impulsivity rats escalated cocaine-reinforced responding during the extended access condition, but low impulsivity rats did not. High impulsivity rats also earned significantly more infusions than low impulsivity rats under the post-escalation short access fixed-ratio condition. This work suggests that individual differences in impulsivity predict escalation of cocaine self-administration in rats, which may have implication in prediction of binge-like patterns of cocaine intake in humans. Anker JJ, Perry JL, Gliddon LA, Carroll ME. Impulsivity predicts the escalation of cocaine self-administration in rats. Pharmacol Biochem Behav. 2009 Sept; 93(3):343-348.

Spinal Microglia Play a Role in Visceral Hyperalgesia and NK1R Up-Regulation in a Rat Model of Chronic Stress

Chronic stress has been known to be associated with visceral hyperalgesia and increased expression of spinal NK1 receptors (NK1Rs). Dr. Yaksh and his associates sought to identify the role of spinal microglia in this process by exposing rats to the chronic stress of a water avoidance procedure or a sham stress procedure in control animals. Rats were given an injection of minocycline, a p38 inhibitor (SB203580), or saline each day. Phosphorylation levels of kinase p38 (P-p38), the microglia marker OX42, NK1R, and IκBα were assessed by immunoblotting and/or immunostaining of spinal samples collected on the day following the last exposure to the water stress (day 11). The investigators found that protein levels of P-p38 and immunoreactivity were increased in the stressed rats, and these changes were co-localized with OX42-positive cells and neurons in the dorsal horn of the spinal cord. Furthermore, the investigators found that these increases were reversed by minocycline or SB203580 exposure. They also reported that the stress-induced increase in NK1R expression was blocked by minocycline, but not by the SB compound. The water stress-induced hyperalgesia was blocked by minocycline and the SB compound when administered intrathecally. Dr. Yaksh and his colleagues conclude that this is the first demonstration that stress-induced activation of spinal microglia has a key role in visceral hyperalgesia and associated spinal NK1R up-regulation. Radesi R, Svensson CI, Steinauer J, Pothoulakis C, Yaksh TL, Mayer EA. FEBS Let. 2009 Apr;136(4):1339-1348.

Significant Association of ANKK1 and Detection of a Functional Polymorphism with Nicotine Dependence in an African-American Sample

The dopaminergic system in the brain plays a critical role in nicotine addiction. Genetic variants in the dopaminergic system, including those in dopamine receptor genes, represent plausible candidates for the genetic study of nicotine dependence (ND). Dr. Li and colleagues investigated various polymorphisms in the dopamine D(2) receptor gene (DRD2) and its neighboring ankyrin repeats and kinase domain containing 1 gene (ANKK1) to determine whether they were associated with ND. They examined 16 single nucleotide polymorphisms (SNPs) at DRD2 and 7 SNPs at ANKK1 in their Mid-South Tobacco Family cohort, which consisted of 2037 participants representing two distinct American populations.

Several SNPs (rs7131056, rs4274224, rs4648318, and rs6278) in DRD2, along with the Taq IA polymorphism (rs1800497) in ANKK1, revealed initial significant associations with ND in European Americans, but not after correction for multiple testing, indicating a weak association of DRD2 with ND. In contrast, associations for ANKK1 with ND in the African-American and pooled samples, specifically for SNP rs2734849, remained significant after correction. With a non-synonymous G to A transition, rs2734849 produces an amino-acid change (arginine to histidine) in C-terminal ankyrin repeat domain of ANKK1. Using the luciferase reporter assay, the research team further demonstrated that the variant alters expression level of NF-kappaB-regulated genes. Since DRD2 expression is regulated by transcription factor NF-kappaB, they suspect that rs2734849 may indirectly affect dopamine D(2) receptor density. Dr. Li and colleagues conclude that ANKK1 is associated with ND and polymorphism rs2734849 in ANKK1 represents a functional causative variant for ND in African-American smokers. Huang W, Payne TJ, Ma JZ, Beuten J, Dupont RT, Inohara N, Li MD. Significant association of ANKK1 and detection of a functional polymorphism with nicotine dependence in an African-American sample. Neuropsychopharmacology. 2009 Jan;34(2):319-330.

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

Research Findings - Basic Behavioral Research

Cellular Mechanisms of Corticostriatal Plasticity and Associated Striatal-Dependent Learning

Adenylyl cyclase 5 (AC5), the enzyme that catalyzes cAMP production, is essential for induction of long-term potentiation. AC5 couples glutamate-mediated increases in calcium to cAMP accumulation, and has been successfully knocked out in AC5 KO mice. Jeff Beeler and colleagues used this genetically altered mouse to examine the contribution of cAMP to corticostriatal plasticity and dorsal striatum-dependent learning. Water cross maze performance was used to evaluate dorsal striatal-dependent response learning. In the water cross maze task, wildtype (WT) and knockout (KO) mice were trained to find a submerged hidden platform using an egocentric response strategy (e.g. making the same body turn on each trial to find the goal arm). The KO mice took significantly longer to learn this task as compared to WT mice. This does not appear to be a global learning deficit, as there was no significant difference between WT and KO performance on the Morris water maze, in which the mice find a hidden platform using spatial cues. Performance on an accelerating rotorod was used to evaluate corticostriatal plasticity in motor learning. Although initial performance was comparable, the WT mice improved their performance over the first day's trials (4 trials/day) whereas the KO mice did not. This resulted in significant differences between the groups after 3 days of testing. The difference was not due to general locomotion, as 3 days of locomotor activity testing revealed no group differences. Involvement in cAMP signaling in the corticostriatal long-term depression (LTD) was evaluated using electrophysiological and electrochemical recordings. AC5 KO mice exhibited larger miniature excitatory post synaptic current (mEPSC) amplitudes, likely due to an increased density of AMPA and NMDA receptors, as there were no differences in AMPA to NMDA ratios. Long-term potentiation (LTP) was induced by pairing high-frequency electrical stimulation of glutamatergic afferent fibers with post-synaptic depolarization. In tissue slices from AC5 KO mice, although there was some heterogeneity, there was no overall induction of LTP. To investigate whether this deficit was due to presynaptic deficits, a cannabinoid 1 (CB1) agonist was applied. Tissue slices from both KO and WT mice exhibited robust excitatory post synaptic currents (EPSCs). Application of a mGluR agonist to elicit dopamine-independent endocannabinoid-mediated LTP also elicited LTP in both KO and WT tissue slices. Thus, there was no difference in endocannabinoid-mediated LTP. In summary, the behavioral deficits were correlated with deficits in LTP in the dorsal striatum. These deficits in LTP could be rescued by activation of the endocannabinoid system, suggesting that AC5 regulation of cAMP production during LTP induction facilitates endocannabinoid release and activation of presynaptic CB1 receptors, to suppress glutamatergic signaling. These findings provide insight into the molecular mechanisms underlying development of plasticity (LTD and LTP) in the dorsal striatum and

to the dopaminergic regulation of this plasticity via an AC5-cAMP-endocannabinoid-CB1 pathway. Kheirbek MA, Britt JP, Beeler JA, Ishikawa Y, McGehee DS, Zhuang X. Adenylyl cyclase type 5 contributes to corticostriatal plasticity and striatum-dependent learning. J Neurosci. 2009; 29:12115-12124.

Alpha6 Receptor Subunit is Involved in Nicotine Reward and Affective Changes during Nicotine Withdrawal

The alpha6 (a6) nicotinic receptor subunit has recently been found to play a role in nicotine-induced locomotor activity and reinforcement. In the current study, Darlene Brunzell sought to expand on these recent findings demonstrating that mice lacking the a6 subunit fail to self-administer nicotine. However, nicotine is self-administered by mice after restoration of this subunit in the VTA via lenti-viral re-expression. Using a selective a6 antagonist alpha-conotoxin as a pharmacological blockade, Dr. Brunzell and colleagues further examined the role of this subunit in the pharmacological and behavioral effects of nicotine. They employed a battery of behavioral tests, including tail flick and hot-plate tests for analgesia, measures of locomotor activity, conditioned place preference, and the elevated plus maze. Pretreatment with alpha-conotoxin prevented the expression of nicotine conditioned place preference. Affective and somatic signs of withdrawal were assessed following chronic infusion of nicotine with a osmotic mini-pump. Nicotine-withdrawn mice show anxiety (spend less time in the open arms of a plus maze) and decreased latencies on the hot-place (withdrawal-induced hyperalgesia). Pretreatment with the a6 antagonist blocked affective (anxiety, measured on the plus maze), but not physical (including hyperalgesia), signs of nicotine withdrawal. Under conditions of continuous nicotine infusion (animals in which osmotic pumps were not removed), administration of the a6 antagonist did not precipitate withdrawal. Administration of mecamylamine, a nicotinic receptor antagonist, did precipitate withdrawal, as evidenced by the development of a significant conditioned taste aversion (CTA). The CTA could be blocked by some doses of the a6 antagonist. Taken together, these data suggest that a6-containing subunits play a critical role in nicotine's rewarding effects following chronic nicotine administration. Therefore, blocking a6 subunits may provide a novel target for treating nicotine addiction, and may be particularly useful for alleviation of the negative withdrawal symptoms. Jackson KJ, McIntosh JM, Brunzell DH, Sanjakdar SS, Damaj MI. The role of alpha6-containing nicotinic acetylcholine receptors in nicotine reward and withdrawal. J Pharmacol Exp Ther. 2009; 331(2):547-54. Epub 2009 Jul 30.

Differential Involvement of Ventral Tegmental Area in Motivated Maternal Behavior Versus Cocaine-Conditioned Reinforcement

In rats, as well as every other mammalian species, females demonstrate a remarkable motivation to seek out and interact with unique natural stimuli, such as offspring. In addition, female rats are also highly responsive to pharmacological stimuli, such as cocaine, and are consistently more motivated to seek out and consume drugs of abuse compared with their male counterparts. Motivated behaviors directed toward natural and drug stimuli are mediated by an extended, overlapping neural circuitry that includes the ventral tegmental area (VTA) and its ascending mesocorticolimbic projections. Limited research has explored how discrete components of this extended circuit participate in females' motivation to seek out natural and/or drug stimuli and the contexts that predict them. Thus, it remains unclear whether intact VTA function is necessary for female motivated behavior to seek contexts repeatedly paired with natural stimuli and/or pharmacological stimuli. In this study, conditioned place preference (CPP) was induced with highly salient natural or drug stimuli attributed with strong incentive-motivational value in each of two paradigms: (1) Postpartum females were conditioned to associate one unique context in the CPP apparatus with young offspring (pups) and a

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second context with a neutral stimulus, and (2) virgin females were conditioned to associate unique contexts with either cocaine (5 mg/kg ip) or saline injections. Immediately before CPP testing, each female received a microinfusion of bupivacaine bilaterally into the VTA to transiently inactivate the region; control subjects received a saline microinfusion. In postpartum females, VTA inactivation prevented pup CPP. Additionally, it disrupted select maternal behaviors, including reduction of anogenital licking of pups, and extended latencies to retrieve all pups to the nest, hover over them, and assume a low crouch position over them, suggesting that in postpartum females, intact VTA function is required for the expression of both pup CPP and motivated pup-directed behaviors. Neither cocaine CPP nor locomotion was affected by VTA inactivation. The researchers concluded that the VTA is differentially involved in the expression of conditioned preference for contexts paired with pups, a salient natural stimulus, and contexts paired with cocaine. Seip KM, Morrell JI. Transient inactivation of the ventral tegmental area selectively disrupts the expression of conditioned place preference for pup- but not cocaine-paired contexts. Behav Neurosci. 2009;123:1325-1338.

Two-Phases of Drug-Induced Microglia Migration May Be Involved in Undesirable Effects of Morphine Therapy

Research conducted with animal behavioral models demonstrate that microglia play a critical role in chronic pain and opioid-induced hyperalgesia. The present study, conducted by Drs. Ryan Horvath and Joyce DeLeo (Dartmouth Medical School), employed an in vitro culture system with rat neurons. These researchers found that morphine rapidly increased microglial migration via a novel interaction between mu-opioid and P2X4 receptors, and that this increase was dependent upon PI3K/Akt pathway activation. In particular, morphine enhanced the migration of primary microglial cells toward adenosine diphosphate in a dose-dependent fashion. Migration was confirmed to be mu-opioid receptor-dependent through the use of selective agonists and antagonists. Furthermore, Iba1 protein, a microglial marker, and P2X4 receptor expression, were significantly increased after 6, 12, 24, and 48 hours of morphine stimulation. Collectively, these results suggest that there are two phases of morphine effects on microglia migration. The initial phase takes place in minutes and involves PI3K/Akt pathway activation. A longer-term phase occurs over hours and involves increased expression of Iba1 and P2X4 receptor proteins. These data implicate microglial migration as an important process in opioid-induced hyperalgesia, and may suggest novel targets for agents that prevent or attenuate morphine's undesirable side effects, including the development of tolerance and hyperalgesia. Additional behavioral pain studies will be needed to assess the functional impact of altering microglial migration on pain and opioid tolerance. Horvath RJ, DeLeo JA. Morphine enhances microglial migration through modulation of P2X4 receptor signaling. J Neurosci. 2009;29(4):998-1005.

The Cognitive Enhancer D-cycloserine Shows Promise for Improving Cue-Exposure Therapy

Augmentation of cue exposure (extinction) therapy with pharmacotherapies may offer an effective strategy to combat cocaine relapse. Kathleen Kantak and her colleagues are studying combined extinction-drug treatment effects with self-administration paradigms in rats and squirrel monkeys. Animals in their studies are trained to self-administer cocaine paired with a brief visual cue. Then lever pressing is extinguished by withholding cocaine injections while maintaining response-contingent presentations of the cue. They evaluated two doses of the glycine partial agonist D-cycloserine (DCS) on rate of extinction and subsequent reacquisition of cocaine self-administration. In rats, pretreatment with the higher dose of DCS, administered half an hour before training enhanced extinction (measured by a decrease in the number of

responses and the latency to reach the extinction criterion). By contrast, neither dose altered extinction responding in monkeys. In both species, pretreatment with the higher dose of DCS before extinction training significantly reduced reacquisition of cocaine self-administration. These results suggest that DCS augments consolidation of extinction learning, to deter reacquisition of cocaine self-administration, in both rats and monkeys. Further, the results suggest that DCS combined with exposure therapy may constitute a rational strategy for the clinical management of cocaine relapse. Nic Dhonnchadha BA, Szalay JJ, Achat-Mendes C, Platt DM, Otto MW, Spealman RD, Kantak KM. D-cycloserine deters reacquisition of cocaine self-administration by augmenting extinction learning. Neuropsychopharmacology. 2010 Jan;35(2):357-67. [Epub].

Relapse to Cocaine Seeking Comprises both Habitual and Goal-Directed Behaviors

Cues present during cocaine self-administration become associated with the drug and if encountered during abstinence, increase the probability of relapse. However, despite much research on human relapse, including the use of animal behavioral models, the way in which relapse-inducing cues are interpreted by the user has remained elusive. Recent theories propose that, after long experience with self administration, drug taking shifts from goal-directed to a habit-like behavior, and therefore cues induce relapse automatically, thus bypassing information processing related to the consequences of relapse. But an alternative hypothesis is that relapse-inducing cues produce an expectation of the drug's consequences, triggering a goal-directed relapse. In animal behavioral experiments, a common procedure used to discriminate between habit and goal-directed responding is reward devaluation: if responding occurs despite devaluation, then the response is considered a habit, or automatic behavior; whereas, if responding is modulated by the current value of the reward, then the response is determined to be goal directed. The current report, by Mark West and colleagues, is the first study to test for goal-directed vs. habitual responding by directly devaluing cocaine reward in a self-administration paradigm. Rats were presented with a tone signaling availability of cocaine, which the rat obtained by pressing a lever. After extensive self-administration training, one group of animals received non-contingent cocaine injections, patterned after their individual sessions of self-administration, followed by a lithium chloride (LiCl) injection on the same day - a method of devaluation similar to that used to induce conditioned taste aversions. Animals in an explicitly unpaired group received cocaine and LiCl on separate days. After several cycles of paired or unpaired injections, all rats were kept abstinent for 30 days and then their propensity to press the lever in the absence of cocaine was assessed. For the first hour of relapse testing, animals were in a self-administration chamber with the lever present, but the tone was not presented. During this time, both groups pressed the lever the same amount, suggesting a habitual component to relapse in the presence of non-discrete cues. However, when the tone cue was turned on for the remainder of the test session, the cocaine-LiCl paired animals showed greatly decreased cue-induced responding relative to unpaired controls, indicating goal-directed behavior. In the last phase of the experiment, the animals were allowed to self-administer again. In this phase, under the influence of cocaine, both groups self-administered the same amount of drug. The study shows that both habitual and goal-directed responding occurs during abstinence and that habitual or goal-directed responding appears to be induced by cues that differ in their correlation with the cocaine infusion. The non-discriminative cues (chamber and lever), which were weakly correlated with drug infusion, failed to evoke a representation of the value of cocaine which leads to habitual behavior. However, the discriminative stimulus (tone), which was nearly perfectly correlated with the infusion, likely evoked a representation of the "value" of the infusion, leading to goal-directed behavior. These data indicate

that abstinent cue-induced responding is multifaceted, comprised of both habitual and goal-directed components. Since goal-directed behavior terminated the habitual component during testing, therapeutic approaches aimed at reducing the perceived value of cocaine in addicted individuals may reduce the capacity of cues to induce relapse. Root DH, Fabbricatore AT, Barker DJ, Ma S, Pawlak AP, West MO. Evidence for habitual and goal-directed behavior following devaluation of cocaine: A multi-faceted interpretation of relapse. PLoS One. 2009 Sep 25;4(9):e7170.

Changes in Dendritic Morphology After Psychostimulant Exposure Correspond to Associative Conditioning Rather than Non-Associative Drug Sensitization

Studies have shown that systemic exposure to amphetamine (AMPH) produces a number of changes in dendritic morphology in the nucleus accumbens (NAcc) and cortical areas of the rat. The current study by Paul Vezina and colleagues was designed to determine whether these changes relate to associative drug conditioning or to non-associative drug sensitization, two forms of behavioral plasticity produced by repeated exposure to AMPH. Non-associative sensitization is reflected by increased locomotor response to AMPH, following previous exposures to the drug, and increased dopamine overflow in the NAcc, whereas associative conditioning is demonstrated by increased locomotor activity in the environment where drug was previously received, but in the absence of the drug. The investigators compared behavioral, neuronal, and morphological consequences of exposing rats either to intraperitoneal (IP) AMPH or AMPH applied to the ventral tegmental area (VTA). Direct infusions into VTA sensitizes AMPH-induced locomotion and NAcc DA overflow, but unlike systemic infusions, this mode of exposure does not produce conditioned locomotion. In the morphological analysis, they found that IP AMPH exposure increased spine density and dendritic length and branching in the NAcc and cortical areas, while exposure to VTA AMPH produced the opposite effects. These findings suggest that the morphological changes seen following IP AMPH exposure reflect associative drug conditioning rather than non-associative drug sensitization. Decreases observed in dendritic measures from the VTA in AMPH exposed rats may reflect the inability of these infusions to induce conditioning, which as with other forms of learning, may require increased synaptic transmission supported by increases in dendritic spines, length, and branching. Singer BF, Tanabe LM, Gorny G, et al. Amphetamine-induced changes in dendritic morphology in rat forebrain correspond to associative drug conditioning rather than nonassociative drug sensitization. Biol Psychiatry. 2009 May 15;65(10):835-840.

Underdeveloped Dendrite Stabilization May Underlie Enhanced Sensitivity to Cocaine in Adolescence

Adolescence is a critical period for the maturation of cortico-striatal neurocircuitry and is characterized by increased novelty seeking behavior and vulnerability to addictive drugs that, with repeated use, are associated with cognitive dysfunction in adulthood. The Abl-related gene (Arg) stabilizes cortical dendritic arbors beginning in adolescence. The present study used Arg knockout mice (arg-/-) as a model of adolescent-onset dendritic simplification. Cortical axons, dendrites, and synapses develop normally in arg-/- mice, but their adult dendrites destabilize and regress. Thus, this study used adult arg-/- mice to test the hypothesis that the transition from dendritic refinement and synaptic pruning that occurs in adolescent prefrontal cortex (PFC), to the dendritic stabilization in adulthood, characterizes a period of vulnerability to cocaine. The arg-/- mice were impaired in a behavioral test of inhibitory control, and this deficit was exacerbated by low-dose cocaine administra-tion. This behavior is similar to that seen in animals with orbital frontal cortex (OFC) lesions, and in rats receiving chronic cocaine. Arg-/- mice were also more

sensitive to the locomotor activating effects of cocaine, as has been observed in adolescent animals. Further studies indicated that the behavioral deficits in the arg-/- mice are linked to reduced dopamine D2 receptor signaling in the OFC. These findings provide evidence that stabilization of dendritic structure beginning in adolescence is critical for the development of adaptive and flexible behavior after cocaine exposure. Because cocaine expo-sure itself disrupts dendritic stabilization in OFC, the results also suggest a mechanism to explain why drug use in adolescence has particularly profound effects on later vulnerability to addiction.Gourley SL, Koleske AJ, Taylor JR. Loss of dendrite stabilization by the Abl-related gene (Arg) kinase regulates behavioral flexibility and sensitivity to cocaine. PNAS USA. 2009 Sep 29;106(39):16859-16864.

Behavioral and Neural Interaction of Natural and Drug Reward Experiences

Natural reward and drugs of abuse converge on the mesolimbic system where drugs of abuse induce a number of well-characterized neuronal alterations that are thought to underlie compulsive drug seeking and vulnerability to relapse. It is currently unclear, however, whether similar alterations in the mesolimbic system occur with repeated exposure to natural rewards. Determining what changes are or are not uniquely induced by drugs of abuse could lead to a better understanding of the mechanisms that lead to addictive behaviors. One way to address such a question is to study natural rewards, such as those involved in mating and other social behaviors that can be introduced in a controlled manner. In this study, Lique Coolen and her colleagues tested the effects of sexual experience in male rats on behavioral sensitization and conditioned place preference associated with d-amphetamine (AMPH), and on alterations in dendritic morphology in nucleus accumbens (NAcc). Repeated sexual behavior induced a sensitized locomotor response to AMPH compared to AMPH's effects on sexually naive control subjects. Sexually experienced animals also formed a conditioned place preference for lower doses of AMPH than sexually naive males. Sexual experience also increased the number of dendritic and spines in the NAcc core and shell. Interestingly, this sensitization effect was apparent the first day after the last mating session and lasted for at least 28 days, while the conditioned place preference and dendritic alterations required a period of abstinence of 7-10 days. This delayed effect is similar to the period of abstinence required for the emergence of behavioral and neuronal changes induced by drugs of abuse and suggests that loss of reward may contribute to neuroplasticity in this system. The authors hypothesize that abstinence from natural rewards may induce a generalized state of increased reward seeking and vulnerability to addictive substances. The findings suggest that some alterations in the mesolimbic system are common following the experience of natural and drug reward and may play a role in general reward conditioning. Pitchers KK, Balfour ME, Lehman MN, Richtand NM, Yu L, Coolen LM. Neuroplasticity in the mesolimbic system induced by natural reward and subsequent reward abstinence. Biol Psychiatry. 2009 Dec 14. [Epub ahead of print]

Environmental Enrichment Enhances Nucleus Accumbens Signaling of Reward Predictive Cues

Many environmental influences have been identified as risk factors for drug abuse and addiction. Animal models are useful for studying the neurobiological mechanisms that translate environmental influences into risk or resilience for drug abuse behavior. Rats reared in enriched environments (EC) are more responsive to changing contingencies and demonstrate more adaptive learning than those reared in isolated environments (IC). While much is known about neuroanatomical differences between EC and IC reared animals, Dr. George Rebec and colleagues have recorded electrophysiological activity from single cells in the nucleus accumbens (NAS) of EC versus IC reared rats, to

characterize the functional changes responsible for these behavioral differences. In an appetitive learning paradigm, rats are trained to respond to a reward predictive cue by nosepoking in the correct hole of the chamber to receive sucrose. Over three training sessions, EC animals acquired the discrimination faster than IC rats, with significant group differences apparent on the third session. However, even before behavioral differences emerged, a significantly greater proportion of NAS core neurons in the EC group responded to motor aspects of the discrimination task; that is, corresponding to correct nosepoke responses and to sucrose consumption. Thus, it appears that enhanced neuronal responses in EC animals may underlie accelerated learning in this appetitive task. Moreover, the patterning of cellular responses in EC rats was also significantly different during the third session: At the time EC animals demonstrated increased accuracy of the discrimination response, recording from NAS core cells revealed a significantly greater proportion of excitations (increases above baseline firing rates) triggered by onset of an important sensory aspect of discrimination learning - the predictive cue for correct nosepoking, in EC than in IC rats. The authors infer that EC enhances core reactivity to both motor and sensory aspects of appetitive learning and a shift in core signaling from motor response to reward predictive cues over training is responsible for accelerated learning. Wood DA, Rebec GV. Environmental enrichment alters neuronal processing in the nucleus accumbens core during appetitive conditioning. Brain Res. 2009; 1259:59-67.

Escalation of Cocaine Intake is Related to Impulsivity in Female Rats

Dr. Marilyn Carroll has been studying individual differences in impulsivity as a predictor of drug self-administration and relapse. In a recent study, she extends these studies to examine a role for impulsivity in escalated drug intake seen when cocaine is made available during extended access conditions. Whereas animals provided with access to drug for 2 h per day (Short Access, SA) demonstrate stable intake over many days, those provided with access for 6 h per day (Long Access, LA) escalate their intake over days. Impulsivity is a multidimensional construct and can be assessed in different behavioral paradigms. In the present study, Dr. Carroll tested female rats selected for high (HI) or low impulsivity (LI) on a delay-discounting task that measures impulsive choice. In this task, animals are presented with two levers that produce either a small-immediate reinforcer, or a large-delayed reinforcer, contingent upon lever presses. HI and LI rats were trained to self-administer cocaine on a FR1 schedule, followed by progressive ratio (PR) testing to determine the animal's motivation for the drug. After PR testing, all rats were given daily 2hr SA self-administration sessions until stable and then switched to LA for 21 days. Then animals were returned to the SA testing, and the PR assessment was repeated. While HI and LI groups did not differ on acquisition (a rapid acquisition that does not allow for usual HI versus LI differences), or SA intake, HI rats infused significantly more cocaine over sessions 17-21 of LA than LI animals, and significantly exceeded their own initial intake on this LA schedule (sessions 7-21significantly greater than sessions 1-3 for HI only). Moreover, HI rats exposed to LA conditions continued to take significantly more drug than LI rats when switched back to SA. Comparisons on PR responding for 0.2, 0.8 and 3.2 mg/kg cocaine revealed no significant differences between HI and LI rats on the rate of infusions for any dose, either before or after LA experience. These results demonstrate that individual differences in impulsive choice may confer vulnerability for the development of uncontrollable drug taking in female abusers, who are prone to develop binge-like patterns of cocaine intake. However, results from PR testing suggest that impulsive choice may not influence reward sensitivity or hedonic tolerance, since there were no group differences on PR responding. Thus, the mechanism for this enhanced vulnerability remains to be determined. Anker JJ, Perry JL, Gliddon LA, Carroll ME. Impulsivity predicts the escalation of cocaine self-administration in rats.

Pharmacol Biochem Beh. 2009; 93:343-346.

Different Dimensions of Affective Responding Predict Cocaine Intake in Adolescent Versus Adult Rats

Adolescents who begin abuse at a younger age are more likely to escalate to addiction and dependence than those who begin later. Animal studies reveal differences in vulnerability as a function of age, and a differential sensitivity to both rewarding and aversive properties of many drugs of abuse. Drs. Cynthia Kuhn, Nicole Schramm-Sapyta and their colleagues have been investigating individual differences in adolescent rats that predict addiction-like behaviors. Recently they have examined choice behavior for animals provided with cocaine in drinking solutions (combined as a saccharin+cocaine mixture) versus the natural reward, saccharin (sacc). Choice behavior is a powerful and ecologically relevant metric in the study of addiction because drugs of abuse are often prioritized above other rewards, such as family, health and safety. Prior to measuring drug intake, rats were tested for individual differences in response to novelty and in an elevated plus measure of anxiety. They found that adolescent rats (Ado) drank more of a sacc+cocaine solution than their adult (Adu) counterparts, and more of the sacc+drug mixture when a second bottle of sacc was offered in a two bottle choice test. Furthermore, while there were no age differences in ambulation or open arm entries from individual differences testing, regression analyses were conducted to examine the relationships between these behavioral traits and drug consumption. Locomotion in a novel environment predicted intake of the sacc+drug solution for Ado animals, but not for Adu. The novelty response also predicted greater cocaine intake from a sacc+drug mixture when a second bottle of sacc alone was presented in a choice situation, but again for Ado animals only. By contrast, for Adu rats, regression analyses revealed that animals spending a lower percentage of time on open arms of the maze (thus, more "anxious" rats) consumed higher cocaine doses in the choice (sacc+drug versus sacc alone) situation. While these findings may be specific for the consumption model employed by the present group of investigators and should be further examined in different drug intake paradigms, they suggest that different behavioral traits may serve as vulnerability phenotypes in different stages of development. Walker QD, Schramm-Sapyta NL, Caster JM, Waller, ST, Brooks MP, Kuhn CM. Novelty-induced locomotion is positively associated with cocaine ingestion in adolescent rats; anxiety is correlated in adults. Pharmacol Biochem Beh. 2009; 91:398-408.

An Animal Model of Sleep Deprivation: Effects on Cocaine Intake

During drug abstinence human drug abusers have difficulty sleeping and report insomnia. Sleep deprivation can also lead to relapse. Until now, few studies have studied the effect of sleep deprivation on the rewarding effects of drugs of abuse. Dr. Sue Grigson and her colleagues at Pennsylvania State University have examined the effects of 0, 4 or 8 h sleep deprivation in studies of i.v. cocaine administration in the rat. Animals trained to self-administer this psychostimulant were grouped on the basis of their intake patterns: Low (LI) and high intake (HI) animals. HI rats made more total responses, more responses on an active lever to infuse drug, and increased their response rates as trials progressed. They were also faster to take the first infusion when placed in the self-administration chambers. Both groups responded on an active lever during extinction when drug was removed from the infusion pump. As others have reported, HI drug histories predicted greater reinstatement when animals were tested for drug-induced relapse by delivering a single, passive infusion of cocaine during extinction (a model of human relapse). Comparisons between sleep deprivation (SD) conditions revealed that SD had no effect on HI rats, but abolished reinstatement in LI animals. SD was also examined for effects on progressive ratio (PR) responding, to determine if SD

effects an animal's willingness to "work" to receive cocaine (thus, perceived value). While HI animals had higher break points on the PR schedule, thus, making a greater number of responses to receive drug, SD conditions were without effect on this measure. SD did affect inter-infusion intervals on the PR schedule, however, for both groups (i.e., increasing the rate at which rats self-administer drug). When comparing responding on the active (drug-associated) and inactive lever in this paradigm, investigators found that low drug-takers distributed an equal number of responses on active versus inactive levers during PR testing with 0 h of SD. By contrast, 4 and 8 h of SD in the LI group enhanced "goal directed" behavior in this PR procedure. The researchers infer that motivation for drug was high in the HI group and the motivation induced by another deprivation state could not overcome this drive. LI groups, by contrast, were affected by motivation to sleep during drug-primed reinstatement after 4 and 8 h of SD. These results reveal an increased drive to respond for drug in LI animals, who made greater responses on the drug-correct lever after an imposed period of SD, and in both groups with increased infusion rates under PR testing. Additional studies are needed to more precisely characterize SD effects on the motivation to seek and take drugs of abuse, at various stage of an addiction cycle. Puhl MD, Fang J, Grigson PS. Acute sleep deprivation increases the rate and efficiency of cocaine self-administration, but not the perceived value of cocaine reward in rats. Pharmacol Biochem Beh. 2009; 94:262-270.

A Role for Hormones in Subjective Drug Affects and Potential Addictions Pharmacotherapy

In a recent review, Dr. Nancy Mello from McLean Hospital summarizes research on subjective responses to cigarette smoking and concomitant changes in HPA-axis hormone levels using a rapid sampling procedure to collect measures at 2 minute intervals for 20 minutes following smoking and at 25, 30, 40, 50, 50, 80, 100 and 120 minutes. Smoking a single cigarette was associated with increases in both cortisol and DHEA. Results from previous studies reveal higher basal levels of these hormones in smokers than nonsmokers, and a relation between decreased cortisol on the first day of cigarette cessation and relapse during a subsequent week. DHEA is an adrenal androgen precursor of testosterone and is believed to improve feelings of well being and sexuality in the elderly, although the evidence is conflicting. Although other HPA axis hormone levels fluctuated over smoking one, two or three cigarettes in succession, peak levels of DHEA did not differ significantly across successive cigarettes, and ratings of cigarette "craving" increased as DHEA and plasma nicotine levels decreased at the end of each smoking interval. Interestingly, in prior research, Dr. Mello has shown that i.v. cocaine also increases levels of this hormone in blood, suggesting a relationship to abuse-related subjective effects of both drugs. In prior studies from McLean, a significant temporal covariance between cocaine's positive subjective effects and activation of the HPA axis has been observed in cocaine abusers. Thus, Dr. Mello and her colleagues have proposed that the hormonal milieu may be an important modulator of the reinforcing effects of drugs. Given research showing that DHEA treatment improves mood and alleviates depression, Dr. Mello further speculates that DHEA may contribute to the subjective effects of nicotine, including mood elevation and reduced anxiety and depression. She points out that DHEA has been suggested as a potential medication for smoking cessation. Data from her studies with cocaine support this possibility and suggest that DHEA's potential as an addiction medication may not be limited to smoking cessation. This line of research contributes significantly to understanding of the neurobiological effects of drugs of abuse that may induce their addiction, in part, through activation of the HPA axis. Whether these hormones might play a differential role in addiction, and addiction treatment, in male versus female drug abusers remains to be investigated. Mello, NK. Hormones, nicotine, and cocaine: Clinical studies. Hormones and Behavior.

[Epub ahead of print], 2009.

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

Research Findings - Brain and Behavioral Development Research

Altered White Matter Microstructure in Adolescent Substance Users

Chronic marijuana use during adolescence is frequently comorbid with heavy alcohol consumption and associated with CNS alterations, yet the influence of early cannabis and alcohol use on microstructural white matter integrity is unclear. Building on evidence that cannabinoid receptors are present in myelin precursors and affect glial cell processing, and that excessive ethanol exposure is associated with persistently impaired myelination, Dr. Sunita Bava and her colleagues used diffusion tensor imaging (DTI) to characterize white matter integrity in heavy substance using and non-using adolescents. The investigators evaluated 36 marijuana and alcohol-using (MJ+ALC) adolescents (ages 16-19) and 36 demographically similar non-using controls with DTI. The diffusion parameters fractional anisotropy (FA) and mean diffusivity (MD) were subjected to whole-brain voxelwise group comparisons using tract-based spatial statistics. MJ+ALC teens had significantly lower FA than controls in 10 regions, including left superior longitudinal fasciculus (SLF), left postcentral gyrus, bilateral crus cerebri, and inferior frontal and temporal white matter tracts. These diminutions occurred in the context of increased FA in right occipital, internal capsule, and SLF regions. Changes in MD were less distributed, but increased MD was evident in the right occipital lobe, whereas the left inferior longitudinal fasciculus showed lower MD in MJ+ALC users. Findings suggest that fronto-parietal circuitry may be particularly impacted in adolescent users of the most prevalent intoxicants: marijuana and alcohol. Disruptions to white matter in this young group could indicate aberrant axonal and myelin maturation with resultant compromise of fiber integrity. Findings of increased anisotropic diffusion in alternate brain regions suggest possible neuroadaptive processes and can be examined in future studies of connectivity to determine how aberrancies in specific tracts might influence efficient cognitive processing. Bava S, Frank LR, McQueeny T, et al. Altered white matter microstructure in adolescent substance users. Psychiatry Res. 2009 Sept 30;173(3):228-237.

Prefrontal Cortex Morphometry in Abstinent Adolescent Marijuana Users: Subtle Gender Effects

Adult human studies suggest frontal dysfunction associated with chronic marijuana (MJ) use, but due to continued neuromaturation, adult studies may not generalize to adolescents. Dr. Krista Medina and her colleagues aimed to replicate this finding in adolescents by examining prefrontal cortex (PFC) morphometry in chronic MJ-using adolescents following 1 month of monitored abstinence. Data were collected from MJ users (n = 16) and controls (n = 16)

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aged 16-18. Extensive exclusionary criteria included co-morbid psychiatric and neurologic disorders. Substance use and anatomical measures were collected after 28 days of monitored abstinence. PFC volumes were ascertained from manual tracing by reliable raters on high-resolution magnetic resonance images. After controlling for lifetime alcohol use, gender and intracranial volume, MJ users did not differ from controls in PFC volume. However, marginal group-by-gender interactions were observed ($P < 0.09$): Female MJ users demonstrated comparatively larger PFC volumes while male MJ users had smaller volumes compared with same-gender controls. Further, group status and total PFC volume interacted in predicting executive functioning ($P < 0.05$). Among MJ users, smaller PFC total volume was associated with better executive functioning while the opposite pattern was seen among the controls. These preliminary results indicate that gender may moderate the relationship between MJ use and PFC morphometry. Given the relationship between larger PFC total volumes and poorer executive functioning among MJ users, female MJ users may be at increased risk for neurocognitive consequences. Future research will measure PFC gray and white matter separately and follow boys and girls over adolescence to examine the influence of MJ use on neurodevelopment. Medina KL, McQueeny T, Nagel BJ, Hanson KL, Yang TT, Tapert SF. Prefrontal cortex morphometry in abstinent adolescent marijuana users: Subtle gender effects. Addiction Biol. 2009 Sept;14(4):457-468.

Adolescent Engagement in Dangerous Behaviors is Associated with Increased White Matter Maturity of Frontal Cortex

Myelination of white matter in the brain continues throughout adolescence and early adulthood. This cortical immaturity has been suggested as a potential cause of dangerous and impulsive behaviors in adolescence. Dr. Gregory Berns and his colleagues examined this hypothesis in a group of healthy adolescents, age 12-18 ($N = 91$), who underwent diffusion tensor imaging (DTI) to delineate cortical white matter tracts. As a measure of real-world risk taking, participants completed the Adolescent Risk Questionnaire (ARQ) which measures engagement in dangerous activities. After adjusting for age-related changes in both DTI and ARQ, engagement in dangerous behaviors was found to be positively correlated with fractional anisotropy and negatively correlated with transverse diffusivity in frontal white matter tracts, indicative of increased myelination and/or density of fibers (ages 14-18, $N = 60$). The direction of correlation suggests that rather than having immature cortices, adolescents who engage in dangerous activities have frontal white matter tracts that are more adult in form than their more conservative peers. Berns GS, Moore S, Capra CM. Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. PloS One 2009 August 26;4(8):e6773.

Infant Neurobehavioral Dysregulation: Behavior Problems in Children with Prenatal Substance Exposure

In this study Dr. Barry Lester and his colleagues from the Maternal Lifestyles Study tested a developmental model of neurobehavioral dysregulation relating prenatal substance exposure to behavior problems at age 7. The sample included 360 cocaine-exposed and 480 unexposed children from lower to lower middle class families of which 78% were black. Structural equation modeling was used to test models whereby prenatal exposure to cocaine and other substances would result in neurobehavioral dysregulation in infancy, which would predict externalizing and internalizing behavior problems in early childhood. Structural equation models were developed for individual and combined parent and teacher report for externalizing, internalizing, and total problem scores on the Child Behavior Checklist. The paths in the models indicate that there are direct effects of prenatal substance exposure on 7-year behavior problems as well as indirect effects, including neurobehavioral

dysregulation. Prenatal substance exposure affects behavior problems at age 7 through two mechanisms. The direct pathway is consistent with a teratogenic effect. Indirect pathways suggest cascading effects whereby prenatal substance exposure results in neurobehavioral dysregulation manifesting as deviations in later behavioral expression. Developmental models provide an understanding of pathways that describe how prenatal substance exposure affects child outcome and have significant implications for early identification and prevention. Lester BM, Bagner DM, Liu J, et al. Infant neurobehavioral dysregulation: Behavior problems in children with prenatal substance exposure. Pediatrics. 2009 Nov;124(5):1355-1362.

Neonatal Neurobehavior Predicts Medical and Behavioral Outcomes

This study examined the NICU Network Neurobehavioral Scale (NNNS) as a predictor of negative medical and behavioral findings at 1 month to 4.5 years of age. The sample included 1248 mother-infant dyads (42% born at <37 weeks' gestational age [GA]) who were participating in the Maternal Lifestyles Study (MLS), a longitudinal study of the effects of prenatal substance exposure on child development. Mothers were recruited at four urban university-based centers and were mostly black and on public assistance. At 1 month of age, infants were tested with the NNNS. Latent profile analysis was conducted on NNNS summary scales to identify discrete behavioral profiles. The validity of the NNNS was examined by using logistic regression to predict prenatal drug exposure and medical and developmental outcomes through 4.5 years of age including adjustment for GA and socioeconomic status. Five discrete behavioral profiles were reliably identified; the most extreme negative profile was found in 5.8% of the infants. The profiles showed statistically significant associations with prenatal drug exposure; GA and birth weight; head ultrasound; neurologic and brain disease findings; and abnormal scores on measures of behavior problems, school readiness, and IQ through 4.5 years of age. The NNNS may be useful to identify infant behavioral needs to be targeted in well-infant pediatric care, as well as for referrals to community-based early intervention services. Liu J, Bann C, Lester B, et al. Neonatal neurobehavior predicts medical and behavioral outcome. Pediatrics. 2009 Dec 7. [Epub ahead of print].

Neurobehavioral Assessment Predicts Motor Outcome in Preterm Infants

This study examined whether the Neonatal Intensive Care Unit Network Neurobehavior Scales (NNNS) at 44 weeks predict motor outcome at 2 years in preterm infants from the Maternal Lifestyles Study (MLS). Data were collected on all preterm infants (<36 weeks) in the MLS who underwent an NNNS at 44 weeks (n = 395) and neurologic examination at 12 to 36 months or Bayley Psychomotor Development Index (PDI) at 24 months (n = 270). Logistic regression analyzed NNNS summary scores associated with cerebral palsy (CP) or PDI <70, while controlling for birth weight

Prenatal Cocaine Exposure and Physiological Regulation at 13 Months of Age

This study examined the association between prenatal cocaine exposure (PCE) and autonomic regulation at 13 months of age. Measures of respiratory sinus arrhythmia (RSA) were obtained from 156 (79 exposed, and 77 nonexposed) infants during baseline and during tasks designed to elicit positive (PA) and negative affect (NA). There was a significant suppression of RSA during the negative affect task for nonexposed infants but not for exposed infants. Maternal symptoms of depression or anxiety (MDA) did not mediate this association. However, gender and MDA did moderate this association such that

exposed boys and exposed infants whose mothers had higher levels of MDA had an increase in RSA during a task designed to elicit NA rather than the typical pattern of RSA suppression. These results suggest that there are several possible pathways from PCE to physiological dysregulation during late infancy. Schuetze P, Eiden RD, Danielewicz S. The association between prenatal cocaine exposure and physiological regulation at 13 months of age. J Child Psychol Psychiatry. 2009 Nov;50(11):1401-1409.

Maternal Report of Sleep Problems in Children with Prenatal Polydrug Exposure

Sleep data were collected by maternal report in a prospective longitudinal follow up of cocaine-exposed and unexposed children. There were 139 participants: 23 with no prenatal drug exposure, 55 exposed to cocaine alone or in combination with other drugs, and 61 exposed to drugs other than cocaine. Characteristics differed between exposure groups including birth size, caretaker changes, maternal socioeconomic status, and postnatal drug use. Compared to those with no drug exposure, children with prenatal drug exposure other than cocaine experienced greater sleep problems according to mother's report. Prenatal nicotine exposure was a unique predictor of sleep problems. Early sleep problems predicted later sleep problems. Together, these preliminary findings suggest possible neurotoxic sleep effects that persist over time. Larger studies, however, need to be conducted that better control for potential postnatal confounding factors. Stone KC, High PC, Miller-Loncar CL, Lagasse LL, Lester BM. Longitudinal study of maternal report of sleep problems in children with prenatal exposure to cocaine and other drugs. Behav Sleep Med. 2009;7(4):196-207.

Reward-Related Brain Function and Sleep in Pre/Early Pubertal and Mid/Late Pubertal Adolescents

The onset of adolescence is a time of dramatic changes, including changes in sleep, and a time of new health concerns related to increases in risk-taking, sensation seeking, depression, substance use, and accidents. As part of a larger study examining puberty-specific changes in adolescents' reward-related brain function, Dr. Stephanie Holm and her colleagues at the University of Pittsburgh examined the relationship between functional neuroimaging measures of reward and measures of sleep. A total of 58 healthy participants 11-13 years of age completed a functional magnetic resonance imaging scan using a guessing task with monetary rewards and 4 days of at-home actigraphy and self-reported sleep ratings. Sleep variables included actigraph measures of mean weekend minutes asleep, sleep onset time, and sleep offset time, as well as self-reported sleep quality. During reward anticipation, less activation in the caudate nuclues was associated with fewer minutes asleep, later sleep onset time, and lower sleep quality. During reward outcome, less caudate activation was associated with later sleep onset time, earlier sleep offset time, and lower sleep quality. It has been hypothesized that adolescents' low reactivity in reward-related brain areas could lead to compensatory increases in reward-driven behavior. This study's findings suggest that sleep could contribute to such behavior. Because decreased sleep has been associated with risky behavior and negative mood, these findings raise concerns about a negative spiral whereby the effects of puberty and sleep deprivation may have synergistic effects on reward processing, contributing to adolescent behavioral and emotional health problems. Holm SM, Forbes EE, Ryan ND, Phillips ML, Tarr JA, Dahl RE. Reward-related brain function and sleep in pre/early pubertal and mid/late pubertal adolescents. J Adolesc Health 2009 Oct;45(4):319-320.

Smoking in Pregnancy and Disruptive Behaviour in 3-year-old

Boys and Girls

Maternal smoking during pregnancy has been consistently associated with disruptive behaviour in male offspring; however, results for girls are inconsistent and little is known about emergent patterns in young children. Additionally, it is unclear whether maternal smoking is independently associated in offspring with hyperactivity-inattention or only when it co-occurs with conduct problems. Further, few studies have controlled for a broad range of maternal psychosocial problems. Associations between self-reported smoking in pregnancy and maternal reports of externalizing behaviour were analyzed in more than 13,000 3-year-old boys and girls in the UK Millennium Cohort Study. Conduct and hyperactivity-inattention problems were assessed using the Strength and Difficulties Questionnaire. Boys whose mothers persistently smoked throughout pregnancy were at significant risk of conduct and hyperactivity-inattention problems compared with sons of non-smokers: the effect was stronger for heavy smokers. After excluding children with co-occurring problems, conduct-only problems remained a significant risk for sons of heavy smokers; and hyperactivity-inattention only for sons of light or heavy smokers. Daughters of light or heavy smokers were at significant risk of conduct-only problems. Relative to non-smokers, daughters of pregnancy quitters had significantly reduced odds of having conduct or co-occurring problems, although only 79 and 20 girls met these criteria, respectively. Associations between maternal smoking during pregnancy and disruptive behaviour in 3-year-old children vary by sex, smoking status and whether or not conduct or hyperactivity problems occur together or separately. Hutchinson J, Pickett E, Green J, Wakschlag LS. Smoking in pregnancy and disruptive behaviour in 3-year-old boys and girls: An analysis of the UK Millennium Cohort Study. J Epidemiol Community Health 2010 Jan;64(1):82-88.

Prenatal Alcohol Exposure and Interhemispheric Transfer of Tactile Information

Previous research has demonstrated that heavy prenatal alcohol exposure affects the size and shape of the corpus callosum (CC) and compromises interhemispheric transfer of information. The aim of this study was to confirm the previous reports of poorer performance on a finger localization test (FLT) of interhemispheric transfer in a cohort of heavily exposed children and to extend these findings to a cohort of moderately exposed young adults. In Study 1, the FLT was administered to 40 heavily exposed and 23 nonexposed children from the Cape Coloured community of Cape Town, South Africa, who were evaluated for fetal alcohol syndrome (FAS) dysmorphology and growth. Anatomical images of the CC were obtained using structural MRI on a subset of these children. In Study 2, the FLT was administered to a cohort of 85 moderate-to-heavily exposed young adults participating in a 19-year follow-up assessment of the Detroit Prenatal Alcohol Exposure cohort, whose alcohol exposure had been ascertained prospectively during gestation. In Study 1, children with FAS showed more transfer-related errors than controls after adjustment for confounding, and increased transfer-related errors were associated with volume reductions in the isthmus and splenium of the CC. In Study 2, transfer-related errors were associated with quantity of alcohol consumed per occasion during pregnancy. More errors were made if the mother reported binge drinking (> or =5 standard drinks) during pregnancy than if she drank regularly (M > or = 1 drink/day) without binge drinking. These findings confirm a previous report of impaired interhemispheric transfer of tactile information in children heavily exposed to alcohol in utero and extend these findings to show that these deficits are also seen in more moderately exposed individuals, particularly those exposed to binge-like pregnancy drinking. Dodge NC, Jacobson JL, Molteno CD, et al. Prenatal alcohol exposure and interhemispheric transfer of tactile information: Detroit and Cape Town findings. Alcohol Clin Exp Res. 2009 Sep;33(9):1628-1637.

Identification of Prenatal Amphetamines Exposure by Maternal Interview and Meconium Toxicology

The Infant Development Environment and Lifestyle study is investigating the effects of prenatal methamphetamine (MAMP) exposure on infant and child development. Potential concurrent exposure to cannabis and tobacco also are evaluated. Maternal self-reported drug use and/or meconium toxicology results defined drug exposure status. It is unclear how the frequency, duration, and magnitude of maternal MAMP exposure affect qualitative and quantitative meconium results. Interviews regarding maternal drug use were collected shortly after birth; meconium specimens were screened for amphetamines, cannabis, and cotinine by immunoassay and confirmed by gas chromatography mass spectrometry. The majority of MAMP- and cannabis-exposed infants were identified by maternal interview alone. Meconium tests were more likely to be positive if the mother reported MAMP and cannabis use, particularly in the third trimester. Less than half of immunoassay-positive amphetamines (31.0%) and cannabis (17.9%) meconium results were confirmed by gas chromatography mass spectrometry. Tobacco exposure was equally detected by immunoassay cotinine screening and maternal report. Meconium concentrations did not correlate with maternal self-report status or trimester of use or frequency or route of MAMP use. Maternal self-report was more sensitive than meconium testing for identifying MAMP and cannabis-exposed neonates; however, the timing of drug exposure may influence meconium toxicology results. Most women stopped MAMP and cannabis use before the third trimester. In the first trimester, meconium has not yet formed, and based on our recent results for opiates and cocaine, drug use in the second trimester appears to be poorly reflected in meconium. Low confirmation rates in meconium reinforce the need for confirmatory testing following positive screening results and additional research to identify alternative biomarkers. Gray TR, LaGasse LL, Smith LM, et al. Identification of prenatal amphetamines exposure by maternal interview and meconium toxicology in the Infant Development, Environment and Lifestyle (IDEAL) study. Ther Drug Monit. 2009 Dec;31(6):769-775.

Amphetamine and Methamphetamine in Umbilical Cord

The use of meconium as a drug-screening matrix for newborns has been the gold standard of care for the past two decades. A recent study using matched pairs of meconium and umbilical cord demonstrated a high degree of agreement. The use of liquid chromatography-tandem mass spectrometry as a means to confirm amphetamines presumptive positive umbilical cord specimens for amphetamine and methamphetamine is described here for the first time. The limit of detection for both compounds was 0.2 ng/g. The limit of quantitation for both compounds was 0.6 ng/g. The assay was linear for both compounds up to 100 ng/g. Jones J, Rios R, Jones M, Lewis D, Plate C. Determination of amphetamine and methamphetamine in umbilical cord using liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2009 Nov 1;877(29):3701-3706.

Precuneus Shares Intrinsic Functional Architecture in Humans and Monkeys

Evidence from macaque monkey tracing studies suggests connectivity-based subdivisions within the precuneus, offering predictions for similar subdivisions in the human. This study describes functional connectivity analyses of this region using resting-state functional MRI data collected from both humans and macaque monkeys. Three distinct patterns of functional connectivity were demonstrated within the precuneus of both species, with each subdivision suggesting a discrete functional role: (i) the anterior precuneus, functionally connected with the superior parietal cortex, paracentral lobule, and motor

cortex, suggesting a sensorimotor region; (ii) the central precuneus, functionally connected to the dorsolateral prefrontal, dorsomedial prefrontal, and multimodal lateral inferior parietal cortex, suggesting a cognitive/associative region; and (iii) the posterior precuneus, displaying functional connectivity with adjacent visual cortical regions. These functional connectivity patterns were differentiated from the more ventral networks associated with the posterior cingulate, which connected with limbic structures such as the medial temporal cortex, dorsal and ventromedial prefrontal regions, posterior lateral inferior parietal regions, and the lateral temporal cortex. These findings are consistent with predictions from anatomical tracer studies in the monkey, and provide support that resting-state functional connectivity (RSFC) may in part reflect underlying anatomy. These subdivisions within the precuneus suggest that neuroimaging studies will benefit from treating this region as anatomically (and thus functionally) heterogeneous. Furthermore, the consistency between functional connectivity networks in monkeys and humans provides support for RSFC as a viable tool for addressing cross-species comparisons of functional neuroanatomy. Margulies DS, Vincent JL, Kelly C, et al. Precuneus shares intrinsic functional architecture in humans and monkeys. Proc Natl Acad Sci USA. 2009 Nov 24;106(47):20069-20074.

Exclusion and Micro-Rejection: ERP Response Predicts Mitigated Distress

Dr. Mayes and her colleagues studied time-based neural activity with event-related potentials (ERPs) in young adults during a computer-simulated ball-toss game. Experiencing fair play initially, participants were ultimately excluded by other players. Dense-array ERPs showed time-dependent associations between slow-wave activity (580-900 ms) in left prefrontal/medial frontal cortical regions for exclusion events and self-reported distress. More subtle 'micro-rejections' during fair play showed a similar distress to ERP association (420-580 ms). In both cases, greater positive amplitude neural activity was associated with less post-exclusion distress. These findings suggest that rapidly occurring neural responses to social exclusion events are linked to individual differences in ostracism-related distress. Relations emerged even during fair play, providing a window into the neural basis of more subtle social-cognitive perceptual processes. Crowley MJ, Wu J, McCarty ER, David DH, Bailey CA, Mayes LC. Exclusion and micro-rejection: Event-related potential response predicts mitigated distress. Neuroreport. 2009 Nov 25;20(17):1518-1522.

Item Response Theory Analysis of Lifetime Cannabis-Use Disorder Symptom Severity in an American Indian Community

Dr. David Gilder and his colleagues used Item Response Theory to assess Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), lifetime cannabis-use disorder (CUD) symptom severity and its relationship to first cannabis use before age 15 years, male gender, and childhood conduct disorder in an American Indian community sample. The Semi-Structured Assessment for the Genetics of Alcoholism was used to determine demographic information, age at first use, and DSM-III-R childhood conduct disorder and lifetime CUD symptoms in a community sample of 349 American Indian participants who had used cannabis at least 21 times in a single year. Two-parameter Item Response Theory models generated marginal maximum likelihood estimates for discrimination (a) and threshold (b) parameters for nine DSM-III-R CUD symptoms along an underlying latent CUD severity continuum. Differential Item Functioning (DIF) analysis was used to assess for differences in symptom severity in groups defined by presence versus absence of age at first use before 15 years, male gender, and childhood conduct disorder. CUD symptoms of "use in larger amounts or over longer periods of time," "activities given up," and "role failure" were the most severe. All CUD symptoms fell on the moderate portion of the severity continuum.

"Time spent" was more severe in individuals who first used cannabis after age 15 years, "hazardous use" was more severe in females, and "use in larger amounts or over longer periods of time" was more severe in individuals with co-morbid childhood conduct disorder. Specific risk factors for the development of lifetime CUD are associated with increased severity of several CUD symptoms in this high-risk group. Gilder DA, Lau P, Ehlers, CL. Item response theory analysis of lifetime cannabis-use disorder symptom severity in an American Indian community. J Stud Alcohol Drugs. 2009 Nov;70(6):839-849.

Predictors of School Dropout among Adolescents in Puerto Rico

This study aims to understand the circumstances associated with school dropout in a cohort of Puerto Rican adolescents. Information related to school dropout was obtained from adolescents and their parents employing a self-administered and a face-to-face interview protocol. Prediction of school dropout was assessed through adolescent characteristics, family background, school experiences and behaviors. During the second follow-up, two years after the baseline assessment, approximately 6.2% of the adolescents reported dropping out from school. Logistic regression analysis indicates that older adolescents, whose mothers used drugs during pregnancy, who reported high rates of absenteeism, high school grade retention, and attended school where teachers were attacked or wounded by students were more likely to drop out of school. These findings emphasize the need to further understand the effects of different elements of adolescents' environment such as family and school. It has been posited that dropping out of school is a process whose characteristics can be detected long before it occurs. The fact that students who drop out are more likely to report skipping classes and grade retention can be relevant elements in prevention and early intervention for teachers and other school personnel. Calder—n JM, Robles RR, Reyes JC, Matos TD, Negr—n JL, Cruz MA. Predictors of school dropout among adolescents in Puerto Rico. P R Health Science J 2009 Dec;28(4):307-312.

Postpartum Antiretroviral Drug Resistance in HIV-1-Infected Women Receiving Pregnancy-Limited Antiretroviral Therapy

Pregnancy-limited antiretroviral therapy (PLAT) drastically reduces HIV-1 transmission to the newborn, but may select for antiretroviral drug resistance mutations in mothers. The Women and Infants Transmission Study (WITS) evaluated antiretroviral-naive, HIV-1-infected pregnant women who received PLAT between 1998 and 2005, and had 2-month or 6-month postpartum plasma samples available with HIV-1 RNA levels more than 500 copies/ml. Postpartum drug resistance mutation rates were assessed blindly using population sequencing and allele-specific PCR (ASPCR) of the M184V, K103N and D30N mutations. Factors associated with selection of drug resistance mutations were investigated. One hundred and forty-six women were included. All women received zidovudine and lamivudine during pregnancy; 76% also received nelfinavir and 8.2% nevirapine. Resistance data were available from 114 women (78%). Postpartum rates of single-class, dual-class, and triple-class resistance were, respectively, 43, 6.1 and 0% (63.2, 10.5 and 1.7% by ASPCR). In women receiving dual or triple PLAT, respectively, postpartum M184V/I rates were 65% (95% by ASPCR) and 28.7% (51.6% by ASPCR), respectively. Postpartum nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance rates among women receiving nevirapine were 25% for K103N (37.5% by ASPCR) and 12.5% for Y188C. Protease inhibitor resistance rates in women receiving nelfinavir were 1.1% for D30N (1.1% by ASPCR) and 1.1% for L90M. Dual versus triple PLAT and prolonged zidovudine exposure were associated with selection of M184V. Nevirapine use and length of zidovudine and lamivudine exposure were associated with selection of K103N. PLAT is associated with frequent selection of resistance to drugs with low-genetic barrier. Triple-drug PLAT decreases the odds for M184V selection. Routine

postpartum genotypic resistance testing may be useful to guide future treatment decisions in mothers. Paredes R, Cheng I, Kuritzkes DR, Tuomala RE, Women and Infants Transmission Study (WITS) Group. Postpartum antiretroviral drug resistance in HIV-1-infected women receiving pregnancy-limited antiretroviral therapy. AIDS. 2010 Jan 2;24(1):45-53.

Antiretroviral Exposure and Lymphocyte mtDNA Content among Uninfected Infants of HIV-1-infected Women

Concern for potential adverse effects of antiretroviral (ARV) chemotherapy used to prevent mother-to-child HIV transmission has led the US Public Health Service to recommend long-term follow-up of ARV-exposed children. Nucleoside reverse transcriptase inhibitor ARV agents can inhibit DNA polymerase gamma, impairing mitochondrial DNA (mtDNA) synthesis and resulting in depletion or dysfunction. The WITS study measured the mtDNA content of stored peripheral blood mononuclear cells (PBMCs) of 411 healthy children who were born to HIV-uninfected women and 213 uninfected infants who were born to HIV-infected women with or without in utero and neonatal ARV exposure. Geometric mean PBMC mtDNA levels were lower at birth in infants who were born to HIV-infected women. Among HIV-exposed children, mtDNA levels were lowest in those who were not exposed to ARVs, higher in those with exposure to zidovudine alone, and higher still in those with combination nucleoside reverse transcriptase inhibitor exposure. A similar pattern was observed in the corresponding women. Levels of mtDNA increased during the first 5 years of life in all HIV-exposed children but achieved normal levels only in those with ARV exposure. Levels of mtDNA are lower than normal in HIV-exposed children. Contrary to expectation, PBMC mtDNA levels are significantly higher in ARV-exposed, HIV-uninfected infants and their infected mothers compared with ARV-unexposed infants and women. By 5 years, levels of PBMC mtDNA rise to normal concentrations in ARV-exposed children but remain depressed in ARV-unexposed children. Aldrovandi GM, Chu C, Shearer WT, et al. Antiretroviral exposure and lymphocyte mtDNA content among uninfected infants of HIV-1-infected women. Pediatrics. 2009 Dec;124(6):e1189-1197.

ART Treatment Interruption After Pregnancy: Effects on Disease Progression and Laboratory Findings

The purpose of this study was to assess clinical progression and inflammatory markers among women stopping or continuing antiretroviral therapy (ART) after pregnancy. ART-na•ve women with CD4+ lymphocyte counts >350 cells/uL initiating ART during pregnancy had clinical events and laboratory markers compared over one year postpartum between those stopping (n = 59) or continuing (n = 147) ART. Slopes in CD4 count and HIV RNA did not differ between groups overall and in subsets of ZDV or combination therapy. The hazard ratio (HR) of a new class B event was 2.09 (95% CI 0.79-5.58) among women stopping ART, 1.24 (0.31-4.95) in those stopping ZDV, and 2.93 (0.64-13.36) among those stopping combination therapy. Women stopping ART had increased immune activation. No significant differences were seen in C-reactive protein, lipids, leptin, or interleukin-6. While changes in CD4 and HIV RNA levels over one year were similar between women stopping or continuing ART postpartum, higher immune activation among women stopping therapy requires further study. Watts DH, Lu M, Thompson B, et al. Treatment interruption after pregnancy: Effects on disease progression and laboratory findings. Infect Dis Obstet Gynecol. 2009;2009:456717.

Mediators of HIV-Related Stigma and Risk Behavior in HIV Infected Young Women

Stigma in HIV positive persons has been associated with numerous negative sequelae, including decreased social support, depressive symptoms, and engagement in risk behaviors. Few studies examined the interrelationships of these factors to facilitate understanding of the mechanisms by which HIV stigma influences risk behavior. This study from the Adolescent Medicine Trials for HIV/AIDS Interventions (ATN) focuses on identifying pathways between HIV-related stigma and risk behavior in 147 young HIV positive women. Depression and social support were hypothesized to mediate between HIV-related stigma and risk behavior. Structural equation modeling was used to test these hypothesized pathways, results suggested that depression was a significant mediator between HIV-related stigma and risk behavior. Implications for interventions with young HIV positive women who report high levels of HIV-related stigma include a focus on depression as a method of reducing engagement in risk behavior and improving mental health and health behaviors in persons living with HIV. Clum G, Chung SE, Ellen JM: Adolescent Medicine Trials Network for HIV/AIDS Interventions. Mediators of HIV-related stigma and risk behavior in HIV infected young women. AIDS Care. 2009 Nov;21(11):1455-1462.

Child Abuse in HIV-Positive Young Women: Linkages to Risk

In this article researchers from the ATN explore the lives of young women living with HIV who experienced physical and/or sexual abuse in childhood. Using a modified version of the Life Story Interview, 40 women recruited from HIV clinics in three different states participated in a qualitative interview. Interviews covered abuse experiences, cognitive and emotional consequences of abuse, coping strategies, and sexual behavior and relationships. Overall, these young women had complex abuse histories, often experiencing more than one type of abuse in the context of other difficult life events. Avoidance and substance use were frequently utilized as coping strategies for abuse-related distress. Young women reported sexual and relationship concerns, including avoidance of sex, sexual dysfunction, sex as a trigger for abuse memories, and difficulty establishing intimacy and trust. Relationships between abuse-related reactions and sexual risk behavior, as well as recommendations for interventions, are discussed. Clum GA, Andrinopoulos , Muessig K, Ellen JM: Adolescent Medicine Trials Network for HIV/AIDS Interventions. Child abuse in young, HIV-positive women: Linkages to risk. Qual Health Res. 2009 Dec;19(12):1755-1768.

Predictors of Suboptimal Virologic Response to Highly Active Antiretroviral Therapy among HIV-Infected Adolescents

This study examined the prevalence and biopsychosocial predictors of suboptimal virologic response to highly active antiretroviral therapy (HAART) among human immunodeficiency virus-infected adolescents. The study was conducted at sixteen academic medical centers across 13 cities in the United States. One hundred fifty-four human immunodeficiency virus-infected adolescents who presented for at least 2 consecutive visits after initiation of HAART were included in the study. Viral load (plasma concentration of human immunodeficiency virus RNA) and CD4(+) lymphocyte count were assessed. Of the 154 adolescents enrolled in the study, 50 (32.5%) demonstrated early and sustained virologic suppression while receiving HAART. The remaining 104 adolescents (67.5%) had a poor virologic response. Adequate adherence (>50%) - reported by 70.8% of respondents - was associated with 60% reduced odds of suboptimal virologic suppression in a multivariable logistic regression model. Exposure to suboptimal antiretroviral therapy prior to HAART, on the other hand, was associated with more than 2-fold increased odds of suboptimal virologic response. Fully two-thirds of human immunodeficiency virus-infected adolescents in the current study demonstrated a suboptimal virologic response to HAART. Nonadherence and prior single or

dual antiretroviral therapy were associated with subsequent poor virologic responses to HAART. These predictors of HAART failure echo findings in pediatric and adult populations. Given the unique developmental stage of adolescence, age-specific interventions are indicated to address high rates of nonadherence and therapeutic failure. Ding H, Wilson CM, Modjarrad K, McGwin G Jr, Tang J, Vermund SH. Predictors of suboptimal virologic response to highly active antiretroviral therapy among human immunodeficiency virus-infected adolescents: Analyses of the reaching for excellence in adolescent care and health (REACH) project. Arch Pediatr Adolesc Med. 2009 Dec;163(12):1100-1105.

Obesity and Dyslipidemia in Behaviorally HIV-infected Young Women

The goal of this study from the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) was to determine the nature and prevalence of abnormalities in lipids, glucose metabolism, and body composition in behaviorally human immunodeficiency virus (HIV)-infected young women and the relationship of these abnormalities to different classes of antiretroviral therapy regimens. This was a cross-sectional, multicenter study involving 173 behaviorally HIV-infected women aged 14-24 years and 61 HIV-seronegative control subjects. HIV-infected women were categorized as follows: antiretroviral therapy naive (n=85), receiving a regimen containing a nonnucleoside reverse-transcriptase inhibitor (NNRTI; n=33), receiving a regimen containing a protease inhibitor (PI; n=36), or receiving a regimen not containing an NNRTI or a PI (n=19). Measurements included fasting lipid levels, glucose and insulin levels before and 2 hours after an oral glucose challenge, high-sensitivity C-reactive protein (hsCRP) levels, anthropometry, fat distribution (measured by dual energy X-ray absorptiometry), and antiretroviral therapy and medical histories. Race-adjusted results were compared across groups and within HIV-infected groups. The median age of participants was 20 years. Of HIV-infected subjects, 77% were African American, 35% smoked cigarettes, and 32% reported exercising regularly. More than 40% had a body mass index > or =25. Triglycerides; total, high-density lipoprotein (HDL), and non-HDL cholesterol; and hsCRP levels differed significantly among groups, with higher levels being most common among those receiving antiretroviral therapy. Indices of glucose metabolism did not differ among groups. In general, cholesterol levels, hsCRP levels, and indices of glucose metabolism worsened as body mass index increased. Obesity, dyslipidemia, and inflammation were prominent among HIV-infected adolescent women and, coupled with other risk factors, may accelerate the lifetime risk of cardiovascular disease and other adverse events. These results underscore the need for a multifaceted approach to addressing risk reduction in this population. Mulligan K, Harris DR, Monte D, et al. Adolescent Trials Network 021 Protocol Team. Obesity and dyslipidemia in behaviorally HIV-infected young women: Adolescent Trials Network study 021. Clin Infect Dis. 2010 Jan 1;50(1):106-114.

HLA-DRB1 Alleles Predict Differential Antibody Responses to Hepatitis B Vaccination in Youth

The purpose of this study by the Adolescent Medicine Trials for HIV/AIDS Interventions (ATN) was to confirm and refine associations of human leukocyte antigen (HLA) genotypes with variable antibody (Ab) responses to hepatitis B vaccination. Study participants included 255 HIV-1 seropositive and 80 HIV-1 seronegative youth. In univariate analyses that focused on HLA-DRB1, -DQA1, and -DQB1 alleles and haplotypes, the DRB1*03 allele group and DRB1*0701 were negatively associated with the responder phenotype. Collectively, DRB1*03 and DRB1*0701 were found in 42 (53.8%) out of 78 non-responders, 65 (40.6%) out of 160 medium responders, and 27 (27.8%) out of 97 high

responders. Meanwhile, DRB1*08 was positively associated with the responder phenotype, mostly due to DRB1*0804. These immunogenetic relationships were all independent of non-genetic factors, including HIV-1 infection status and immunodeficiency. Alternative analyses confined to HIV(+) youth or Hispanic youth led to similar findings. In contrast, analyses of more than 80 non-coding, single nucleotide polymorphisms within and beyond the three HLA class II genes revealed no clear associations. Overall, several HLA-DRB1 alleles were major predictors of differential Ab responses to hepatitis B vaccination in youth, suggesting that T-helper cell-dependent pathways mediated through HLA class II antigen presentation are critical to effective immune response to recombinant vaccines. Li Y, Ni R, Song W, et al. Clear and independent associations of several HLA-DRB1 alleles with differential antibody responses to hepatitis B vaccination in youth. Hum Genet. 2009 Nov;126(5):685-696.

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

Research Findings - Clinical Neuroscience Research

Elevated Cortisol and Learning and Memory Deficits in Cocaine Dependent Individuals

Sinha and colleagues assessed the level of stress in treatment-seeking cocaine dependent individuals and its effect on learning and memory and subsequent relapse. Results demonstrated increased levels of subjective stress, higher morning cortisol levels and selective learning-related deficits compared to healthy controls. Learning deficits included poor immediate verbal recall and recognition as well as selective working memory decrements. Poor verbal learning was associated with more extensive cocaine use (relapse) following discharge from inpatient treatment. The observation that increased perceived stress was associated with learning deficits supports the hypothesis that exposure to increasing levels of glucocorticoids can mediate degeneration of the hippocampus. Of interest, higher cortisol levels in healthy controls was associated with improved recall which seems contradictory but is consistent with the theory that circulating levels of cortisol affect memory in an inverted U-shaped manner. This is the first study to report that a state of high distress may contribute to poor verbal learning and memory in cocaine dependent individuals which, in turn, points to poor treatment outcomes. Fox HC, Jackson ED, Sinha R. Elevated cortisol and learning and memory deficits in cocaine dependent individuals: Relationship to relapse outcomes. Psychoneuroendocrinology. 2009. [Epub ahead of print].

Sleep and Sleep-Dependent Learning Deteriorated in Cocaine Abstinent Men but Not Women

Treatment-seeking cocaine-dependent men and women were assessed for sleep quality and sleep-dependent learning while in an inpatient unit for three weeks. Sleep efficiency (e.g., time asleep while in bed) and total sleep steadily declined in men when assessed approximately two and three weeks from the onset of abstinence; for women there was practically no change. Coincidentally overnight improvement on a motor sequence task deteriorated in men but not women. These findings are the first indication of a sex difference in sleep in persons with substance dependence of any kind. While all women entered the study during their menstrual or early follicular period, hormones were not measured. There is clear indication for follow-up studies addressing the apparent sex differences in cocaine-abstinence effects as these may have important consequences for successful treatment. Morgan PT, Paliwal P, Malison RT, Sinha R. Sex differences in sleep and sleep-dependent learning in abstinent cocaine users. Pharmacol Biochem Behav. 2009. [Epub ahead of print].

Sleep Deprivation Differentially Impairs Cognitive Performance in

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Abstinent Ecstasy Users

McCann and colleagues at Johns Hopkins School of Medicine examined whether the cognitive deficits reported in MDMA users may be due, in part, to sleep disturbances. In this study, abstinent MDMA (Ecstasy) users were sleep deprived for 40 hours and tested on a computerized battery of cognitive tests. The MDMA users performed less accurately on a task of working memory and more impulsively on several tests and they became increasingly impulsive (and less accurate) on tests of working and short-term memory following deprivation. These findings are the first to demonstrate that memory problems in MDMA users may be related, in part, to sleep disturbance and that such deficits may be exacerbated in situations of sleep deprivation. McCann UD, Wilson MJ, Sgambati FP, Ricaurte GA. Sleep deprivation differentially impairs cognitive performance in abstinent methylenedioxymethamphetamine ("Ecstasy") users. J Neurosci. 2009 Nov 4;29(44):14050-14056.

Increased Sleep Apnea in Young Abstinent Recreational Ecstasy Consumers

McCann and colleagues at Johns Hopkins School of Medicine studied sleep characteristics in two-week abstinent MDMA (Ecstasy) users in a controlled inpatient research setting. There were significantly increased rates of obstructive sleep apnea and hypopnea. The odds ratio of the increase was 8.5, even greater than that associated with obesity. In addition, apnea rates were significantly related to lifetime MDMA exposure. These results point to a greater risk of obstructive sleep apnea in these individuals which suggests a role of brain serotonin neuronal dysfunction as a consequence of MDMA use. McCann UD, Sgambati FP, Schwartz AR, Ricaurte GA. Increased sleep apnea in young abstinent recreational Ecstasy consumers, Neurology. 2009;73(23):2011-2017.

Dopaminergic Response to Drug Words in Cocaine Addiction

Goldstein and colleagues at Brookhaven National Laboratory demonstrated that words related to drug addiction stimulated the mesencephalic regions (as assessed by BOLD fMRI) possibly related to dopaminergic and/or glutamatergic mechanisms in individuals with cocaine use disorders. It has been known for some time that visual and environmental cues stimulate drug craving; this is the first study that demonstrates that cue words alone may have a similar effect. It was also demonstrated that this response correlated with a verbal fluency test, suggesting its use as a biomarker. Goldstein RZ, Tomasi D, Alia-Klein N, Carrillo JH, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. Dopaminergic response to drug words in cocaine addiction. J Neurosci. 2009 May 6;29(18):6001-6006.

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

M.J. Kreek and associates divided a sample of methadone-maintained heroin dependent individuals into two groups depending on the effective stabilizing dosage of methadone needed: a"high" dosage group >150 mg/day and a "low" dosage group ² 150 mg. Selecting gene variants of the P-glycoprotein encoded by the ABCB1 (MDR1) gene, it was determined that individuals bearing the 3-locus genotype pattern TT-TT-TT have an approximately 5-fold chance of requiring the "high" dose, while individuals heterozygous for these three SNPs have an approximately 3-fold chance of stabilizing at the "low" dose. These data suggest that specific ABCB1 variants may have clinical relevance by influencing the methadone dose required to prevent withdrawal symptoms and relapse. Levran O, O'Hara K, Peles E, Li D, Barral S, Ray B, Borg L, Ott J, Adelson, M, Kreek MJ. ABCB1 (MDR1) genetic variants are associated with

methadone doses required for effective treatment of heroin dependence. Hum Mol Genet 2008 April 17;17(14):2219-2227.

Cue Elicited Craving in Marijuana Users Increases BOLD Activations in Several Structures of the Reward Pathway

F.M. Filbey and her colleagues recruited regular marijuana users and, following 3-day abstinence, had them tactually handle marijuana paraphernalia while being scanned. Activations relative to neutral cues were found in the ventral tegmental area, dorsal anterior cingulate cortex, cerebellum, thalamus, pre- and post-central gyri, inferior frontal gyrus/insula, thalamus, amygdala, fusiform gyrus, pre- and post- central gyri, inferior parietal lobe, and superior temporal gyrus. The activated areas were positively correlated with total marijuana problems scale score in both the orbitofrontal cortex and the nucleus accumbens. However, the activation was not correlated with subjective urges. The results demonstrate that cue-induced craving for marijuana elicits the same brain activation as for other drugs of abuse. Filbey FM, Schacht JP, Myers US, Chavez RS, Hutchison, KE. Marijuana craving in the brain. PNAS 2009 August 4;106(31):13016-13021.

Sex Differences in Autonomic and HPA Response to Stress and Drug Cues in Alcohol-Dependent Patients with Cocaine Abuse

R. Sinha and M. J. Kreek and associates assessed physiological measures in alcohol and cocaine co-dependents and healthy controls during stress and drug-associated (compared to neutral) imagery. Substance abusing males showed increased ACTH and epinephrine basal tone but not increase in ACTH and cortisol levels following stress and alcohol cue imagery. Females demonstrated a typically increased stress response in both measures. Also, substance abusing males showed no increase in cardiovascular response to either stress or cue, and no increase in catecholamine response to cue. By contrast, females showed an enhanced ACTH and cortisol response to stress and cue. The results demonstrated that while males showed a generalized suppression of the hypothalamic-pituitary-adrenal and sympathetic adrenal medullary stress systems and cardiovascular markers following stress and cue, women demonstrated a selective sympatho-adrenal suppression to stress only and an enhanced HPA response to both stress and cue. These sex differences may affect both relapse vulnerability and effective treatment strategy and outcome. Fox HC, Hong K-I A, Siedlarz KM, Bergquist K, Anderson G, Kreek MJ, Sinha R. Sex-specific dissociations in autonomic and HPA responses to stress and cues in alcohol-dependent patients with cocaine abuse. Alcohol & Alcoholism. 2009 Sep 30. [Epub ahead of print].

A Functional Haplotype Implicated in Vulnerability to Develop Cocaine Dependence is Associated with Reduced PDYN Expression in Human Brain

Kreek and associates tested six SNPs of the prodynorphin (PDYN) gene for association with cocaine dependence and cocaine/alcohol co-dependence. There were point-wise significant associations of three SNPs which were in high linkage disequilibrium comprising a haplotype block. One haplotype was significantly associated. Using one SNP, allele-specific gene expression of PDYN was assessed in post-mortem brains. One variant was associated with significantly lower expression in the caudate and nucleus accumbens. This study provides evidence that a particular haplotype of the PDYN gene (implicated in cocaine addiction vulnerability) is related to lower mRNA expression in the human dorsal and ventral striatum. Yuferov V, Ji F, Nielsen, DA, Levran O, Ho A, Morgello S, Shi R, Ott J, Kreek MJ. A functional haplotype implicated in vulnerability to develop cocaine dependence is associated with

reduced PDYN expression in human brain. Neuropsychopharm. 2009;34:1185-1197.

Reduced Prefrontal Cortical Gray Matter Volume in Young Adults Exposed to Harsh Corporal Punishment

M.H. Teicher and colleagues assessed brain volume in young adults who reported having undergone harsh corporal punishmentÑdefined as punishment in childhood by paddling with an object (as opposed to open hand) several times a year for at least three years. Results demonstrated reduced gray matter volume in the right medial frontal gyrus by 19.1%, by 14.5% in the left medial frontal gyrus, and by 16.9% in the right anterior cingulate gyrus. Furthermore, there were significant correlations between brain volume in these regions and performance IQ. It was concluded that harsh corporal punishment may have detrimental effects on trajectories of brain development in areas that are related to vulnerabilities to drug abuse. Tomoda A, Suzuki H, Rabi K, Sheu Y-S, Polcari A, Teicher MH. Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. NeuroImage. 2009 Aug.;47 Suppl2:T66-71.

History of Childhood Abuse is Associated with Cerebellar Size and Alcohol and Drug Use in Young Adults

C.M. Anderson, M.H. Teicher and colleagues collected histories of physical abuse (including harsh corporal punishment) and emotional abuse during childhood plus drug and alcohol use in otherwise healthy young adults. These data were associated with MRI scans with focus on the lobules of the cerebellar vermis. The subjects were divided into three categories depending on the size of the lingula (which may be lobule I [thin] or lobule I+II [thick]). Thicker lobule I of the cerebellar vermis was associated with greater consumption of drugs and hard liquor, particularly in physically maltreated subjects. Physically maltreated subjects consumed more than 2.5 times more alcohol and used drugs 6 times more than comparison groups of individuals who were neither physically nor emotionally maltreated or even those who did experience emotional maltreatment (alone without physical maltreatment). These results indicate that physical maltreatment impacts cerebellar morphology in association with drug and alcohol abuse. Anderson CM, Rabi K, Lukas SE, Teicher MH. Cerebellar lingual size and experiential risk factors associated with high levels of alcohol and drug use in young adults. Cerebellum. 2009 Oct 28. [Epub ahead of print].

Effect of Daily Caffeine Use on Cerebral Blood Flow

Addicott and colleagues, at the Wake Forest University School of Medicine, conducted this study to investigate the effects of caffeine on cerebral blood flow (CBF) as a function of increasing levels of chronic caffeine use. Caffeine is a commonly used neurostimulant that also produces cerebral vasoconstriction by antagonizing adenosine receptors. Chronic caffeine use results in an adaptation of the vascular adenosine receptor system presumably to compensate for the vasoconstrictive effects of caffeine. Low (45 mg/day), moderate (405 mg/day), and high (950 mg/day) caffeine users underwent quantitative perfusion magnetic resonance imaging on four separate occasions: twice in a caffeine abstinent state (abstained state) and twice in a caffeinated state following their normal caffeine use (native state). In each state, there were two drug conditions: participants received either caffeine (250 mg) or placebo. Gray matter CBF was tested with repeated-measures analysis of variance using caffeine use as a between-subjects factor, and correlational analyses were conducted between CBF and caffeine use. Caffeine reduced CBF by an average of 27% across both caffeine states. In the abstained placebo

condition, moderate and high users had similarly greater CBF than low users; but in the native placebo condition, the high users had a trend towards less CBF than the low and moderate users. These results suggest that the cerebrovascular adenosine system has a limited ability to compensate for high amounts of daily caffeine use. Addicott MA, Yang LL, Peiffer AM, et al. The effect of daily caffeine use on cerebral blood flow: How much caffeine can we tolerate? Hum Brain Mapp. 2009 Oct;30(10):3102-3114.

Effects of Treatment for Tobacco Dependence on Resting Cerebral Glucose Metabolism

Brody and colleagues at UCLA investigated whether two commonly used treatments for tobacco dependence, bupropion HCl and practical group counseling (PGC), have measurable effects on regional cerebral brain metabolism. 54 tobacco-dependent cigarette smokers underwent resting (18)F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning before and after 8 weeks of treatment with bupropion HCl, PGC, or pill placebo. Subjects who received one of the two active treatments (bupropion HCl and PGC) had reduced metabolism in the posterior cingulate gyrus relative to subjects who received placebo. PGC had a greater effect than bupropion HCl on glucose metabolism in this region. There were positive correlations between daily cigarette use and glucose metabolism in the left occipital gyrus and parietal-temporal junction, but no significant negative correlations were found between daily cigarette use and glucose metabolism. These findings suggest that bupropion HCl and PGC reduce neural activity much as the performance of a goal-oriented task does in the default mode network of the brain, including the posterior cingulate gyrus. Thus, this study suggests that active treatments for tobacco dependence increase the brain's ability to engage in a more goal-oriented state. Costello MR, Mandelkern MA, Shoptaw S, et al. Effects of treatment for tobacco dependence on resting cerebral glucose metabolism. Neuropsychopharmacology, 2009 October. [Epub ahead of print].

Rapid Cognitive Screening of Patients with Substance Use Disorders

To date, there has not been a time-efficient and resource-conscious way to identify cognitive impairment in patients with substance use disorders (SUDs). In this study, Marc Copersino and colleagues at Harvard Medical School assessed the validity, accuracy, and clinical utility of a brief (10-min) screening instrument, the Montreal Cognitive Assessment (MoCA), in identifying cognitive impairment among patients with SUDs. The Neuropsychological Assessment Battery-Screening Module, a 45-min battery with known sensitivity to the mild to moderate deficits observed in patients with SUDs, was used as the reference criterion for determining agreement, rates of correct and incorrect decision classifications, and criterion-related validity for the MoCA. Classification accuracy of the MoCA, based on receiver operating characteristic (ROC) analysis, was strong, with an area under the ROC curve of 0.86, 95% confidence interval [0.75, 0.97]. The MoCA also showed acceptable sensitivity (83.3%) and specificity (72.9%) for the identification of cognitive impairment. Using a cutoff of 25 on the MoCA, the overall agreement was 75.0%; chance-corrected agreement (kappa) was 41.9%. These findings indicate that the MoCA provides a time-efficient and resource-conscious way to identify patients with SUDs and neuropsychological impairment, thus addressing a critical need in the addiction treatment research community. Copersino ML, Fals-Stewart W, Fitzmaurice G, Schretlen DJ, Sokoloff J, Weiss RD. Rapid cognitive screening of patients with substance use disorders. Exp Clin Psychopharmacol. 2009 Oct;17(5):337-344.

GABAA-Benzodiazepine Receptor Availability in Smokers and

Nonsmokers: Relationship to Subsyndromal Anxiety and Depression

Many smokers experience subsyndromal anxiety symptoms while smoking and during acute abstinence, which may contribute to relapse. Cosgrove and colleagues at Yale University hypothesized that cortical gamma aminobutyric acid(A)-benzodiazepine receptor (GABA(A)-BZR) availability in smokers and nonsmokers might be related to the expression of subsyndromal anxiety, depressive, and pain symptoms. Cortical GABA(A)-BZRs were imaged in 15 smokers (8 men and 7 women), and 15 healthy age and sex-matched nonsmokers, and 4 abstinent tobacco smokers (3 men; 1 woman) using [(123)I]iomazenil and single photon emission computed tomography (SPECT). The relationship between cortical GABA(A)-BZR availability, smoking status, and subsyndromal depression and anxiety symptoms, as well as pain tolerance and sensitivity, were evaluated. There were no statistically significant differences in overall GABA(A)-BZR availability between smokers and nonsmokers or between active and abstinent smokers; however, cortical GABA(A)-BZR availability negatively correlated with subsyndromal state anxiety symptoms in nonsmokers but not in smokers. In nonsmokers, the correlation was seen across many brain areas with state anxiety [parietal, frontal, anterior cingulate, temporal, occipital cortices, and cerebellum], trait anxiety [parietal, frontal, and occipital cortices] and depressive symptoms [parietal, frontal, anterior cingulate, and temporal cortices]. The finding that a similar relationship between GABA(A)-BZR availability and anxiety symptoms was not observed in smokers suggests that there is a difference in GABA(A)-BZR function, but not number, in smokers. Thus, while subsyndromal anxiety and depressive symptoms in nonsmokers may be determined in part by GABA(A)-BZR availability, smoking disrupts this relationship. Aberrant regulation of GABA(A)-BZR function in vulnerable smokers may explain why some smokers experience subsyndromal anxiety and depression. Esterlis I, Cosgrove KP, Batis JC, et al. GABAA-benzodiazepine receptor availability in smokers and nonsmokers: relationship to subsyndromal anxiety and depression. Synapse. 2009 Dec;63(12):1089-1099.

Brain fMRI Reactivity to Smoking-Related Images Before and During Extended Smoking Abstinence

Reactivity to smoking-related cues may play a role in the maintenance of smoking behavior and may change depending on smoking status. Whether smoking cue-related functional MRI (fMRI) reactivity differs between active smoking and extended smoking abstinence states currently is unknown. Jane and colleagues at the Brain Imaging Center of McLean Hospital used fMRI to measure brain reactivity in response to smoking-related versus neutral images in 13 tobacco-dependent subjects before a smoking cessation attempt and again during extended smoking abstinence (52 +/- 11 days) aided by nicotine replacement therapy. Prequit smoking cue induced fMRI activity patterns paralleled those reported in prior smoking cue reactivity fMRI studies. Greater fMRI activity was detected during extended smoking abstinence than during the prequit assessment subcortically in the caudate nucleus and cortically in prefrontal (BA 6, 9, 44, 46), primary somatosensory (BA 1, 2, 3), temporal (BA 22, 41, 42), parietal (BA 7, 40) anterior cingulate (BA 24, 32), and posterior cingulate (BA 31) cortex. These data suggest that during extended smoking abstinence, fMRI reactivity to smoking versus neutral stimuli persists in brain areas involved in attention, somatosensory processing, motor planning, and conditioned cue responding. In some brain regions, fMRI smoking cue reactivity is increased during extended smoking abstinence in comparison to the prequit state, which may contribute to persisting relapse vulnerability. Janes AC, Frederick B, Richardt S, et al. Brain fMRI reactivity to smoking-related images before and during extended smoking abstinence. Exp Clin Psychopharmacol. 2009 Dec;17(6):365-373.

Effects of Sleep Deprivation on Sleep Homeostasis and Restoration During Methadone-Maintenance: A ([31])P MRS Brain Imaging Study

Insomnia afflicts many individuals, but particularly those in chronic methadone treatment. Studies examining sleep deprivation (SD) have begun to identify sleep restoration processes involving brain bioenergetics. The technique ([31])P magnetic resonance spectroscopy (MRS) can measure brain changes in the high-energy phosphates: alpha-, beta-, and gamma-nucleoside triphosphate (NTP). In the present study conducted by Lukas and colleagues at McLean Hospital, 21 methadone-maintained (MM) and 16 control participants underwent baseline (BL), SD (40 wakeful hours), recovery1 (RE1), and recovery2 (RE2) study nights. Polysomnographic sleep was recorded each night and ([31])P MRS brain scanning conducted each morning using a 4T MR scanner (dual-tuned proton/phosphorus head-coil). Increases in total sleep time (TST) and sleep efficiency index (SEI) commonly associated with RE sleep were not apparent in MM participants. Analysis of methadone treatment duration revealed that the lack of RE sleep increases in TST and SEI was primarily exhibited by short-term MM participants (methadone <12 months), while RE sleep in long-term MM (methadone >12 months) participants was more comparable to control participants. Slow wave sleep increased during RE1, but there was no difference between MM and control participants. Spectral power analysis revealed that compared to control participants; MM participants had greater delta, theta, and alpha spectral power during BL and RE sleep. ([31])P MRS revealed that elevations in brain beta-NTP (a direct measure of ATP) following RE sleep were greater in MM compared to control participants. Results suggest that differences in sleep and brain chemistry during RE in MM participants may be reflective of a disruption in homeostatic sleep function. Trksak GH, Jensen JE, Plante DT, et al. Effects of sleep deprivation on sleep homeostasis and restoration during methadone-maintenance: A ([31])P MRS brain imaging study. Drug Alcohol Depend. 2009 Sep. [Epub ahead of print].

Transcutaneous Electric Acupoint Stimulation as Adjunctive Treatment for Opioid Detoxification

Lukas and colleagues at McLean Hospital tested the effectiveness of transcutaneous electric acupoint stimulation (TEAS) as an adjunctive treatment for inpatients receiving opioid detoxification with buprenorphine-naloxone at a private psychiatric hospital. Participants (N = 48) were randomly assigned to active or sham TEAS and received three 30-minute treatments daily for 3 to 4 days. In active TEAS, current was set to maximal tolerable intensity (8-15 mA); in sham TEAS, it was set to 1 mA. By 2 weeks postdischarge, participants in active TEAS were less likely to have used any drugs (35% vs. 77%, $p < .05$). They also reported greater improvements in pain interference ($F = 4.52$, $p < .05$) and physical health ($F = 4.84$, $p < .01$) over time. TEAS is an acceptable, inexpensive adjunctive treatment that is feasible to implement on an inpatient basis and may be a beneficial adjunct to pharmacological treatments for opioid detoxification. Meade CS, Lukas SE, McDonald LJ, Fitzmaurice GM, Eldridge JA, Merrill N, Weiss RD. A randomized trial of transcutaneous electric acupoint stimulation as adjunctive treatment for opioid detoxification. J Subst Abuse Treat. 2010 Jan;38(1):12-21.

Sensory Gating Impairments in Heavy Cannabis Users are Associated with Altered Neural Oscillations

Central cannabinoid receptors mediate neural oscillations and are localized to networks implicated in auditory P50 sensory gating, including the hippocampus and neocortex. Skosnik and colleagues at Indiana University conducted this

study to examine whether neural oscillations evoked by the paired clicks (S1, S2) are associated with abnormal P50 gating reported in cannabis users. Seventeen heavy cannabis users and 16 cannabis na•ve controls participated. Analyses included P50 amplitudes, and time-frequency analyses (event-related spectral perturbations, ERSPs; intertrial coherence, ITC). Consistent with prior studies, cannabis users exhibited reduced P50 gating. The ERSP analysis yielded attenuated high frequency activity in the beta range (13-29 Hz) post-S1 and in the gamma range (30-50 Hz) post-S2 in the cannabis group, compared with the control group. Greater levels of cannabis use were positively associated with high P50 ratios and negatively with post-S2 ERSP gamma power. Findings suggest that heavy cannabis use is associated with aberrant beta and gamma activity in the dual-click procedure, which corroborates recent work demonstrating disruption of beta/gamma by cannabinoid receptor (CB1) agonists in a rat analogue of this task and highlights the translational potential of the dual-click procedure. Edwards CR, Skosnik PD, Steinmetz AB, O'Donnell BF, Hetrick WP. Sensory gating impairments in heavy cannabis users are associated with altered neural oscillations. Behav Neurosci. 2009 Aug;123(4):894-904. Erratum in: Behav Neurosci. 2009 Oct;123(5):1065.

A Single Amino Acid Difference in Human APOBEC3H Variants Determines HIV-1 Vif Sensitivity

Several variants of APOBEC3H (A3H) variants have been identified in different human populations. Certain variants of this protein are particularly potent inhibitors of retrotransposons and retroviruses, including HIV-1. It is not clear whether HIV-1 Vif can recognize and suppress the antiviral activity of A3H variants, as it does to other APOBEC3 proteins. Dr. Yu's study found that A3H_Haplotype II (HapII), a potent inhibitor of HIV-1 in the absence of Vif, can indeed be degraded by HIV-1 Vif. Vif-induced degradation of A3H_HapII was blocked by the proteasome inhibitor MG132 and a Cullin5 (Cul5) dominant negative mutant. In addition, Vif mutants that were incapable of assembly with the host E3 ligase complex factors Cul5, ElonginB, and ElonginC were also defective for A3H_HapII suppression. Although Vif hijacks the same E3 ligase to degrade A3H_HapII as it does to inactivate APOBEC3G (A3G) and APOBEC3F (A3F), more Vif motifs were involved in A3H_HapII inactivation than for either A3G or A3F suppression. In contrast to A3H_HapII, A3H_Haplotype I (HapI), which differs in only 3 amino acids from A3H_HapII, was resistant to HIV-1 Vif-mediated degradation. Residue 121 was found to be critical for determining A3H sensitivity and binding to HIV-1 Vif. Zhen A, Wang T, Zhao K, Xiong Y, Yu XF. A single amino acid difference in human APOBEC3H variants determines HIV-1 Vif sensitivity. J Virol. 2009 Nov 25. [Epub ahead of print].

The Loss of APOBEC3B May Increase Host Susceptibility to HIV-1 Acquisition and Progression to AIDS

The human APOBEC3 family of cytidine deaminases provides intrinsic immunity to retroviral infection. A naturally occurring 29.5-kb deletion removes the entire APOBEC3B gene. Dr. Yu examined the impact of the APOBEC3B gene deletion in over 4000 individuals from 5 human immunodeficiency virus type 1 (HIV-1) natural history cohorts. The hemizygous genotype had no effect on either acquisition of HIV-1 infection or progression to AIDS. However, the homozygous deletion was significantly associated with unfavorable outcomes for HIV-1 acquisition, progression to AIDS, and viral set point. These findings suggest that the loss of APOBEC3B may increase host susceptibility to HIV-1 acquisition and progression to AIDS. An P, Johnson R, Phair J, Kirk GD, Yu XF, Donfield S, Buchbinder S, Goedert JJ, Winkler CA. APOBEC3B deletion and risk of HIV-1 acquisition. J Infect Dis. 2009 Oct 1;200(7):1054-1058.

Amino Acids Surrounding HIV-1 Vif Involved in A3G Binding and

Inactivation Amino-terminal region of the Vif molecule contains a conserved SLV/Ix4Yx9Y motif in HIV-1, HIV-2, and simian immunodeficiency virus (SIV)

This study found this region is critical for APOBEC3 suppression. In particular, amino acids K22, K26, Y30, and Y40 were important for the Vif-induced degradation and suppression of cellular APOBEC3G (A3G). However, mutation of these residues had little effect on the Vif-mediated suppression of A3F, A3C, or A3DE, suggesting that these four residues are not important for Vif assembly with the Cul5 E3 ubiquitin ligase or protein folding in general. The LV portion of the Vif SLV/Ix4Yx9Y motif was required for optimal suppression of A3F, A3C, or A3DE. Thus, the SLV/Ix4Yx9Y motif and surrounding amino acids represent an important functional domain in the Vif-mediated defense against APOBEC3. In particular, the positively charged K26 of HIV-1 Vif was invariably conserved within the SLV/Ix4Yx9Y motif of HIV/SIV Vif molecules and was the most critical residue for A3G inactivation. A patch of positively charged and hydrophilic residues (K(22)x(3)K(26)x(3)Y(30)x(9)YRHHY(44)) and a cluster of hydrophobic residues (V(55)xIPLx(4-5)LxPhix2YWxL(72)) were both involved in A3G binding and inactivation. These structural motifs in HIV-1 Vif represent attractive targets for the development of lead inhibitors to combat HIV infection. Chen G, He Z, Wang T, Xu R, Yu XF. A patch of positively charged amino acids surrounding the human immunodeficiency virus type 1 Vif SLVx4Yx9Y motif influences its interaction with APOBEC3G. J Virol. 2009 Sep;83(17):8674-8682.

Incorporation of Multi-faceted Approaches for Effective Reduction of Risky Sexual Behavior

Cross-sectional data was collected in this study to elucidate the inconsistent reports regarding contextual influence of methamphetamine dependence (METH), HIV-infection and their combination on mood states and risky sexual behavior (frequency of condom use) among men who have sex with men (MSM). Dr. Grant and colleagues found that METH+ and HIV+ status were both associated with irregular condom use and higher score of negative mood status (depression, tension, anger, fatigue and confusion). Although METH+/HIV+ participants reported significantly less frequent condom use (25% of the time) than reported by METH-/HIV+ participants (51-75% of the time), neither METH nor HIV status showed a moderate (i.e., contextual) effect on the relationships between negative mood and condom use. Since among non-monogamous MSM the METH dependence, HIV+ and negative moods were all associated with reduced condom use without contextual effect, the study suggested that sexual risk reduction interventions for MSM should incorporate multi-faceted approaches, including substance abuse and mental health treatment. Bousman CA, Cherner M, Ake C, Letendre S, Atkinson JH, Patterson TL, Grant I, Everall IP; HNRC Group. Negative mood and sexual behavior among non-monogamous men who have sex with men in the context of methamphetamine and HIV. J Affect Disord. 2009 Dec;119(1-3):84-91.

Antiretroviral Therapy Shifts Cliniconeuropathologic Correlates of HIV from Florid Virus Replication to Diverse Mechanisms

This cross-sectional survey analyzed prospective clinical and neuropathological data collected by the National NeuroAIDS Tissue Consortium (NNTC), comprising 589 brain samples from individuals with advanced HIV disease collected since 1999. It assessed gender, ethnicity/race, mode of transmission, age, year of death, nadir CD4, plasma viral load, last antiretroviral regimen, the presence of parenchymal HIV brain pathology, HIV-associated neurocognitive disorder, and major depressive disorder. The study compared cohort demographic variables with Centers for Disease Control and Prevention

US HIV/AIDS statistics and examined associations of parenchymal HIV brain pathology with demographic, clinical, and HIV disease factors. With regard to Centers for Disease Control and Prevention US data, the NNTC cohort had similar age distribution, fewer females and African Americans but more Hispanics and men who have sex with men. Only 22% of the brains examined were neuropathologically normal. Opportunistic infections occurred in 1% to 5% of the cohort. Parenchymal HIV brain pathology was observed in 17.5% of the cohort and was associated with nadir CD4 and plasma viral load. Brains without parenchymal HIV brain pathology often had other noninfectious findings or minimal nondiagnostic abnormalities that were associated with HIV-associated neurocognitive disorder. Clinically, 60% of the cohort reported a lifetime episode of major depressive disorder and 88% had a HIV-associated neurocognitive disorder. No pathological finding correlated with major depressive disorder. Both antiretroviral treatment regimen and elevated plasma HIV viral load were associated with presence of parenchymal HIV brain pathology; however, multivariate analyses suggested a stronger association with plasma viral load. The frequency of HIV brain pathology was lower than previous pre-antiretroviral reports, and was predicted by lower nadir CD4 and higher plasma viral load. Noninfectious pathologies and minimal changes correlated with HIV-associated neurocognitive disorder, suggesting a shift in pathogenesis from florid HIV replication to other, diverse mechanisms. Everall I, Vaida F, Khanlou N, et al. HIV Neurobehavioral Research Center (HNRC). Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. J Neurovirol. 2009 Sep 8:1-11.

The Semantic Relatedness of Cue-intention Pairings Influences Event-based Prospective Memory Failures in Older HIV+ Adults

HIV infection and aging are each independently associated with prospective memory impairment, which increases the risk of poor functional outcomes, including medication non-adherence. The incidence and prevalence of HIV infection among older adults has increased in recent years, thereby raising questions about the combined effects of these risk factors on prospective memory. The present study showed significant additive effects of HIV and aging on event-based prospective memory, with the greatest deficits evident in the older HIV+ group, even after controlling for other demographic factors and potential medical and psychiatric confounds. Event-based prospective memory impairment was particularly apparent in the older HIV+ group on trials for which the retrieval cue and intention were not semantically related. Worse performance on the semantically unrelated cue-intention trials was associated with executive dysfunction, older age, and histories of immunocompromise in the older HIV+ cohort. These data suggest that older HIV-infected adults are significantly less proficient at engaging the strategic encoding and retrieval processes required to execute a future intention when the cue is unrelated to the intended action, perhaps secondary to greater neuropathological burden in the prefrontostriatal systems critical to optimal prospective memory functioning. Woods SP, Dawson MS, Weber E, Grant I. The semantic relatedness of cue-intention pairings influences event-based prospective memory failures in older adults with HIV infection. J Clin Exp Neuropsychol. 2009 Sep 17:1-10.

HIV-Associated Deficits in Action (Verb) Generation May Reflect Astrocytosis

Commensurate with the hypothesized neural dissociation between verb and noun generation, research in HIV infection shows that, relative to noun fluency, action (verb) fluency is disproportionately impaired, more strongly related to executive dysfunction, and more sensitive to declines in everyday functioning. However, whether the neurobiological correlates of HIV-associated deficits in verb and noun generation are separable have not heretofore been investigated.

The present study examined the biomarker correlates of action and noun fluency in HIV+ participants. Biomarkers of viral burden, neuroaxonal damage, macrophage activation, neuroprotection, inflammation, and astrocytosis were measured in plasma and cerebrospinal fluid (CSF). Deficits in action, but not noun generation, were significantly associated with higher CSF levels of S100beta, a marker of astrocyte activation, even after controlling for antiretroviral therapy, current immune compromise, and general cognitive impairment. Concurrent validity for the frontal systems hypothesis of verb generation was provided by post hoc analyses demonstrating that S100beta was also associated with measures of executive functions, but not semantic memory or psychomotor speed. Overall, these findings suggest that HIV-associated impairment in action fluency, and executive dysfunction more generally, may reflect astrocytosis (i.e., elevated S100beta). Complementing the literature in HIV and other clinical populations with frontal systems involvement, these data also support the possible neurobiological dissociation of noun and verb generation. Woods SP, Iudicello JE, Dawson MS, Weber E, Grant I, Letendre SL. HIV-associated deficits in action (verb) generation may reflect astrocytosis. J Clin Exp Neuropsychol. 2009 Oct 19:1-6.

Role of Metabolic Syndrome Components in HIV-Associated Sensory Neuropathy

Metabolic syndrome, a cluster of risk factors for atherosclerosis and microvascular disease, is associated with sensory neuropathy. This study assessed whether the syndrome or its components predispose individuals to HIV-associated sensory neuropathy. After controlling for HIV-SN risk factors such as age, CD4 current, length of HIV infection, use of dideoxynucleoside reverse transcriptase inhibitors and protease inhibitors, it found that the risk of HIV-associated sensory neuropathy was increased in HIV+ individuals having diabetes mellitus type 2 and elevated TRG but not those having other components of the Metabolic syndrome. Ances BM, Vaida F, Rosario D, et al. CNS HIV Antiretroviral Therapy Effects Research (CHARTER) Metabolic Study Group. Role of metabolic syndrome components in HIV-associated sensory neuropathy. AIDS. 2009 Nov 13;23(17):2317-2322.

Translating Endogenous Opioid System Activation into Pain Treatment

Dr. Younger's work in this study revealed that a therapeutic effect can be achieved in patients with fibromyalgia symptoms by modulating activity of endogenous opioid system. The opioid antagonist naltrexone at very small doses could stimulate the release of endogenous opioids after an initial short blockage of the receptor activity, inhibit the activity of microglia, and reverse central and peripheral inflammation. Administration of naltrexone reduced diffuse musculoskeletal pain and sensitivity to mechanical stimulation with side effects being infrequent. A greater than 30% reduction of pain symptoms over the placebo effect was evident in the entire cohort. In addition, laboratory testing showed that mechanical and heat pain thresholds were raised after naltrexone treatment. Although it is recognized that drug efficacy needs to be tested in larger samples, the data suggest that low-dose naltrexone might be an effective, highly tolerable, and inexpensive treatment for fibromyalgia. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. Pain Med. 2009 May-Jun 10;(4):663-672.

Turning Quantitative Sensory Testing and Mapping into the Assessment of Neuropathic Pain

To complement the neurologic, musculoskeletal, and general physical examinations, a standard, validated, office evaluation of signs of neuropathic

pain is essential to allow for better monitoring of treatment effectiveness and for mechanistic studies of pain. Based upon a comprehensive analysis of available methodologies for quantitative sensory testing and specific tests for the neuropathic pain evaluation, Dr. Wasan and colleagues have proposed a protocol to quantify sensory features of neuropathic pain, including the evaluation of sensory deficits, allodynia and hyperalgesia, which could be evoked by a physiologically representative array of stimuli. Such an examination should include mapping of areas of stimulus-evoked neuropathic pain and standardized, reproducible quantitative sensory testing (QST) of tactile, punctuate, pressure, and thermal modalities. Walk D, Sehgal N, Moeller-Bertram T, Edwards RR, Wasan A, Wallace M, Irving G, Argoff C, Backonja MM. Quantitative sensory testing and mapping: A review of nonautomated quantitative methods for examination of the patient with neuropathic pain. Clin J Pain. 2009 Sep 25;(7):632-640.

Filling-in, Spatial Summation, and Radiation of Pain: Evidence for a Neural Population Code in the Nociceptive System

The receptive field organization of nociceptive neurons suggests that noxious information may be encoded by population-based mechanisms. Although electrophysiological evidence of population coding mechanisms is limited, psychophysical studies examining interactions between multiple noxious stimuli can provide indirect evidence that neuron population recruitment can contribute to both spatial and intensity-related percepts of pain. In this study, Dr. Coghill evaluated pain intensity and perceived spatial attributes of stimuli. Perceived pain spread beyond areas stimulated (radiation of pain), most frequently at 5- and 10-cm distances. Perceived connectivity between two noxious stimuli (filling-in) was influenced by the distance between stimuli, with the greatest connectivity reported at 5- and 10-cm separation distances. Spatial summation of pain occurred over probe separation distances as large as 40 cm and six dermatomes, but was maximal at 5- and 10-cm separation distances. Taken together, all three of these phenomena suggest that interactions between recruited populations of neurons may support both spatial and intensity-related dimensions of the pain experience. Quevedo AS, Coghill RC. Filling-in, spatial summation, and radiation of pain: Evidence for a neural population code in the nociceptive system. J Neurophysiol. 2009 ec102; (6):3544-3553.

Brain Mechanisms Supporting Discrimination of Sensory Features of Pain: A New Model

Pain can be very intense or only mild, and can be well localized or diffuse. Little is known as to how such distinct sensory aspects of noxious stimuli are processed by the human brain. Using functional magnetic resonance imaging and a delayed match-to-sample task, Dr. Coghill's laboratory showed that discrimination of pain intensity, a nonspatial aspect of pain, activated a ventrally directed pathway extending bilaterally from the insular cortex to the prefrontal cortex. This activation was distinct from the dorsally directed activation of the posterior parietal cortex and right dorsolateral prefrontal cortex that occurs during spatial discrimination of pain. Both intensity and spatial discrimination tasks activated highly similar aspects of the anterior cingulate cortex, suggesting that this structure contributes to common elements of the discrimination task such as the monitoring of sensory comparisons and response selection. These results provide the foundation for a new model of pain in which bidirectional dorsal and ventral streams preferentially amplify and process distinct sensory features of noxious stimuli according to top-down task demands. Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC. Brain mechanisms supporting discrimination of sensory features of pain: A new model. J Neurosci. 2009 Nov 25;29(47):14924-14931.

Cognitive Function May Improve in Individuals with Protracted Drug Abstinence

Chronic methamphetamine (MA) abuse is associated with disruption of frontostriatal function as well as deficits in cognitive control. Dr. Salo found in this study that recently abstinent MA-abusing individuals exhibited greater Stroop reaction time (RT) interference compared with both the control group and the long-term abstinent MA-abusing individuals. There was no difference between long-term abstinent MA-abusing individuals and controls. Stroop RT interference correlated positively with both duration of drug use and drug abstinence. These data suggest that cognitive function may improve with protracted drug abstinence. Salo R, Nordahl TE, Galloway GP, Moore CD, Waters C, Leamon MH. Drug abstinence and cognitive control in methamphetamine-dependent individuals. Subst Abuse Treat. 2009 Oct 37; (3):292-297.

Nicotine Reduced Symptoms and Negative Moods of ADHD Patients

This study tested the effects of nicotine in the everyday lives of smokers and nonsmokers with attention-deficit/hyperactivity disorder (ADHD). The effects of nicotine on ADHD symptoms, moods, and side effects were assessed with electronic diaries. Cardiovascular activity was recorded with ambulatory blood pressure monitors and physical activity was monitored with actigraphs. Nicotine reduced reports of ADHD symptoms by 8% and negative moods by 9%, independent of smoking status. In addition, nicotine increased cardiovascular activity during the first 3 to 6 hours after nicotine patch administration. The results support the self-medication hypothesis for nicotine in adults with ADHD and suggest that smoking cessation and prevention efforts for individuals with ADHD will need to address both the symptom reducing and mood enhancing effects of nicotine. Gehricke JG, Hong N, Whalen CK, Steinhoff K, Wigal TL. Effects of transdermal nicotine on symptoms, moods, and cardiovascular activity in the everyday lives of smokers and nonsmokers with attention-deficit/hyperactivity disorder. Psychol Addict Behav. 2009 Dec 23;(4):644-655.

HIV Nef Inhibited T Cell Migration Involves Multiple Cellular Domains

Lymphocyte trafficking is a multistep, intricate process and involves a number of host factors such as integrins and chemokine receptors on lymphocytes, adhesion molecules on endothelial cells, and chemokines present in the local microenvironment. Previous studies have shown that HIV-1 Nef inhibits T cell chemotaxis in response to the physiological ligand SDF-1alpha. The inhibitory mechanisms and the molecular determinants of HIV-1 Nef for this phenotype were evaluated in this study. It showed that HIV-1 Nef inhibited transwell and transendothelial migration of T cells. HIV-1 Nef protein impaired T cell chemotaxis toward SDF-1alpha without altering CXCR4 expression. HIV-1 Nef protein down-modulated LFA-1 expression on T lymphocytes and diminished adhesion and polarization of T lymphocytes and, as a result, led to decreased migration across the endothelium. The myristoylation site and DeltaSD domain played important roles in Nef-mediated inhibition of transwell and transendothelial migration and polarization of T lymphocytes. However, different sites or domains were needed for Nef-mediated LFA-1 down-modulation and impaired adhesion of T lymphocyte. These results demonstrated that HIV-1 Nef inhibited T lymphocyte migration at multiple steps and suggest that membrane localization and intracellular signaling events likely contribute to the inhibitory effects of Nef on T cell migration and subsequently, the pathobiology of the HIV-1 Nef protein. Park IW, He JJ. HIV-1 Nef-mediated inhibition of T cell migration and its molecular determinants. J

Leukoc Biol. 2009 Nov 86;(5):1171-1178.

Sam68 as a Multi-Functional Host RNA-binding Protein

Sam68 has been implicated in a variety of important cellular processes such as RNA metabolism and intracellular signaling. The Sam68 cytoplasmic mutants induced stress granules (SG) and inhibit HIV-1 nef mRNA translation. In this study, Dr. He evaluated the possibility and the underlying mechanisms of the wild-type counterpart Sam68 SG recruitment. Sam68 was significantly recruited into cytoplasmic SG under oxidative stress. Domain aa269-321 and KH domain were both essential for this recruitment while Sam68 knockdown had no effects on SG assembly, indicating that Sam68 is not a constitutive component of the SG. Moreover, Sam68 cytoplasmic mutant-induced SG formation was independent of eIF2alpha phosphorylation. Sam68 was complexed with T-cell intracellular antigen-1 (TIA-1), a core SG component, and that the complex formation was correlated with Sam68 SG recruitment. These results provide direct evidence for the first time that Sam68 is recruited into SG through complexing with TIA-1 in response to oxidative stress and suggest that cytoplasmic SG recruitment of Sam68 and ensuing changes in Sam68 physiological functions are part of the host response to external stressful conditions. Henao-Mejia J, He JJ. Sam68 relocalization into stress granules in response to oxidative stress through complexing with TIA-1. Exp Cell Res. 2009 Nov 5;315(19):3381-3395.

Age-Related Decline in Nicotinic Receptor Availability

Human postmortem studies have reported age-related decreases in brain high affinity nicotine binding. Staley and colleagues at Yale School of Medicine investigated the effect of age on beta(2)-containing nicotinic acetylcholine receptor (beta(2)-nAChR) availability in eight brain regions of living human subjects using the ligand [(123)I]5-IA-85380 ([(123)I]5-IA) and single photon emission computed tomography (SPECT). Healthy, nonsmokers (N=47) ranging in age from 18 to 85 were administered [(123)I]5-IA using a bolus plus constant infusion paradigm and imaged 6-8h later under equilibrium conditions. Age and regional beta(2)-nAChR availability were inversely correlated in seven of the eight brain regions analyzed, with decline ranging from 32% (thalamus) to 18% (occipital cortex) over the adult lifespan, or up to 5% per decade. These results in living human subjects corroborate postmortem reports of decline in high affinity nicotine binding with age and may aid in elucidating the role of beta(2)-nAChRs in cognitive aging. Mitsis EM, Cosgrove KP, Staley JK, et al. Age-related decline in nicotinic receptor availability with [(123)I]5-IA-85380 SPECT. Neurobiol. Aging. 2009 Sep 30;(9):1490-1497.

Altered Affective Response in Marijuana Smokers: An FMRI Study

Gruber and colleagues at McLean Hospital used fMRI to investigate alterations in mood and perception in chronic marijuana users. Endogenous cannabinoids regulate a variety of emotional responses, including anxiety, mood control, and aggression; nevertheless, little is known about smokers' responses to affective stimuli. 15 chronic heavy marijuana smokers were compared to 15 non-marijuana smoking control subjects during the viewing of masked happy and fearful faces. No differences were found on clinical or demographic measures between the groups. Marijuana smokers demonstrated a relative decrease in both anterior cingulate and amygdalar activity during masked affective stimuli; in contrast, control subjects exhibited relative increases in activation within these regions during the viewing of masked faces. That chronic heavy marijuana smokers demonstrate altered activation of frontal and limbic systems while viewing masked faces is consistent with autoradiographic studies reporting high CB-1 receptor density in these regions. These data indicate that

marijuana smokers process emotional information differently from those who do not smoke, even when stimuli are presented below the level of conscious processing. Gruber SA, Rogowska J, Yurgelun-Todd DA. Altered affective response in marijuana smokers: An FMRI study. Drug and Alcohol Dependence. 2009 Nov 1;105(1-2):139-153.

Bottom-Up and Top-Down Processes in Emotion Generation: Common and Distinct Neural Mechanisms

Oschner and colleagues at Columbia University used fMRI to investigate the relative contributions of bottom-up and top-down processes on the generation of emotions. 20 female subjects were scanned under two negative emotional conditions: bottom-up perception of aversive images vs. top-down interpretation of neutral images as aversive. Both types of responses activated the amygdala, although bottom-up responses did so more strongly, and bottom-up responses activated systems for attending to and encoding perceptual and affective stimulus properties. On the other hand, top-down responses activated prefrontal regions that represent high-level cognitive interpretations. Self-reported affect correlated with activity in the amygdala during bottom-up responding, but with activity in the medial prefrontal cortex during top-down responding. These findings provide a neural foundation for emotion theories that posit multiple kinds of appraisal processes and help to clarify mechanisms underlying clinically relevant forms of emotion dysregulation. Ochsner KN, Ray RR, Hughes B, McRae K, Cooper JC, Weber J, Gabrieli JD, Gross JJ. Bottom-up and top-down processes in emotion generation: Common and distinct neural mechanisms. Psychological Science. 2009 20;(11):1322-1331.

Cerebral Morphology and Dopamine D2/D3 Receptor Distribution in Humans

Zald and colleagues at Vanderbilt University combined structural MRI and PET receptor ligand imaging to determine the relationship between cerebral morphology and the expression of dopamine receptors in humans. 45 healthy subjects participated in T1-weighted structural MRI as well as PET scanning with the D(2)/D(3) ligand [(18)F]fallypride. Optimized voxel-based morphometry was used to create grey matter volume and density images. Grey matter volume and density images were correlated with D2/D3 receptor binding potential (DaR2-BP) images on a voxel-by-voxel basis. Associations between cerebral morphology and DaR2-BP were also examined for selected regions-of-interest (ROIs) after spatial normalization. Cerebral morphology, particularly grey matter density, correlates with [(18)F]fallypride BP(ND) in a regionally specific manner. Overall, grey matter density appeared more strongly correlated with DaR2-BP than grey matter volume. Voxel-wise analyses indicated that grey matter volume and density positively correlated with DaR2-BP throughout the midbrain, including the substantia nigra. Positive correlations were observed in medial cortical areas, including anterior cingulate and medial prefrontal cortex, and circumscribed regions of the temporal, frontal, and parietal lobes. ROI analyses revealed significant positive correlations between DaR2-BP and cerebral morphology in the caudate, thalamus, and amygdala. Woodward N, Zald D, Ding Z, Riccardi P, Ansari M, Baldwin R, Cowan R, Li R, Kessler R. Cerebral morphology and dopamine D2/D3 receptor distribution in humans: A combined [18F]fallypride and voxel-based morphometry study. Neuroimage. 2009 May 15;46:31-38.

Decoding Cognitive Control in Human Parietal Cortex

Yantis and colleagues at Johns Hopkins University used fMRI to determine how the brain provides efficient execution of perceptual-motor tasks that require

rapid voluntary reconfiguration of cognitive task sets as circumstances unfold. Such acts of cognitive control, which are thought to rely on a network of cortical regions in prefrontal and posterior parietal cortex, include voluntary shifts of attention among perceptual inputs or among memory representations, or switches between categorization or stimulus-response mapping rules. A critical unanswered question is whether task set shifts in these different domains are controlled by a common, domain-independent mechanism or by separate, domain-specific mechanisms. Recent studies have implicated a common region of medial superior parietal lobule (mSPL) as a domain-independent source of cognitive control during shifts between perceptual, mnemonic, and rule representations. Using event-related multivoxel pattern classification it was found that spatial patterns of brain activity within mSPL reliably discriminate which of several domains of cognitive control is at play on a moment-by-moment basis. Critically, these spatio-temporal brain patterns are stable over time within subjects tested several months apart and across a variety of tasks, including shifting visuospatial attention, switching categorization rules, and shifting attention in working memory. Esterman M, Chiu Y, Tamber-Rosenau B, Yantis S. Decoding cognitive control in human parietal cortex. Proceedings of the National Academy of Sciences of the United States of America. 2009 Oct 20;106(42): 17974-17979.

Decreased Brain Dopamine Cell Numbers in Human Cocaine Users

Little and colleagues at Baylor University investigated whether cocaine use might cause a loss of dopamine neurons in humans. Although rodent studies have not detected cocaine-induced dopamine cell damage, Cocaine use diminishes striatal and midbrain dopamine neuronal components in both post-mortem and in vivo human experiments. The present experiment involved counting midbrain dopamine neurons utilizing both melanin and tyrosine hydroxylase immunoreactivity in 10 cocaine users and 9 controls. Sections were also examined for signs of acute pathological injury by counting activated macrophages and microglia. Melanized cells at six midbrain levels were significantly reduced in cocaine users by both drug exposures. The estimated total number of melanized dopamine cells in the anterior midbrain was significantly reduced in cocaine users by 16%. Results with tyrosine hydroxylase immunoreactivity were less conclusive because of variability in staining. Both activated macrophages and activated microglia were significantly increased among cocaine users. These results suggest that cocaine exposure may have neurotoxic effects on dopamine neurons in humans. The infiltration of phagocytic cells suggests that the lower number of dopamine cells found in cocaine users was a relatively recent effect. The loss of dopamine cells could contribute to and intensify cocaine dependence, as well as anhedonic and depressive symptoms, in some cocaine users. Further efforts at clarifying the pathophysiological mechanisms involved may help explain treatment refractoriness, and identify targets for therapeutic intervention. Little K, Ramssen E, Welchko R, Volberg V, Roland C, Cassin B. Decreased brain dopamine cell numbers in human cocaine users. Psychiatry Research. 2009 Aug 15;168(3):173-180.

Delayed Extinction Attenuates Conditioned Fear Renewal and Spontaneous Recovery in Humans

LeBar and colleagues at Duke University investigated whether the return of fear after extinction training depends on the retention interval after an aversive learning experience. After fear conditioning, healthy participants underwent extinction training either 5 min or 1 day later and in either the same room (same context) or a different room (context shift). The next day, conditioned fear was tested in the original room. When extinction took place immediately, fear renewal was robust and prolonged for context-shift participants, and spontaneous recovery was observed in the same-context participants. Delayed

extinction, by contrast, yielded a brief form of fear renewal that reextinguished within the testing session for context-shift participants, and there was no spontaneous recovery in the same-context participants. The authors conclude that the passage of time allows for memory consolidation processes to promote the formation of distinct yet flexible emotional memory traces that confer an ability to recall extinction, even in an alternate context, and minimize the return of fear. Furthermore, immediate extinction can yield spontaneous recovery and prolong fear renewal. These findings have potential implications for treating responses to conditioned cues, such as drug craving, in substance abuse disorders. Huff N, Hernandez J, Blanding N, LaBar K. Delayed extinction attenuates conditioned fear renewal and spontaneous recovery in humans. Behavioral Neuroscience. 2009 Aug;123(4):834-843.

Dopamine and Serotonin Transporter Availability During Acute Alcohol Withdrawal: Effects of Comorbid Tobacco Smoking

Cosgrove and colleagues at Yale School of Medicine used SPECT receptor imaging to evaluate the effects of alcohol drinking alone from comorbid alcohol drinking and tobacco smoking on dopamine (DAT) and serotonin (SERT) transporter availability. Tobacco smoking is highly comorbid with heavy alcohol drinking, yet the interaction of tobacco smoking and alcohol drinking on brain catecholaminergic synaptic markers is unexplored. A total of 14 heavy alcohol drinking smokers (n=6) and nonsmokers (n=8) and 14 age-matched control smokers (n=6) and nonsmokers (n=8) were imaged with [(123)]beta-CIT which measures both DAT and SERT. Alcohol drinking smokers and nonsmokers consumed 134.3+/-100.3 and 196.5+/-139.9 drinks, respectively, over the previous month and were imaged during acute withdrawal, e.g. within 5 days of their last drink. Striatal DA transporter availability was significantly higher (16%) in alcohol drinkers compared to controls. 5-HT transporter availability was also significantly higher in alcohol drinkers vs. controls in the brainstem (25%) and the diencephalon (8%). This elevation was restricted to alcohol drinking nonsmokers with higher DA transporter availability in the striatum (26%), and higher 5-HT transporter availability in the diencephalon (26%) and brainstem (42%). There was a significant positive correlation between days since last drink and 5-HT transporter availability in the diencephalon (r=0.60) and brainstem (r=0.54), in the total group of alcohol drinkers and in the nonsmokers, but not the smokers. These results demonstrate that during the first week of abstinence, smoking appears to suppress neuroadaptive changes in DA and 5-HT transporters during acute withdrawal from alcohol insofar as DA and 5-HT transporter availability is higher in alcohol drinking nonsmokers but not in alcohol drinking smokers. Cosgrove KP, Krantzler E, Frohlich EB, et al. Dopamine and serotonin transporter availability during acute alcohol withdrawal: effects of comorbid tobacco smoking. Neuropsychopharmacology. 2009 Sep 34;(10):2218-2226.

Effects of Acute 3,4-Methylenedioxymethamphetamine on Sleep and Daytime Sleepiness in MDMA Users

Tancer and colleagues at Wayne State University studied whether acute administration of MDMA (Ecstasy) has an effect on sleep and daytime sleepiness under placebo-controlled conditions. MDMA affects monoamine neurotransmitters that play a critical role in sleep and daytime alertness. 7 recreational MDMA-users and 13 matched control subjects were studied. Participants with a history of MDMA use were studied on 3 sessions of 3 nights (baseline, treatment, and recovery) and 2 days (following night 2 and 3) per session. On treatment nights (night 2), participants received placebo or 2 mg/kg of MDMA or underwent a restricted bed schedule with placebo. Sleep restriction was a positive control to compare sleep loss and consequent sleepiness associated with MDMA use. The scheduled sleep period was 8 hours long on nonrestricted nights, and standard sleep recordings and daytime

sleepiness tests were conducted. Age-matched controls received 1 night and day of standard sleep and daytime sleepiness testing. Acute MDMA shortened sleep primarily by increasing sleep latency, and it reduced stage 3/4 sleep and suppressed rapid eye movement (REM) sleep. The MDMA-reduced sleep time was not associated with increased daytime sleepiness the following day, as was seen in the sleep-restriction condition. Compared with control subjects, the MDMA users on the first night in the laboratory had shorter total sleep times and less stage 3/4 sleep. Average daily sleep latency on daytime sleepiness tests the day after nighttime placebo administration was increased in MDMA users compared with the control subjects, and MDMA users had an elevated number of sleep-onset REM periods on these tests, compared with control subjects. Acute MDMA administration disrupts sleep and REM sleep, specifically, without producing daytime sleepiness such as sleep restriction does. Compared with control subjects, recreational MDMA users showed evidence of hyperarousal and impaired REM function. The mechanism behind these effects is likely due to the deleterious effects of MDMA on catecholamines. Randall S, Johanson C, Tancer M, Roehrs T. Effects of acute 3,4-methylenedioxymethamphetamine on sleep and daytime sleepiness in MDMA users: A preliminary study. Sleep. 2009 Nov 1;32(11):1513-1519.

Effects of MDMA on Sociability and Neural Response to Social Threat and Social Reward

de Wit and colleagues at the University of Chicago investigated whether MDMA, (Ecstasy, ±3,4-Methylenedioxymethamphetamine) produces unique subjective effects, including increased sociability, feelings of closeness with others, and reduced interpersonal defensiveness. Despite their apparent importance in recreational and potential psychotherapeutic use of MDMA, the defining characteristics and neurobiological mechanisms of these interpersonal effects are poorly understood. To address these critical questions, the acute effects of MDMA on self-reported sociability and neuronal activation in response to socially threatening (angry and fearful faces) and socially rewarding (happy faces) stimuli were evaluated in 9 volunteers reporting past ecstasy use. The results of this study provide the first evidence that MDMA may increase sociability in humans both by diminishing responses to threatening stimuli and enhancing responses to rewarding social signals. Bedi G, Phan K, Angstadt M, de Wit H. Effects of MDMA on sociability and neural response to social threat and social reward. Psychopharmacology. 2009 Nov 1;207(1):73-83.

Electrophysiological and Hemodynamic Responses to Reward Prediction Violation

Martin and colleagues at the University of South Florida combined scalp recorded electrical event-related epotentials (ERP) and fMRI to investigate whether anterior cingulate cortex detects outcomes that are worse than expected. ERP and fMRI data were obtained from the same participants in different sessions during a reward prediction violation design. Both the medial frontal negativity (MFN) ERP response and anterior cingulate cortex fMRI activity differentiated between reward delivery and expectation. The largest MFN and anterior cingulate cortex fMRI response occurred when predicted rewards were not delivered. Inverse modeling placed the MFN source near the anterior cingulate cortex hemodynamic activation. The fMRI study also showed increased striatal response to rewards regardless of prediction indicating dissociation of neural processing of reward and reward expectation. Martin L, Potts G, Burton P, Montague P. Electrophysiological and hemodynamic responses to reward prediction violation. NeuroReport. 2009 Aug 26;20(13):1140-1143.

Evaluation of Genetic Variability in the Dopamine Receptor D2 in

Relation to Behavioral Inhibition and Impulsivity/Sensation Seeking: An Exploratory Study with D-Amphetamine in Healthy Participants

de Wit and colleagues at the University of Chicago investigated whether inhibition and impulsivity were related to genetic polymorphisms in the DRD2 gene (DRD2) in healthy volunteers (N = 93). The dopamine D2 receptor (DRD2) appears to be involved in impulsive behaviors, and particularly in behavioral inhibition. They therefore investigated the association between 12 single nucleotide polymorphisms (SNPs) and haplotypes in DRD2 and stop task performance in the nondrug (i.e., placebo) session and on the personality measure of impulsivity. Participants received placebo or d-amphetamine in random order. During each session, the participants performed the stop-signal task, measuring behavioral inhibition, rated their mood states, and completed the Zuckerman-Kuhlman Personality Questionnaire, including an Impulsivity subscale. Mood was not related to genotypes in either the drug free condition or in response to drug. However, 2 SNPs, rs4648317 and rs12364283, and a haplotype block consisting of those SNPs, were associated with better performance on the stop-signal task in the drug free condition and lower scores on the Impulsivity subscale. The rs12364283 SNP was associated with effects of d-amphetamine on stop task performance: d-amphetamine decreased stop reaction time (RT) in the A/A group but increased stop RT in the combined A/G + G/G genotype. Of the SNPs evaluated, rs12364283, which has been associated with DRD2 expression, was the most significantly associated with inhibition and impulsivity. The significant relationship between DRD2 genotype and both behavioral inhibition and impulsivity suggests a possible common genetic influence on behavioral and self-report measures of impulsivity. Hamidovic A, Dlugos A, Skol A, Palmer AA, de Wit H. Evaluation of genetic variability in the dopamine receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: an exploratory study with d-amphetamine in healthy participants. Exp Clin Psychopharmacol. 2009 Dec 17;(6):374-383.

Evidence for a Common Representation of Decision Values for Dissimilar Goods in Human Ventromedial Prefrontal Cortex

Rangel and colleagues at the University of Southern California used fMRI to determine how the brain computes representations of values in order to make economic choices between goods. It is a matter of controversy whether there exists a region of the brain that commonly encodes decision values for different types of goods, or if, in contrast, the values of different types of goods are represented in distinct brain regions. To address this question, healthy subjects made real purchasing decisions among different categories of goods (food, nonfood consumables, and monetary gambles) during fMRI scans. Activity in the ventromedial prefrontal cortex (vmPFC), a key brain region previously implicated in encoding goal-values, was correlated with the subjects' value for each category of good. Moreover, a single area in vmPFC was correlated with the subjects' valuations for all categories of goods. These results provide evidence that the brain encodes a "common currency" that allows for a shared valuation for different categories of goods. Chib VS, Rangel A, Shimojo S, O'Doherty JP. Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. J. Neurosci. 2009 Sep 30;29(39):12315-12320.

Executive Control Deficits in Substance-Dependent Individuals: A Comparison of Alcohol, Cocaine, and Methamphetamine and of Men and Women

Bechara and colleagues at the University of Southern California investigated the effect that different drugs and sex have on Executive Function defects. The

performance of alcohol- (n = 33; 18 women), cocaine- (n = 27; 14 women), and methamphetamine-dependent individuals (n = 38; 25 women) were compared with sex-matched healthy comparisons (n = 36; 17 women) on complex decision making as measured with the Iowa Gambling Task, working memory, cognitive flexibility, and response inhibition. Cocaine-and methamphetamine-dependent individuals were impaired on complex decision making, working memory, and cognitive flexibility, but not on response inhibition. The deficits in working memory and cognitive flexibility were milder than the decision-making deficits and did not change as a function of memory load or task switching. Interestingly, decision making was significantly more impaired in women addicted to cocaine or methamphetamine than in men addicted to these drugs. Together, these findings suggest that drug of choice and sex have different effects on executive functioning, which, if replicated, may help tailor intervention. van der Plas E, Crone E, van den Wildenberg W, Tranel D, Bechara A. Executive control deficits in substance-dependent individuals: A comparison of alcohol, cocaine, and methamphetamine and of men and women. Journal of Clinical And Experimental Neuropsychology. 2009 31;(6):706-719.

Higher Diffusion in Striatum and Lower Fractional Anisotropy in White Matter of Methamphetamine Users

Chang and colleagues at the University of Hawaii used Diffusion Tensor Imaging (DTI) to investigate microstructural brain changes in METH users. Prior studies have shown that methamphetamine (METH) users have structural and chemical abnormalities on magnetic resonance imaging (MRI) studies, particularly in the frontal and basal ganglia brain regions. In this study, diffusion tensor measures in frontal white matter and basal ganglia were obtained from 30 adult METH users and 30 control subjects. Compared with healthy control subjects, METH users showed lower fractional anisotropy (FA) in right frontal white matter, and higher average diffusion coefficient (ADC) in left caudate and bilateral putamen. Higher left putamen ADC was associated with earlier initiation of METH use, greater daily amounts, and a higher cumulative lifetime dose. Similarly, higher right putamen ADC was associated with greater daily amounts and a higher cumulative lifetime dose. The lower FA in the right frontal white matter suggests axonal injury in these METH users. The higher ADC in the basal ganglia suggests greater inflammation or less myelination in these brain regions of those with younger age of first METH use and greater METH usage. Alicata D, Chang L, Cloak C, Abe K, Ernst T. Higher diffusion in striatum and lower fractional anisotropy in white matter of methamphetamine users. Psychiatry Res. 2009 Oct 30;174(1):1-8.

Hormonal, Cardiovascular, and Subjective Responses to Acute Stress in Smokers

de Wit and colleagues at the University of Chicago investigated how smoking affects physiological and psychological outcomes after stress and how these may interact to motivate smoking. There are complex relationships between stress and smoking; smoking may reduce the emotional discomfort of stress, yet nicotine activates stress systems and may alter responses to acute stress. This study aimed to examine the magnitude and time course of hormonal, cardiovascular, and psychological responses to acute psychosocial stress in smokers and non-smokers to investigate whether responses to acute stress are altered in smokers. Healthy male non-smokers (n = 20) and smokers (n = 15) participated in two experimental sessions involving a standardized public speaking stress procedure and a control non-stressful task. The outcome measures included self-reported mood, cardiovascular measures (heart rate and blood pressure), and plasma hormone levels (noradrenaline, cortisol, progesterone, and allopregnanolone). Smokers exhibited blunted increases in cortisol after the Trier Social Stress Test, and reported greater and more

prolonged subjective agitation than non-smokers. Stress-induced changes in progesterone were similar between smokers and non-smokers, although responses overall were smaller among smokers. Stress did not significantly alter levels of allopregnanolone, but smokers exhibited lower plasma concentrations of this neurosteroid. These findings suggest that smoking dampens hormonal responses to stress and prolongs subjective discomfort. Dysregulated stress responses may represent a breakdown in the body's ability to cope efficiently and effectively with stress and may contribute to smokers' susceptibility to acute stress, especially during abstinence. Childs E, de Wit H. Hormonal, cardiovascular, and subjective responses to acute stress in smokers. Psychopharmacology (Berl.). 2009 Mar 203;(1):1-12.

Impaired Error Awareness and Anterior Cingulate Cortex Hypoactivity in Chronic Cannabis Users

Garavan and colleagues at Trinity College used fMRI to investigate whether chronic cannabis use leads to a diminished neural response to errors, particularly in the anterior cingulate cortex (ACC), a brain region thought critical to error processing. A diminished capacity for detecting errors has been linked to clinical symptoms including the loss of insight, delusions, and perseverative behavior. 16 active chronic cannabis users and 16 control participants were administered a Go/No-go response inhibition task during event-related fMRI scans. The task provides measures of inhibitory control and error awareness. Cannabis users' inhibitory control performance was equivalent to that of the control group, but the former showed a significant deficit in awareness of commission errors. Cannabis users showed a diminished capacity for monitoring their behavior that was associated with hypoactivity in the ACC and right insula. In addition, increased levels of hypoactivity in both the ACC and right insula regions were significantly correlated with error-awareness rates in the cannabis group (but not controls). These difficulties are consistent with earlier reports of hypoactivity in the neural systems underlying cognitive control and the monitoring of interoceptive awareness in chronic drug users, and highlight the potential relationship between cognitive dysfunction and behavioral deficits that have the potential to contribute to the maintenance of drug abuse. Hester R, Nestor L, Garavan H. Impaired Error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. Neuropsychopharmacology. 2009 Oct 34;(11):2450-2458.

Increased Ventral Striatal BOLD Activity During Non-Drug Reward Anticipation in Cannabis Users

Garavan and colleagues at Trinity College used fMRI to investigate whether chronic cannabis use effects reward processing in the brain. Motivational theories regarding long-term drug use posit contrasting predictions with respect to how drug users are likely to process non-drug incentives. The current study examined BOLD responses during reward and loss anticipation and their outcome deliveries in 14 chronic cannabis users and 14 drug-naive controls during a monetary incentive delay (MID) task. Even though there were no significant behavioural differences between the two groups, cannabis users had significantly more right VS BOLD activity during reward anticipation. Correlation analyses demonstrated that this right VS BOLD response was significantly correlated with life-time use and reported life-time cannabis joints consumed. No correlations between cannabis abstinence and BOLD responses were observed. A number of group differences in brain activity were found following outcome deliveries, most notably hypoactivity in the left insula cortex in response to loss and loss avoidance outcome notifications in the cannabis group. These results may suggest hypersensitivity during instrumental response anticipation for non-drug rewards and a hyposensitivity to loss outcomes in chronic cannabis users; the implications of which are discussed with respect to the potentially sensitizing effects of cannabis for other rewards.

Nestor L, Hester R, Garavan H. Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. Neuroimage. 2010 Jan 1;49(1):1133-1143.

Kinetic Modeling of the Serotonin 5-HT(1B) Receptor Radioligand [(11)C]P943 in Humans

Ding and colleagues at Yale School of Medicine investigated the properties of [(11)C]P943, a new radioligand recently developed to image and quantify serotonin 5-Hydroxytryptamine (5-HT(1B)) receptors with positron emission tomography (PET). The purpose of this study was to evaluate [(11)C]P943 for this application in humans, and to determine the most suitable quantification method. Positron emission tomography data and arterial input function measurements were acquired in a cohort of 32 human subjects. Using arterial input functions, compartmental modeling, the Logan graphical analysis, and the multilinear method MA1 were tested. Both the two tissue-compartment model and MA1 provided good fits of the PET data and reliable distribution volume estimates. Using the cerebellum as a reference region, BP(ND) binding potential estimates were computed. [(11)C]P943 BP(ND) estimates were significantly correlated with in vitro measurements of the density of 5-HT(1B) receptors, with highest values in the occipital cortex and pallidum. To evaluate noninvasive methods, two- and three-parameter graphical analyses, Simplified Reference Tissue Models (SRTM and SRTM2), and Multilinear Reference Tissue Models (MRTM and MRTM2) were tested. The MRTM2 model provided the best correlation with MA1 binding-potential estimates. Parametric images of the volume of distribution or binding potential of [(11)C]P943 could be computed using both MA1 and MRTM2. The results show that [(11)C]P943 provides quantitative measurements of 5-HT(1B) binding potential. Gallezot J, Nabulsi N, Neumeister A, Planeta-Wilson B, Williams WA, Singhal T, Kim S, Maguire RP, McCarthy T, Frost JJ, Huang Y, Ding Y, Carson RE. Kinetic modeling of the serotonin 5-HT(1B) receptor radioligand [(11)C]P943 in humans. J. Cereb. Blood Flow Metab. 2009 Sep 23;30(1):196-210.

Learning and Memory Deficits in Ecstasy Users and their Neural Correlates during a Face-Learning Task

Garavan and colleagues at Trinity College used fMRI to investigate whether MDMA use leads to neural differences in encoding and recalling face-name associations. It has been consistently shown that ecstasy users display impairments in learning and memory performance. In addition, working memory processing in ecstasy users has been shown to be associated with neural alterations in hippocampal and/or cortical regions as measured by functional magnetic resonance imaging (fMRI). 20 recreational drug users whose predominant drug use was ecstasy and 20 controls participated in an initial study. To address the potential confounding effects of the cannabis use of the ecstasy using group, a second analysis included 14 previously tested cannabis users. Ecstasy users performed significantly worse in learning and memory compared to controls and cannabis users. A conjunction analysis of the encode and recall phases of the task revealed ecstasy-specific hyperactivity in bilateral frontal regions, left temporal, right parietal, bilateral temporal, and bilateral occipital brain regions. Ecstasy-specific hypoactivity was evident in the right dorsal anterior cingulate cortex (ACC) and left posterior cingulate cortex. In both ecstasy and cannabis groups, brain activation was decreased in the right medial frontal gyrus, left parahippocampal gyrus, left dorsal cingulate gyrus, and left caudate. These results elucidated ecstasy-related deficits, only some of which might be attributed to cannabis use. These ecstasy-specific effects may be related to the vulnerability of isocortical and allocortical regions to the neurotoxic effects of ecstasy. Roberts G, Nestor L, Garavan H. Learning and memory deficits in ecstasy users and their neural correlates during a face-learning task. Brain Research. 2009 Oct 6;1292:71-81.

Learning to Attend: Effects of Practice on Information Selection

Yantis and colleagues at Johns Hopkins University investigated how practice affects the deployment of selective attention to filter distracting information. This issue was addressed by examining how performance on a task changed after repeated exposure to distractors. Distraction initially slowed response time during task performance, an effect that diminished with repeated exposure to the distractors. When the distractors were consistent in appearance, the practice effect developed quickly but was stimulus-specific. When the distractors were more variable in appearance, the practice effect developed slowly but transferred more readily to other conditions. These data indicate that practice with overcoming distraction leads to improvements in information filtering mechanisms that generalize beyond the training regimen when variable distractor stimuli are experienced. Kelley T, Yantis S. Learning to attend: Effects of practice on information selection. Journal of Vision. 2009 9; (7):26-32.

Lower Level of Endogenous Dopamine in Patients With Cocaine Dependence: Findings From PET Imaging of D2/D3 Receptors Following Acute Dopamine Depletion

Martinez and colleagues at Columbia University investigated whether the decrease in dopamine type 2 and 3 (D2/D3) receptor binding in cocaine-dependent individuals relative to healthy comparison subjects could be due to an increase in baseline dopamine levels. PET receptor imaging was used to measure D2/D3 receptors following acute dopamine depletion in cocaine-dependent volunteers relative to healthy comparison subjects. Cocaine-dependent volunteers (N=15) and healthy matched comparison subjects (N=15) were scanned using PET, with the dopamine receptor radiotracer [11C]raclopride, at baseline and again following acute depletion of endogenous dopamine via alpha-methyl-para-tyrosine (AMPT) administration. Changes in radiotracer binding were measured in the subdivisions of the striatum (caudate, putamen, and ventral striatum) in addition to the striatum as a whole. Findings revealed that cocaine-dependent volunteers exhibited lower levels of endogenous dopamine relative to comparison subjects, which was measured as an increase in [11C]raclopride binding following AMPT administration. The increase in [11C]raclopride binding in the striatum was 11.1% (SD=4.4%) in healthy comparison subjects and 5.7% (SD=5.9%) in cocaine-dependent volunteers. Similar differences were seen in the subdivisions of the striatum. Thus, the decrease in striatal D2/D3 receptors associated with cocaine dependence cannot be attributed to higher levels of endogenous dopamine. Martinez D, Greene K, Broft A, et al. Lower level of endogenous dopamine in patients with cocaine dependence: Findings from PET imaging of D2/D3 receptors following acute dopamine depletion. Am J Psychiatry. 2009 Oct 1;166(10):1170-1177.

Momentary Reductions of Attention Permit Greater Processing of Irrelevant Stimuli

Weissman and colleagues at the University of Michigan used fMRI to investigate whether increased distraction from irrelevant stimuli can produce momentary reductions of attention which can have extremely adverse outcomes (e.g., during driving). To investigate this hypothesis, trial-by-trial relationships between brain activity and response time were determined in twenty healthy adults while they performed a cross-modal selective attention task. In each trial, participants identified a relevant visual letter while ignoring an irrelevant auditory letter, which was mapped either to the same response as the visual letter (congruent trials) or to a different response (incongruent trials). As

predicted, reductions of attention (i.e., increases of response time) were associated not only with decreased activity in sensory regions that processed the relevant visual stimuli, suggesting a failure to enhance the processing of those stimuli, but also with increased activity in sensory regions that processed the irrelevant auditory stimuli, suggesting a failure to suppress the processing of those stimuli. Reductions of attention were also linked to larger increases of activity in incongruent than in congruent trials in anterior cingulate regions that detect response conflict, suggesting that failing to suppress the sensory processing of the irrelevant auditory stimuli during attentional reductions allowed those stimuli to more readily activate conflicting responses in incongruent trials. These findings indicate that heightened levels of distraction during momentary reductions of attention likely stem, at least in part, from increased processing of irrelevant stimuli. Weissman DH, Warner LM, Woldorff MG. Momentary reductions of attention permit greater processing of irrelevant stimuli. Neuroimage. 2009 Nov 15;48(3):609-615.

Risk Prediction and Aversion by Anterior Cingulate Cortex

Brown and Braver used fMRI to test whether the anterior cingulate cortex (ACC) and surrounding areas will become active in proportion to the perceived likelihood of an error (error-likelihood hypothesis). The hypothesis was originally derived from a computational model prediction. The same computational model now makes a further prediction that ACC will be sensitive not only to predicted error likelihood, but also to the predicted magnitude of the consequences, should an error occur. The product of error likelihood and predicted error consequence magnitude collectively defines the general "expected risk" of a given behavior in a manner analogous but orthogonal to subjective expected utility theory. The fMRI results from an incentive change signal task now replicate the error-likelihood effect, validate the further predictions of the computational model, and suggest why some segments of the population may fail to show an error-likelihood effect. In particular, error-likelihood effects and expected risk effects in general indicate greater sensitivity to earlier predictors of errors and are seen in risk-averse but not risk-tolerant individuals. Taken together, the results are consistent with an expected risk model of ACC and suggest that ACC may generally contribute to cognitive control by recruiting brain activity to avoid risk. Brown JW, Braver TS. Risk prediction and aversion by anterior cingulate cortex. Cogn Affect Behav Neurosci. 2007 Dec 7;(4):266-277.

Neural Correlates of Risk Prediction Error During Reinforcement Learning in Humans

Bechara and colleagues at the University of Southern California used fMRI to address how the human brain learns which decisions are risky. Reinforcement learning has never been used to estimate reward variance, a common measure of risk in economics and psychology. It is thus unknown which brain regions are involved in risk learning. To address this question, participants completed a decision-making task during fMRI. They chose repetitively from four decks of cards and each selection was followed by a stochastic payoff. Expected reward and risk differed among the decks. Participants' aim was to maximize payoffs. Risk and reward prediction errors were calculated after each payoff based on a novel reinforcement learning model. For reward prediction error, the strongest correlation was found with the BOLD response in the striatum. For risk prediction error, the strongest correlation was found with the BOLD responses in the insula and inferior frontal gyrus. The results suggest that risk and reward prediction errors are processed by distinct neural circuits during reinforcement learning. Additional analyses revealed that the BOLD response in the inferior frontal gyrus was more pronounced for risk aversive participants, suggesting that this region also serves to inhibit risky choices. d'Acremont M, Lu Z, Li X, Van der Linden M, Bechara A. Neural correlates of risk prediction error during

reinforcement learning in humans. Neuroimage. 2009 Oct 1;47(4):1929-1939.

Neural Mechanisms Underlying Drug-Related Cue Distraction in Active Cocaine Users

Garavan and Hester at Trinity College used fMRI to investigate the neuronal basis of the difficulty that human drug abusers have with disengaging attention from drug-related stimuli, a symptom previously shown to be predictive of relapse during treatment. The neural mechanisms underlying this attentional bias in cocaine users was investigated by varying working memory (WM) load to reflect the demands imposed by ruminative craving thoughts. Sixteen active users of cocaine were administered a WM task that manipulated the requirement for selective attention by varying the background contents, cocaine-related or neutral, upon which a recall probe item was shown. Behavioral and fMRI data were collected. Cocaine users had significantly poorer attentional control under high WM demands, suffering both increased response times and reduced recall accuracy, with this effect more pronounced for cocaine stimuli (when compared to neutral stimuli). The presence of background cocaine stimuli was associated with increases in occipital cortex activity, consistent with increased visual processing of the irrelevant stimuli for these trials. In addition, the cocaine stimuli were associated with increased right prefrontal activity with those participants with higher levels of right prefrontal activity having lower levels of attentional bias. Cocaine users under high cognitive demands had difficulty modulating the neural mechanisms underlying cognitive control which appear necessary for restricting the visual processing of task-irrelevant, but salient, drug-related stimuli, a finding that may be relevant to identifying those at most risk of relapse. Hester R, Garavan H. Neural mechanisms underlying drug-related cue distraction in active cocaine users. Pharmacology Biochemistry and Behavior. 2009 Sep 93;(3):270-277.

Neural Responses to Sanction Threats in Two-Party Economic Exchange

Montague and colleagues at Baylor University used fMRI to investigate how sanctions used to enforce obedience to social norms are processed in the brain. Recent studies have demonstrated that cooperation is sometimes reduced when incentives meant to promote prosocial decisions are added to the environment. Although various explanations for this effect have been suggested, the neural foundations of the effect have not been fully explored. Using a modified trust game, it was found that trustees reciprocate relatively less when facing sanction threats, and that the presence of sanctions significantly reduces trustee's brain activity in regions involved in social reward valuation (ventromedial prefrontal cortex (VMPFC), lateral orbitofrontal cortex, and amygdala) while it simultaneously increases brain activity in the parietal cortex, which has been implicated in rational decision making. Moreover, neural activity in a trustee's VMPFC area predicted future level of cooperation under both sanction and no-sanction conditions, and this predictive activity was dynamically modulated by the presence of a sanction threat. Li J, Xiao E, Houser D, Montague P. Neural responses to sanction threats in two-party economic exchange. PNAS USA. 2009 Sep 29;106(39):16835-16840.

PET Imaging of the Effects of Age and Cocaine on the Norepinephrine Transporter in the Human Brain Using (S,S)-[(11)C]O-Methylreboxetine and HRRT

Ding and colleagues at Yale School of Medicine used a novel PET radiotracer to investigate the role of the norepinephrine transporter (NET) in cocaine dependence. This study used the most promising C-11 labeled positron-emission tomography (PET) radioligand for NET developed to date: (S,S)-

[(11)C]methylreboxetine ([(11)C]MRB). 10 cocaine abusers (COC) and 12 healthy controls (HC)underwent dynamic (11)C-MRB-PET acquisition using a High Resolution Research Tomograph (HRRT). Binding potential (BP(ND)) parametric images were computed using the simplified reference tissue model (SRTM2) with occipital cortex as reference region. BP(ND) values were compared between the two groups. Locus coeruleus (LC), hypothalamus, and pulvinar showed a significant inverse correlation with age among HC (age range = 25-54 years). The BP(ND) was significantly increased in thalamus (27%) and dorsomedial thalamic nuclei (30%) in COC as compared to HC. Upon age normalization, the upregulation of NET in COC also reached significance in LC (63%) and pulvinar (55%) . These results suggest that (a) brain NET concentration declines with age in HC, and (b) there is a significant upregulation of NET in thalamus and dorsomedial thalamic nucleus in COC as compared to HC. These results demonstrate that [(11)C]MRB and HRRT provide an effective strategy for studying alterations of the NET system in humans. Ding Y, Singhal T, Planeta-Wilson B, et al. PET imaging of the effects of age and cocaine on the norepinephrine transporter in the human brain using (S,S)-[(11)C]O-methylreboxetine and HRRT. Synapse. 2010 Jan 64;(1):30-38.

Striatal Dopamine D2/D3 Receptor Availability Is Reduced in Methamphetamine Dependence and Is Linked to Impulsivity

London and colleagues at the University of California-Los Angeles investigated whether impulsivity is related to striatal dopamine D2/D3 receptor deficits in methamphetamine addicts. Methamphetamine-dependent and healthy control subjects were administered the Barratt Impulsiveness Scale (version 11, BIS-11) and had positron emission tomography scans with [18F]fallypride to measure striatal dopamine D2/D3 receptor availability. The methamphetamine-dependent subjects reported recent use of the drug 3.3 g per week, and a history of using methamphetamine, on average, for 12.5 years. Methamphetamine-dependent subjects had higher scores than healthy control subjects on all BIS-11 impulsiveness subscales. Volume-of-interest analysis found lower striatal D2/D3 receptor availability in methamphetamine-dependent than in healthy control subjects and a negative relationship between impulsiveness and striatal D2/D3 receptor availability in the caudate nucleus and nucleus accumbens that reached statistical significance in methamphetamine-dependent subjects. Combining data from both groups, voxelwise analysis indicated that impulsiveness was related to D2/D3 receptor availability in left caudate nucleus and right lateral putamen/claustrum. The findings suggest that low striatal D2/D3 receptor availability may mediate impulsive temperament and thereby influence addiction. Lee B, London ED, Poldrack RA, et al. Striatal dopamine D2/D3 receptor availability Is reduced in methamphetamine dependence and is linked to impulsivity. J. Neurosci. 2009 Nov 25;29(47):14734-14740.

Relation of Genetic Variability in the Dopamine Receptor D2 and Behavioral Inhibition and Impulsivity/Sensation Seeking

Hamidovic, de Wit and associates assessed the effects of d-amphetamine on healthy volunteers and assessed 12 SNPs and haplotypes in DRD2 in stop task performance and for self-rated impulsivity measures. Variants of two of the SNPs and a haplotype block containing them were associated with better performance on the stop task in the drug free condition and lower scores on an Impulsivity subscale. A variant of one of the SNPs was associated with a decreased stop reaction time with d-amphetamine. This SNP has been associated with DRD2 expression. Therefore it is concluded that genetic variation has an influence on behavioral and self-report measures of impulsivity. Hamidovic A, Dlugos A, Skol A, Palmer AA, de Wit H. Evaluation of genetic variability in the dopamine receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: An exploratory study with d-

amphetamine in healthy participants. Exptl Clin Psychopharm 2009;17(6):374-383.

High Impulsiveness Associated with Higher µ-Receptor Concentrations and Endogenous Opioid Activation

J-K Zubieta assessed binding potential in healthy men using PET and [11C]carfentanil both at rest and during a (pain) stress challenge. The NEO personality inventory was used determine impulsivity (tendency to act without careful consideration to obtain more immediate gratification) which is believed to be related to problem behaviors such as drug use. Greater binding potential for the µ-receptor was seen for subjects with high impulsivity scores in the right anterior cingulate, right ventral basal ganglia (nucleus accumbens and ventral pallidum), and basolateral area of the right amygdala. When stressed with induced pain, those with the high scores demonstrated significantly greater activation of µ-receptor-mediated neurotransmission. These effects accounted for up to half the variance in trait scores (impulsivity) and provide the first evidence in humans that behavioral facets relevant to motivated behaviorÑthe pursuit of reward, and risk-taking both associated with drug abuseÑare related to the individual function of the endogenous opioid system. Love TF, Stohler CS, Zubieta J-K. Positron emission tomography measures of endogenous opioid neurotransmission and impulsiveness traits in humans. Arch Gen Psychiat. 2009 Oct;66(10):1124-1134.

Enhanced Striatal Recruitment by Prospective Immediate Rewards Relative to Equally-Preferred Delayed Rewards

Drug abusers are characterized by severe discounting of delayed rewards. John Monterosso and colleagues at the University of Southern California used fMRI to examine the response of incentive-motivational neurocircuitry to immediate and delayed prospective rewards that were equally preferred by the subject in pre-scan behavioral testing. Anatomical region of interest analysis as well as whole-brain analysis indicated greater response recruited by the immediate rewards (relative to the preference-matched delayed rewards) in regions previously implicated as sensitive to incentive value using the same task (including bilateral putamen, bilateral anterior insula, and midbrain). Reaction time to the target was also faster during the immediate relative to delayed reward trials ($p < 0.01$), and individual differences in reaction time between immediate versus delayed reward trials correlated positively with variance in magnetic resonance signal in those clusters that responded preferentially to immediate rewards. These findings indicate a discrepancy in incentives associated with the immediate versus the preference-matched delayed rewards. This discrepancy may mark the contribution of self-control processes that are recruited during decision-making but that are absent when rewards are individually anticipated. That this difference in motivational neurocircuitry recruitment was detected in healthy controls suggests that this may contribute to pronounced preference for immediate gratification in drug abusers. Luo S, Ainslie G, Giragosian L, Monterosso JR. Behavioral and neural evidence of incentive bias for immediate rewards relative to preference-matched delayed rewards. J Neurosci. 2009 Nov 25;29(47):14820-14827.

The Neurocircuitry of Impaired Insight in Drug Addiction

More than 80% of addicted individuals fail to seek treatment, which might reflect impairments in recognition of severity of disorder. Considered by some as intentional deception, such 'denial' might instead reflect dysfunction of brain networks subserving insight and self-awareness. This review covers the scant literature on insight in addiction and integrates this perspective with the role of: (i) the insula in interoception, self-awareness and drug craving; (ii) the

anterior cingulate in behavioral monitoring and response selection (relevant to disadvantageous choices in addiction); (iii) the dorsal striatum in automatic habit formation; and (iv) drug-related stimuli that predict emotional behavior in addicted individuals, even without conscious awareness. Implications for clinical treatment, including the design of interventions to improve insight into illness severity in addiction are discussed. Goldstein RZ, Craig ADB, Bechara A, Garavan H, Childress AR, Paulus MP, Volkow ND. The neurocircuitry of impaired insight in drug addiction. Trends Cogn. Sci. (Regul. Ed.). 2009 Sep 13;(9):372-380.

The Role of Interoception and Alliesthesia in Addiction

Paulus and colleagues propose a novel conceptualization of addiction, integrating the concepts of interoception (i.e., the CNS representation of visceral feelings) and alliesthesia (i.e., that rewarding properties of stimuli are dependent on the internal state of the individual) with existing theories. It is argued that the body state, as defined by the integration of interoceptive information, is a crucial arbiter of the risk for initiation of and transition to compulsive use of addictive compounds. Overall, individuals at risk for drug dependence are characterized by an altered internal bodily state that leads to a change in hedonic and incentive motivational properties of addictive drugs. Specifically, drug dependent individuals experience alliesthesia of interoceptive processing, leading to increased incentive motivational properties of the drug over time and thereby increasing the probability of subsequent use. This extension of previous theories of addiction to include interoception and alliesthesia is based upon a clearly delineated set of neural substrates mediating interoception, key elements of which also recently have been implicated in drug addiction. The model thereby provides new potential targets for interventions that are aimed at changing the internal state that puts the individual at risk for continued substance use. Paulus MP, Tapert SF, Schulteis G. The role of interoception and alliesthesia in addiction. Pharmacol Biochem Behav. 2009 Nov 94;(1):1-7.

The Role of the Dorsal Anterior Cingulate in Evaluating Behavior for Achieving Gains and Avoiding Losses

Garavan and colleagues at Trinity University investigated how effective goal-directed behavior relies on a network of regions including anterior cingulate cortex and ventral striatum to learn from negative outcomes in order to improve performance. This study also investigated whether this frontal-striatal system is involved in instances of behavior that do not presume negative circumstances. Participants performed a visual target/nontarget search game in which they could optionally abort a trial to avoid errors or receive extra reward for highly confident responses. Anterior cingulate and prefrontal cortex were equally activated for error avoidance and high reward trials but were not active on error trials, demonstrating their primary involvement in self-initiated behavioral adjustment and not error detection or prediction. In contrast, the insula and the ventral striatum were responsive to the high reward trials. Differential activation patterns across conditions for the nucleus accumbens, insula, and prefrontal cortex suggest distinct roles for these structures in the control of reward-related behavior. Magno E, Sim›es-Franklin C, Robertson IH, Garavan H. The role of the dorsal anterior cingulate in evaluating behavior for achieving gains and avoiding losses. J Cogn Neurosci. 2009 Dec 21;(12):2328-2342.

Worth the ÔEEfRT'? The Effort Expenditure for Rewards Task as an Objective Measure of Motivation and Anhedonia

Zald and colleagues at Vanderbilt University used a novel behavioral paradigm

as a means of exploring effort-based decision-making in humans. Drug abuse is generally assumed to reflect aberrant motivation and reward responsivity. However, research has been limited by a lack of objective measures of reward motivation. The Effort-Expenditure for Rewards Task (EEfRT or "effort") was used to test the hypothesis that effort-based decision-making is related to trait anhedonia. 61 subjects completed self-report measures of mood and trait anhedonia, and completed the EEfRT. Across multiple analyses, a significant inverse relationship between anhedonia and willingness to expend effort for rewards was found. These findings suggest that anhedonia is specifically associated with decreased motivation for rewards, and provide initial validation for the EEfRT as a laboratory-based behavioral measure of reward motivation and effort-based decision-making in humans. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the ÔEEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. PLoS ONE. 2009;4(8):e6598.

Traditional Chinese Acupuncture and Placebo (Sham) Acupuncture are Differentiated by their Effects on Mu-Opioid Receptors (MORs)

Zubieta and colleagues at the University of Michigan used PET receptor imaging to investigate whether acupuncture analgesia involves the activation of endogenous opioid antinociceptive systems and mu-opioid receptors (MORs). This is also a neurotransmitter system that mediates the effects of placebo-induced analgesia. This overlap in potential mechanisms may explain the lack of differentiation between traditional acupuncture and either non-traditional or sham acupuncture in multiple controlled clinical trials. The short- and long-term effects of traditional Chinese acupuncture (TA) were compared with sham acupuncture (SA) treatment on in vivo MOR binding availability in chronic pain patients diagnosed with fibromyalgia (FM). Patients were randomized to receive either TA or SA treatment over the course of 4 weeks. Positron emission tomography (PET) with C-11-carfentanil was performed once during the first treatment session and then repeated a month later following the eighth treatment. Acupuncture therapy evoked short-term increases in MOR binding potential in multiple pain and sensory processing regions including the cingulate (dorsal and subgenual), insula, caudate, thalamus, and amygdala. Acupuncture therapy also evoked long-term increases in MOR binding potential in some of the same structures including the cingulate (dorsal and perigenual), caudate, and amygdala. These short- and long-term effects were absent in the sham group where small reductions were observed, an effect more consistent with previous placebo PET studies. Long-term increases in MOR BP following TA were also associated with greater reductions in clinical pain. These findings suggest that divergent MOR processes may mediate clinically relevant analgesic effects for acupuncture and sham acupuncture, Harris R, Zubieta J, Scott D, Napadow V, Gracely R, Clauw D. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). Neuroimage. 2009 Sep 47;(3):1077-1085.

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

Research Findings - Epidemiology and Etiology Research

Motives for Nonmedical Use of Prescription Opioids among High School Seniors in the United States: Self-treatment and Beyond

This study assessed motives for nonmedical use of prescription opioids among US high school seniors and examined associations between motives for nonmedical use and other substance use behaviors. Data were obtained from nationally representative samples of US high school seniors (modal age 18 years) surveyed during the spring of their senior year via self-administered questionnaires. Data were collected in public and private high schools. The sample consisted of 5 cohorts (2002-2006) of 12,441 high school seniors. Self-reports of motives for nonmedical use of prescription opioids and substance use behaviors were examined. More than 1 in every 10 high school seniors reported nonmedical use of prescription opioids and 45% of past-year nonmedical users reported "to relieve physical pain" as an important motivation. The odds of heavy drinking and other drug use were lower among nonmedical users of prescription opioids motivated only by pain relief compared with nonmedical users who reported pain relief and other motives and those who reported non-pain relief motives only. The odds of medical use of prescription opioids were lower among nonmedical users who reported only non-pain relief motives compared with other types of nonmedical users. The findings indicate motives should be considered when working with adolescents who report nonmedical use of prescription opioids. The authors stress that future efforts are needed to identify adolescents who may need appropriate pain management and those at increased risk for prescription opioid abuse. McCabe S, Boyd C, Cranford J, Teter C. Motives for nonmedical use of prescription opioids among high school seniors in the United States: Self-treatment and beyond. Arch Pediatr Adolesc Med. 2009;163(8):739-744.

Specific Sex Drug Combinations Contribute to the Majority of Recent HIV Sero-conversions among MSM in the MACS

New HIV infections continue to be observed among men who have sex with men (MSM). Understanding the convergence of risky sexual behaviors and use of stimulants and erectile dysfunction drugs with HIV seroconversion may provide new focus to prevention interventions. During the follow-up period (1998-2008) of the Multicenter AIDS Cohort Study (MACS), researchers identified 57 HIV seroconversions among 1667 initially HIV-seronegative men. Time to seroconversion was modeled using Cox proportional hazards regression analysis for 7 combinations of drug use (including inhaled nitrites or "poppers", stimulants, and erectile dysfunction drugs) at the current or previous semiannual visit, adjusting for other risk factors, specifically sexual behavior, alcohol and other drug use, and depression. Model-based adjusted attributable risks were then calculated. Results showed that risk of seroconversion

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increased linearly with the number of unprotected receptive anal sex partners (URASP), with hazard ratios ranging from 1.73 [95% confidence interval (CI): 0.75 to 4.01] for 1 partner, to 4.23 (95% CI: 1.76 to 10.17) for 2-4 partners, and to 14.21 (95% CI: 6.27 to 32.20) for 5+ partners, independent of other risk factors. After adjustment, risks for seroconversion increased from 2.99 (95% CI: 1.02 to 8.76) for men who reported using stimulants only (1 drug) to 8.45 (95% CI: 2.67 to 26.71) for men who reported using all 3 sex drugs. The use of any of the 7 possible sex drug combinations accounted for 63% of the 9-year HIV seroincidence in the MACS. When contributions of increased URASP and combination drug use were analyzed together, the total attributable risk for HIV seroconversion was 74%, with 41% attributable to URASP alone and a residual of 33% due to other direct or indirect effects of drug use. These findings highlight the role of drug use, particularly use of poppers, stimulants, and erectile dysfunction drugs, in the significantly increased risk for HIV seroconversion in the MACS cohort. These data reinforce the importance of implementing focused interventions that target drug reduction as part of comprehensive and efficacious HIV prevention strategies. Ostrow D, Plankey M, Cox C, Li X, Shoptaw S, Jacobson L, Stall R. Specific sex drug combinations contribute to the majority of recent HIV seroconversions among MSM in the MACS. J Acquir Immune Defic Syndr. 2009;51(3):349-355.

HIV Preexposure Prophylaxis in the United States: Impact on Lifetime Infection Risk, Clinical Outcomes, and Cost-Effectiveness

The combination of tenofovir and emtricitabine shows promise as HIV preexposure prophylaxis (PrEP). Researchers sought to forecast clinical, epidemiologic, and economic outcomes of PrEP, taking into account uncertainties regarding efficacy, the risks of developing drug resistance and toxicity, behavioral disinhibition, and drug costs. They adapted a computer simulation of HIV acquisition, detection, and care to model PrEP among men who have sex with men and are at high risk of HIV infection (i.e., 1.6% mean annual incidence of HIV infection) in the United States. Base-case assumptions included 50% PrEP efficacy and monthly tenofovir-emtricitabine costs of $753. They used sensitivity analyses to examine the stability of results and to identify critical input parameters. In a cohort with a mean age of 34 years, PrEP reduced lifetime HIV infection risk from 44% to 25% and increased mean life expectancy from 39.9 to 40.7 years (21.7 to 22.2 discounted quality-adjusted life-years). Discounted mean lifetime treatment costs increased from $81,100 to $232,700 per person, indicating an incremental cost-effectiveness ratio of $298,000 per quality-adjusted life-year gained. Markedly larger reductions in lifetime infection risk (from 44% to 6%) were observed with the assumption of greater (90%) PrEP efficacy. More-favorable incremental cost-effectiveness ratios were obtained by targeting younger populations with a higher incidence of infection and by improvements in the efficacy and cost of PrEP. These data suggest that PrEP could substantially reduce the incidence of HIV transmission in populations at high risk of HIV infection in the United States. Although it is unlikely to confer sufficient benefits to justify the current costs of tenofovir-emtricitabine, price reductions and/or increases in efficacy could make PrEP a cost-effective option in younger populations or populations at higher risk of infection. Given recent disappointments in HIV infection prevention and vaccine development, additional study of PrEP-based HIV prevention is warranted. Paltiel A, Freedberg K, Scott C, Schackman B, Losina E, Wang B, Seage G, Sloan C, Sax P, Walensky R. HIV preexposure prophylaxis in the United States: Impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clin Infect Dis. 2009;48(6):806-815.

Trends in Multidrug Treatment Failure and Subsequent Mortality among Antiretrovira Therapy-Experienced Patients with HIV Infection in North America

Although combination antiretroviral therapy continues to evolve, with potentially more effective options emerging each year, the ability of therapy to prevent multiple regimen failure and mortality in clinical practice remains poorly defined. In this analysis, 16 cohorts representing over 60 sites, including the AIDS Linked to the IntraVenous Experience (ALIVE) and the Johns Hopkins HIV Clinical Cohort (JHHCC) studies, contributed data on all individuals who initiated combination antiretroviral therapy. Researchers identified those individuals who experienced virologic failure (defined as a HIV RNA level >1000 copies/mL), received modified therapy, and subsequently had a second episode of virologic failure. Multivariate Cox regression was used to assess factors associated with time to second regimen failure and the time to death after the onset of second regimen failure. Of the 42,790 individuals who received therapy, 7159 experienced a second virologic failure. The risk of second virologic failure decreased from 1996 (56 cases per 100 person-years) through 2005 (16 cases per 100 person-years. The cumulative mortality after onset of second virologic failure was 26% at 5 years and decreased over time. A history of AIDS, a lower CD4 (+) T cell count, and a higher plasma HIV RNA level were each independently associated with mortality. Similar trends were observed when analysis was limited to the subset of previously treatment-naive patients. These findings indicate that, although the rates of multiple regimen failure have decreased dramatically over the past decade, mortality rates for those who have experienced failure on at least 2 regimens have remained high. Plasma HIV RNA levels, CD4(+) T cell counts at time of treatment failure, and a history of AIDS remain independent risk factors for death, which underscores the importance of these factors as targets for those in need of more-aggressive therapeutic interventions. Deeks S, Gange S, Kitahata M, et al. Trends in multidrug treatment failure and subsequent mortality among antiretroviral therapy-experienced patients with HIV infection in North America. Clin Infect Dis. 2009;49(10):1582-1590.

Associations Between Alcohol and Depression In Adolescents

Alcohol use-related problems and depressive symptoms are clearly associated with each other, but data on the nature of this association have been inconsistent. In addition, the possible moderating effects of age and gender have not been comprehensively examined. The goals of this study were to clarify: (i) how depressive symptoms affect the levels and trajectory of alcohol use-related problems, (ii) how alcohol use-related problems affect the levels and trajectory of depressive symptoms, and (iii) whether there are differences in these associations at different points in development or between males and females. Participants for this study were drawn from the National Longitudinal Study of Adolescent Health (Add Health) data set (wave 1 of data collection in 1994 to 1995), a community-based sample of 20,728 adolescents followed from adolescence through early adulthood. Multilevel models were used to assess how each problem affected the level and rate of change in the other problem over time; gender was considered as a possible moderator of these associations. The results indicated that alcohol use-related problems and depressive symptoms had reciprocal, positive associations with each other during the period from early adolescence through early adulthood; however, these effects differed somewhat by gender and age. High levels of depressive symptoms were associated with higher initial levels of alcohol problems (particularly among females), as well as faster increases in alcohol problems over time among males. High levels of alcohol problems were associated with higher initial levels of depressive symptoms (particularly among females) as well as less curvature in the slope of depressive symptoms, so that although there was a large difference between people with high and low depressive symptoms in early adolescence, by early adulthood the difference was smaller (particularly among females). These results highlight the importance of examining gender and age in studies of associations between affective disorders and substance use disorders. Marmorstein, N. Longitudinal

associations between alcohol problems and depressive symptoms: Early adolescence through early adulthood. Alcohol Clin Exp Res. 2009;33(1):49-59.

Role of GABRA2 Across Behavior By Parental Monitoring

As investigators identify genes involved in psychiatric disorders, they are also studying how the risk associated with susceptibility genes manifests across development and in conjunction with the environment. These analyses aim to characterize the pathway of risk associated with GABRA2, a gene previously associated with adult alcohol dependence, to test for an association between GABRA2 and trajectories of externalizing behavior from adolescence to young adulthood and for moderation of genetic effects by parental monitoring. Data were analyzed from the Child Development Project; a community-based sample of families enrolled at 3 sites in Nashville and Knoxville, Tennessee, and Bloomington, Indiana, as children entered kindergarten in 1987 and 1988, with yearly assessments conducted since that time. A saliva sample was collected for DNA at the 2006 follow-up, with a 93% response rate in the target sample. The analyses reported in this paper were on the white subset of the sample (n = 378). Growth mixture modeling was conducted using Mplus to identify trajectories of externalizing behavior and to test for effects of GABRA2 sequence variants and parental monitoring. Parental monitoring was measured at 11 years of age; Child Behavior Checklist youth reports of externalizing behavior at ages 12, 14, 15, 16, 17, 19, 20, 21, and 22 years. Two classes of externalizing behavior emerged: a stable high externalizing class and a moderate decreasing externalizing behavior class. The GABRA2 gene was associated with class membership, with subjects who showed persistent elevated trajectories of externalizing behavior more likely to carry the genotype previously associated with increased risk of adult alcohol dependence. A significant interaction with parental monitoring emerged; the association of GABRA2 with externalizing trajectories diminished with high levels of parental monitoring. These findings underscore the importance of studying genetic effects across development and of identifying environmental factors that moderate risk. Dick D, Latendresse S, Lansford J, Budde J, Goate A, Dodge K, Pettit G, Bates J. Role of GABRA2 in trajectories of externalizing behavior across development and evidence of moderation by parental monitoring. Arch Gen Psychiatry 2009;66(6):649-657.

GABRA2 and Risk for Substance Abuse and Dependence

A number of studies have shown that genetic variation at GABRA2 alters vulnerability to alcohol dependence. The exact identity of the causal variant (s) and the relationship of these variants to other forms of substance use and behavioral illness are, however, uncertain. This study analyzed genotype data from 516 individuals from the Iowa Adoption Studies, a large longitudinal case and control adoption study of substance use. Thirty-nine single nucleotide polymorphisms encompassing the GABRA2 locus were analyzed with respect to their lifetime history of three common forms of substance use dependence [alcohol dependence (AD), nicotine dependence (ND), and cannabis dependence (CD)] and relevant exposure variables. Using regression analysis, substantial evidence was found that both GABRA2 genotype and haplotype are significantly related to vulnerability to AD, ND, and CD, with the strongest relationships noted with respect to ND. Consistent with earlier studies suggesting exposure is an important step in the development of substance use, investigators found the inclusion of substance exposure data in analytic models markedly increased the strength of the genetic associations of GABRA2 haplotype with substance use. Finally, genetic effects were markedly more pronounced in females than in males. Investigators conclude that genetic variation at or near the GABRA2 locus significantly affects vulnerability not only to AD, but to other forms of substance use including ND and CD, and that the effects may be sex dependent. Philibert R, Gunter T, Beach S, Brody G,

Hollenbeck N, Andersen A, Adams W. Role of GABRA2 on risk for alcohol, nicotine, and cannabis dependence in the Iowa Adoption Studies. Psychiatr Genet. 2009;119(2):91-98.

Predictors of Drug Abuse Among Alcoholics

Individuals with alcohol dependence (AD) are at increased risk for developing dependence on illicit and prescription drugs. The goal of this cross-sectional study was to identify factors associated with drug dependence among individuals with AD. Data were collected from 1998 to 2002. The sample consisted of 855 adults (mean ages for males and females were 42.6 and 42.4, respectively) from the Irish Affected Sib Pair Study of Alcohol Dependence, who were treated in inpatient or outpatient alcohol treatment programs and met Diagnostic and Statistical Manual of Mental Disorders criteria for lifetime AD. The investigators studied predictors of dependence on six classes of drugs: cannabis, sedatives, stimulants, cocaine, opioids, and hallucinogens. Potential predictors examined included gender, age, education, and socioeconomic status; the personality traits of extraversion, neuroticism, and novelty seeking; conduct disorder, major depressive disorder, nicotine dependence, age at onset of alcohol use, early illicit drug use, and parental AD. Nicotine dependence, depression that began before substance use and drug use before age 19 each increased the risk for dependence on several substance classes. Male gender, younger age, maternal AD, fewer years of education, higher neuroticism scores, conduct disorder, and early alcohol use each increased the risk of dependence on one or more substance classes. Among individuals in treatment for AD, cigarette smoking, early onset of major depression, and early drug use were associated with increased risk for drug dependence. These results suggest individuals with these risk factors may benefit from more intensive screening to prevent the onset of, or to identify and treat, drug dependence. Sintov N, Kendler K, Walsh D, Patterson D, Prescott C. Predictors of illicit substance dependence among individuals with alcohol dependence. J Stud Alcohol Drugs 2009;70(2):269-278.

Concurrent Partnerships and HIV Prevalence Disparities by Race: Linking Science and Public Health Practice

Biological and behavioral risk factors fail to explain racial disparities in rates of HIV and other STIs. Analysis of network "connectivity," by contrast, suggests a way to gain an understanding of sexual networks and how they may influence disease spread. In this study, researchers found that concurrent sexual partnerships explained the disproportionately high prevalence of HIV and other sexually transmitted infections among African Americans. The persistence of such racial disparities would also require strong assortative mixing by race. They used data from 4 nationally representative US surveys (the National Health and Social Life Survey, the National Survey of Men and its companion, the National Survey of Women, the National Survey of Family Growth, and wave 3 of Add Health). The studies provided comparable data on concurrency and assortative mixing to allow for comparisons of adults 20-38 years and young adults 19 to 25 years. They found consistent support for both elements of this hypothesis; specifically, using a data-driven network simulation model, they showed that the levels of concurrency and assortative mixing observed produced a 2.6-fold racial disparity in the epidemic potential among young African American adults. The simulations were in accord with observed survey data: reported rates of concurrency among African American men and women age 20-38 years were on average 3.5 and 2.1 times higher than those among white men and white women, respectively; and rates of concurrency among African American men and women age 19-25 years were on average 2.9 and 1.4 times higher than those among white men and white women, respectively. These findings suggest that it is not only an individual's behavior that defines his or her risk, but it is his or her partner's behavior and ultimately his or her

position in a sexual network. Understanding sexual networks and the interactional contexts that constrain behavioral changes is important for the development of effective HIV prevention interventions to reduce racial disparities in HIV and other STIs. Morris M, Kurth A, Hamilton D, Moody J, Wakefield S. Concurrent partnerships and HIV prevalence disparities by race: Linking science and public health practice. Am J Public Health 2009;99(6):1023-1031.

Assessment of Liver Fibrosis by Transient Elastography in Persons with Hepatitis C Virus Infection or HIV-Hepatitis C Virus Coinfection

Transient elastography is a novel, noninvasive method for staging liver fibrosis. Researchers compared elastography with histologic methods among hepatitis C virus (HCV)-infected and human immunodeficiency virus (HIV)-HCV-coinfected participants in the urban, predominantly black study population. Participants were recruited from the AIDS Linked to the Intravenous Experience (ALIVE) and the Johns Hopkins HIV Clinical Cohort (JHHCC) studies, and underwent elastography to determine liver stiffness measurements. Liver biopsy specimens were staged F0-F4 in accordance with the Metavir score. Diagnostic accuracy and determination of liver stiffness cutoff values, compared with histologic methods, were determined by receiver operating characteristic analysis. Logistic regression methods identified parameters associated with discordant classification status. Of 192 participants, 139 (72%) were coinfected with HIV and HCV, 121 (63%) had insignificant fibrosis, and 48 (25%) had cirrhosis. Overall, the area-under-the-curve receiver operating characteristic was 0.87 for detection of both significant fibrosis (95% confidence interval, 0.82-0.92) and cirrhosis (95% confidence interval, 0.81-0.93). With use of cutoff values of 9.3 kPa for fibrosis and 12.3 kPa for cirrhosis, 79%-83% of participants were correctly classified by liver stiffness measurement (compared with histologic methods); accuracy appeared to be higher among HIV-uninfected participants than among HIV-infected participants. Most discordance occurred when liver stiffness measurements indicated liver disease and histologic examination did not (in 16% of participants); those with discordant results were more likely to have attributes that increased the odds of significant fibrosis, such as elevated serum fibrosis markers or HIV-related immunosuppression, compared with persons in whom low fibrosis was predicted by both examination of a biopsy specimen and elastography. These findings indicate that, for most HCV-infected persons, fibrosis stage predicted by elastography is similar to that predicted by examination of a biopsy specimen. Elastography-based measurement of liver stiffness holds promise to expand liver disease screening and monitoring, particularly among injection drug users. Kirk G, Astemborski J, Mehta S, et al. Assessment of liver fibrosis by transient elastography in persons with Hepatitis C virus infection or HIV-Hepatitis C virus coinfection. Clin Infect Dis. 2009;48(7):963-972.

Association Between CNR1 and Cannabis Dependence Symptoms in Young Adults

This study examined the genetic association between variation in the cannabinoid receptor 1 (CNR1) gene and cannabis dependence symptoms. Adolescent and young adult subjects were recruited from three settings: a treatment program for youth with substance use disorders, the criminal justice system, and the community. A case-control sample was interviewed and consisted of 224 cases who endorsed at least one dependence symptom and 108 controls who tried cannabis but endorsed no symptoms. A family-based sample of 219 families was also analyzed. Case-control analysis identified a nominal association between SNP rs1049353 and having one or more cannabis dependence symptoms ($p=.029$), but the association did not hold up in a combined sample. Family-based analysis found a trend for the same SNP

(p=.07). The authors did not replicate a previous report that SNP rs806380 was associated with the development of cannabis dependence. These results provide inconclusive evidence of association between rs1049353/rs806380 and the development of cannabis dependence, and underscore the importance of replicating results of genetic association studies. Additional family-based studies are needed to clarify the role of the CNR1 gene, and its various SNPs, in the development of cannabis use disorders. Hartman C, Hopfer C, Haberstick B, et al. The association between cannabinoid receptor 1 gene (CNR1) and cannabis dependence symptoms in adolescents and young adults. Drug Alcohol Depend. 2009;104(1-2):11-16.

Subtypes of Nonmedical Prescription Drug Misuse

This study used three characteristics (i.e., motive, route of administration, and co-ingestion with alcohol) of nonmedical prescription drug misuse across four separate classes (i.e., pain, sedative/anxiety, sleeping, and stimulant medications) to examine subtypes and drug related problems. A Web survey was self-administered by a randomly selected sample of 3639 undergraduate students attending a large Midwestern 4-year U.S. university. Self-treatment subtypes were characterized by motives consistent with the prescription drug's pharmaceutical main indication, oral only routes of administration, and no co-ingestion with alcohol. Recreational subtypes were characterized by recreational motives, oral or non-oral routes, and co-ingestion. Mixed subtypes consisted of other combinations of motives, routes, and co-ingestion. Among those who reported nonmedical prescription drug misuse, approximately 13% were classified into the recreational subtype, while 39% were in the self-treatment subtype, and 48% were in the mixed subtype. There were significant differences in the subtypes in terms of gender, race and prescription drug class. Approximately 50% of those in subtypes other than self-treatment screened positive for drug abuse. The odds of substance use and abuse were generally lower among self-treatment subtypes than other subtypes. The authors conclude that the findings indicate subtypes should be considered when examining nonmedical prescription drug misuse, especially for pain medication. McCabe S, Boyd C, Teter C. Subtypes of nonmedical prescription drug misuse. Drug Alcohol Depend. 2009;102(1-3):63-70.

Correlates of Later-Onset Cannabis Use in the NESARC

Much of the research surrounding correlates of cannabis initiation has focused on adolescent and young adult populations. However, there is growing evidence that cannabis onset occurs later in life as well and little is known of the risk and protective influences that are associated with late-onset cannabis initiation. The investigators used data on 34,653 individuals that participated in both the first wave and the 3-year follow-up (3YFU) of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Univariate and multivariate logistic regression was used to examine the association between cannabis initiation at 3YFU and socio-demographic, religious/pro-social and psychiatric measures. Analyses were also conducted in age bands to further distinguish across the lifespan. Of the 27,467 lifetime abstainers at wave one, 1509 had initiated cannabis use at 3YFU. Consistent associations between divorce, religious attendance, volunteer/community service, alcohol abuse/dependence, nicotine dependence and cannabis initiation were noted in the full sample and across age-bands. Religious and pro-social activities were negatively associated with late-onset cannabis onset while divorce and alcohol and nicotine-related problems were positively associated with later onset. Agrawal A, Lynskey MT. Correlates of later-onset cannabis use in the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 2009;1-4.

Evidence for Associations between Polymorphisms in Cannabinoid

Receptor 1 Gene and Cannabis Dependence

Genomic studies of cannabis use disorders have been limited. The cannabinoid receptor 1 gene (CNR1) on chromosome 6q14-15 is an excellent candidate gene for cannabis dependence due to the important role of the G-protein coupled receptor encoded by this gene in the rewarding effects of Delta9-tetrahydrocannabinol. Previous studies have found equivocal evidence for an association between SNPs in CNR1 and a general vulnerability to substance use disorders. Researchers investigated the association between 9 SNPs spanning CNR1 and cannabis dependence in 1,923 individuals. Two SNPs that were previously associated with cannabis dependence in other studies were also significant with this phenotype in our analyses [rs806368 (P = 0.05) and rs806380 (P = 0.009)]. Haplotype analyses revealed the association to be largely driven by the SNP rs806380. These results suggest a role for the cannabinoid receptor 1 gene in cannabis dependence. Agrawal A, Wetherill L, Dick D, et al. Evidence for association between polymorphisms in the cannabinoid receptor 1 (CNR1) gene and cannabis dependence. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(5):736-740.

Burden of Psychiatric Morbidity among Lesbian, Gay, and Bisexual Individuals in the California Quality of Life Survey

In recent population-based surveys, minority sexual orientation has been identified as a potential risk indicator for psychiatric morbidity. However, methodological limitations in studies to date have led to concerns that current estimates are biased due to inadequate measurement of sexual orientation and uncontrolled confounding from prevalent HIV infection. In the present study, the researchers investigate associations between sexual orientation and mental health/substance use morbidity using information obtained from 2,272 individuals, including 652 sexual orientation minorities, age 18 to 72 years, interviewed in the California Quality of Life Survey. Results confirm that minority sexual orientation is a risk indicator for psychiatric morbidity. However, levels of increased risk vary within this subpopulation by both gender and patterns of sexual orientation expression. Among gay/bisexual men, much of this greater burden is related to concurrent HIV infection. Reducing excess mental health morbidity risk among sexual orientation minorities could result in possibly a 5% to 11% reduction in the burden of the disorders assessed here among the adult population. Sexual orientation represents an important, but relatively understudied, individual characteristic shaping risk for psychiatric morbidity. Cochran S, Mays V. Burden of psychiatric morbidity among lesbian, gay, and bisexual individuals in the California Quality of Life Survey. J Abnorm Psychol. 2009;118(3):647-658.

Alcohol Consumption Indices of Genetic Risk for Alcohol Dependence

Previous research has reported a significant genetic correlation between heaviness of alcohol consumption and alcohol dependence (AD), but this association might be driven by the influence of AD on consumption rather than the reverse. Researchers tested the genetic overlap between AD symptoms and a heaviness of consumption measure among individuals who do not have AD. A high genetic correlation between these measures would suggest that a continuous measure of consumption may have a useful role in the discovery of genes contributing to dependence risk. Factor analysis of five alcohol use measures was used to create a measure of heaviness of alcohol consumption. Quantitative genetic analyses of interview data from the 1989 Australian Twin Panel (n = 6257 individuals; M = 29.9 years) assessed the genetic overlap between heaviness of consumption, DSM-IV AD symptoms, DSM-IV AD symptom clustering, and DSM-IV alcohol abuse. Genetic influences accounted

for 30%-51% of the variance in the alcohol measures and genetic correlations were .90 or higher for all measures, with the correlation between consumption and dependence symptoms among nondependent individuals estimated at .97 (95% confidence interval: .80-1.00). Heaviness of consumption and AD symptoms have a high degree of genetic overlap even among nondependent individuals in the general population, implying that genetic influences on dependence risk in the general population are acting to a considerable degree through heaviness of use and that quantitative measures of consumption will likely have a useful role in the identification of genes contributing to AD. Grant JD, Agrawal A, Bucholtz K, et al. Alcohol consumption indices of genetic risk for alcohol dependence. Biol Psychiatry. 2009;1-6.

Pathways Between Nonmedical Opioid Use/Dependence and Psychiatric Disorders

This study was designed to address the knowledge gap regarding the temporal ordering between nonmedical opioid use and dependence and psychiatric disorders. Data were gathered in a face-to-face survey of the United States conducted in the 2001-2002 (NESARC wave 1). Participants were household and group quarters residents aged 18 years and older (n=43,093). Cox proportional hazards models with time-dependent covariates were used to investigate potential pathways between lifetime nonmedical opioid use/dependence and psychiatric disorders. Analysis revealed that preexisting psychiatric disorders (mood disorders, major depressive disorder, bipolar I disorder, anxiety disorders, panic and generalized anxiety disorders) were associated with an increased risk of nonmedical opioid use, with hazard ratios ranging from 2.2[95% CI=1.6-3.1] (any anxiety disorder) to 3.1[95% CI=2.4-2.4] (bipolar I disorder). Preexisting nonmedical opioid use was associated with an increased risk of onset of psychiatric disorders, with hazard ratios ranging from 2.8[95% CI=2.2-3.6] (generalized anxiety disorder) to 3.6[95% CI=2.6-4.9] (bipolar I disorder), adjusted for demographics and other illegal drug use. Nonmedical use of opioids led to the development of dependence more often among individuals with preexisting psychiatric disorders, hazard ratios were particularly strong for generalized anxiety disorder (HR=10.8, 95% CI=4.9-23.7) and bipolar I disorder (HR=9.7, 95% CI=5.4-17.3). Preexisting opioid dependence resulting from nonmedical opioid use was associated with an increased risk of onset of psychiatric disorders, with hazard ratios ranging from 4.9[95% CI=3.0-7.9] (mood disorders) to 8.5[95% CI=4.5-16.0] (panic disorder), adjusted for demographics and alcohol and/or other illegal drug dependence. The authors conclude that the study findings suggest a general vulnerability to nonmedical opioid use and major psychopathologies and provide evidence for a ''self-medication'' model for dependence resulting from nonmedical opioid use with bipolar disorder and generalized anxiety disorder. Martins S, Keyes K, Storr C, Zhu H, Chilcoat H. Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2009;103(1-2):16-24.

Extra-medical Stimulant Dependence among Recent Initiates

Researchers sought to examine estimates for the risk of becoming stimulant dependent within 24 months after first extra-medical (EM) use of a stimulant drug compound. The study estimates are derived from a representative sample of United States residents ages 12 and older (N=166,737) obtained from the 2003 to 2005 National Surveys on Drug Use and Health. A total of 1700 respondents were found to have used stimulants extra-medically for the first time within 24 months prior to assessment. Approximately 5% of these recent-onset EM users had become stimulant dependent since onset of EM use. As hypothesized, alcohol dependence cases were found to have experienced an excess risk of becoming stimulant dependent soon after onset of stimulant drug

use; there was no robust male-female difference in risk. Independently, initiates who had used multiple types of stimulants extra-medically, and methamphetamine users, were more likely to have become stimulant dependent soon after onset of use; by comparison, EM users of methylphenidate (Ritalin) were less likely to have developed rapid-onset dependence. These epidemiologic findings help quantify the continuing public health burden associated with new onsets of extra-medical stimulant use. O'Brien M, Anthony J. Extra-medical stimulant dependence among recent initiates. Drug Alcohol Depend. 2009;104(1-2):147-155.

Stable Factors in Externalizing Behaviors in Preadolescent Girls

Relatively little is known about the factor structure of disruptive behavior among preadolescent girls. The present study reports on exploratory and confirmatory factor analyses of disruptive girl behavior over four successive data waves as rated by parents and teachers in a large, representative community sample of girls (N = 2,451). Five factors were identified from in-home interviews parent ratings (oppositional behavior/conduct problems, inattention, hyperactivity/impulsivity, relational aggression, and callous-unemotional behaviors), and four factors were identified derived from teacher ratings (oppositional behavior/conduct problems/callous-unemotional behaviors, inattention, hyperactivity/impulsivity, and relational aggression). There was a high degree of consistency of items loading on equivalent factors across parent and teacher ratings. Year-to-year stability of factors between ages five and 12 was high for parent ratings (ICC = 0.70 to 0.88), and slightly lower for teacher ratings (ICC = 0.56 to 0.83). These findings are discussed in terms of possible adjustment to the criteria for children's disruptive behavior disorders found in the Diagnostic and Statistical Manual for Mental Disorders. Loeber R, Pardini D, Hipwell A, Stouthamer-Loeber M, Keenan K, Sembower M. Are there stable factors in preadolescent girls' externalizing behaviors? J Abnorm Child Psychol. 2009;37(6):777-791.

Juvenile Offenders' Alcohol and Marijuana Risk and Protective Factor Effects

The current study modeled trajectories of substance use from ages 15 to 20 among 1,095 male serious juvenile offenders (M age = 16.54; 42% African-American, 34% Latino, 20% European-American, and 4% other ethnic/racial backgrounds) and prospectively predicted trajectories from risk and protective factors before and after controlling for time spent in a supervised setting. Results indicated that supervised time suppressed age-related growth in substance use. Trajectories of offenders with no supervised time and low levels of supervised time increased in substance use across age, whereas offenders with high levels of supervised time showed no growth. Almost all risk and protective factors had effects on initial substance use but only adolescent history of substance use, impulse control, and psychosocial maturity had an effect on change in substance use over time. Findings highlight the importance of formal sanctions and interventions superimposed on normal developmental processes in understanding trajectories of substance use among serious juvenile offenders. Mauricio A, Little M, Chassin L, Knight G, Piquero A, Losoya S, Vargas-Chanes D. Juvenile offenders' alcohol and marijuana trajectories: Risk and protective factor effects in the context of time in a supervised facility. J Youth Adolesc. 2009;38(3):440-453.

Methamphetamine Use and Rates of Incarceration among Street-Involved Youth in a Canadian Setting: a Cross-Sectional Analysis

Concerns over rising use of methamphetamine, especially among street-involved youth, and the links between exposure to the correctional system and

risks for increased drug use led researchers to assess the relationship between ever using methamphetamine and reporting ever being incarcerated among youth in Vancouver, Canada. They looked at the relationship between ever being imprisoned and ever using methamphetamine using a multivariate logistic regression analysis while also controlling for potentially confounding secondary demographic, social and behavioral variables. Of the 478 youth recruited into the study between September 2005 and October 2006, 385 (80.5%) reported ever being incarcerated overnight or longer. In the multivariate model, methamphetamine use was independently associated with ever being incarcerated (adjusted Odds Ratio: 1.79, 95% Confidence Interval [CI]: 1.03 - 3.13). These findings indicate that incarceration was common in this cohort and strongly linked with ever using methamphetamine, underscoring the need for the development of novel public policies such as community-based drug treatment, to address the use of methamphetamine among street youth. Milloy M, Kerr T, Buxton J, Montaner J, Wood E. Methamphetamine use and rates of incarceration among street-involved youth in a Canadian setting: A cross-sectional analysis. Subst Abuse Treat Prev Policy. 2009;4:17-23.

Identifying Hidden Sexual Bridging Communities in Chicago

Bridge populations can play a central role in the spread of human immunodeficiency virus (HIV) by providing transmission links between higher and lower prevalence populations. While social network methods are well suited to the study of bridge populations, analyses tend to focus on dyads (i.e., risk between drug and/or sex partners) and ignore bridges between distinct subpopulations. This study takes initial steps toward moving the analysis of sexual network linkages beyond individual and risk group levels to a community level in which Chicago's 77 community areas were examined as subpopulations for the purpose of identifying potential bridging communities. Of particular interest are "hidden" bridging communities; that is, areas with above-average levels of sexual ties with other areas but whose below-average AIDS prevalence may hide their potential importance for HIV prevention. Data for this analysis came from the first wave of recruiting at the Chicago Sexual Acquisition and Transmission of HIV Cooperative Agreement Program site. Between August 2005 and October 2006, respondent-driven sampling was used to recruit users of heroin, cocaine, or methamphetamine, men who have sex with men regardless of drug use, the sex partners of these two groups, and sex partners of the sex partners. In this cross-sectional study of the sexual transmission of HIV, participants completed a network-focused computer-assisted self-administered interview, which included questions about the geographic locations of sexual contacts with up to six recent partners. Bridging scores for each area were determined using a matrix representing Chicago's 77 community areas and were assessed using two measures: non-redundant ties and flow betweenness. Bridging measures and acquired immunodeficiency syndrome (AIDS) case prevalence rates were plotted for each community area on charts representing four conditions: below-average bridging and AIDS prevalence, below-average bridging and above-average AIDS prevalence, above-average bridging and AIDS prevalence, and above-average bridging and below-average AIDS prevalence (hidden bridgers). The majority of the 1,068 study participants were male (63%), African American (74%), and very poor, and the median age was 44 years. Most (85%) were sexually active, and 725 provided useable geographic information regarding 1,420 sexual partnerships that involved 57 Chicago community areas. Eight community areas met or came close to meeting the definition of hidden bridgers. Six areas were near the city's periphery, and all eight areas likely had high inflows or outflows of low-income persons displaced by gentrification. The results suggest that further research is warranted on the use of this methodology to duplicate the analysis in other cities. Youm Y, Mackesy-Amiti M, Williams C, Ouellet L. Identifying hidden sexual bridging communities in Chicago. J Urban Health. 2009;86 Suppl

1:107-120.

Evaluation of Human Immunodeficiency Virus Biomarkers: Inferences from Interval and Clinical Cohort Studies

Among individuals infected with the human immunodeficiency virus (HIV), biomarkers that predict mortality are also used to determine the time when antiretroviral therapy is initiated. No studies have evaluated the impact of the frequency of marker measurements for either their predictive value of mortality or how they may influence inference of the effect of therapy initiation in analyses from observational data. Researchers identified 244 persons who were contemporaneously enrolled in both the ALIVE (AIDS Linked to the IntraVenous Experience study, an interval cohort) and the Johns Hopkins HIV Clinical Cohort (JHHCC) between 1995 and 2004. Data from each study were used separately in 2 ways: Researchers applied time-dependent proportional hazards models to examine the predictive associations between markers and mortality, and marginal structural models to examine the causal inference of therapy on mortality. They used biomarkers to derive inverse probability weights. The timing frequencies of marker measurements in the interval cohort (CD4 interquartile range = 175-194 days) were less heterogeneous than in the clinical cohort (interquartile range = 38-121 days). Despite this, results were concordant for CD4 (R = 0.537 [95% confidence interval = 0.345-0.707] and (R = 0.488 [0.297-0.666], respectively). Similar concordance was found for the HIV-1 RNA and hemoglobin analyses. When evaluating the causal effect of highly active antiretroviral therapy (HAART), the relative hazards were 0.34 for the interval cohort study (95% CI = 0.15-0.77) and 0.27 for the clinical cohort study (0.11-0.66). Utilizing a unique co-enrollment of patients in two different types of cohort studies, they found empirical evidence that inferences drawn from these different structures are similar. Lau B, Gange S, Kirk G, Moore R. Evaluation of human immunodeficiency virus biomarkers: Inferences from interval and clinical cohort studies. Epidemiology. 2009;20(5):664-672.

HIV Transmission Networks

Over the past several years one segment of the complex field of HIV transmission dynamics - heterosexual networks - has dominated theoretical and empirical investigation. This paper provides an overview of recent work on HIV risks and networks, with a focus on recent findings in heterosexual network dynamics. Qualitative (ethnographic) assessments have demonstrated the heterogeneity and complexity of heterosexual connections, particularly in Africa, where tradition, official polygamy, and unofficial multiperson arrangements have led to concurrency of sexual partnerships. Data from a large, quantitative study on Likoma Island, Malawi, are examined to demonstrate the considerable, interlocking sexual connections that arise from a high-concurrency sexual setting, even with a low average number of partnerships (low degree) of long duration. Such settings, as suggested by ethnographic studies, may be common in Africa as well as other regions of the world. Combined with newer information about transmissibility during acute and early infection, such studies may provide plausible explanations for endemic transmission and possibly for rapid HIV propagation. The review concludes with a discussion of high-concurrency, low-degree networks. Their relevance to heterosexual transmission, and possible extension to other epidemiologic settings, reinforces the heterogeneity and complexity of HIV transmission dynamics. Rothenberg R. HIV transmission networks. Curr Opin HIV AIDS. 2009;24(4):260-265.

Homonegativity, Substance Use, Sexual Risk Behaviors, and HIV Status in Poor and Ethnic Men Who have Sex with Men in Los Angeles

This study evaluates associations between internalized homonegativity and demographic factors, drug use behaviors, sexual risk behaviors, and HIV status among men who have sex with men (MSM) and with men and women (MSM/W). Participants were recruited in Los Angeles County using respondent-driven sampling (RDS) and completed the Internalized Homonegativity Inventory (IHNI) and questionnaires on demographic and behavioral factors. Biological samples were tested for HIV and for recent cocaine, methamphetamine, and heroin use. The 722 MSM and MSM/W participants were predominantly African American (44%) and Hispanic (28%), unemployed (82%), homeless (50%), and HIV positive (48%) who used drugs in the past 6 months (79.5%). Total and Personal Homonegativity, Gay Affirmation, and Morality of Homosexuality IHNI scores were significantly higher for African American men than for other ethnicities, for MSM/W than for MSM, for recent cocaine users than for recent methamphetamine users, and for HIV-seronegative men than for HIV-seropositive men. Linear regression showed the Gay Affirmation scale significantly and inversely correlated with the number of sexual partners when controlling for effects of ethnicity/race and sexual identification, particularly for men who self-identified as straight. Highest IHNI scores were observed in a small group of MSM/W (n = 62) who never tested for HIV. Of these, 26% tested HIV positive. Findings describe ways in which internalized homophobia is a barrier to HIV testing and associated HIV infection; such distinctions have importance for informing targeted HIV prevention efforts that aim to increase HIV testing, counseling, and behavioral change. Shoptaw S, Weiss R, Munjas B, Hucks-Ortiz C, Young S, Larkins S, Victorianne G, Gorbach P. Homonegativity, substance use, sexual risk behaviors, and HIV status in poor and ethnic men who have sex with men in Los Angeles. J Urban Health 2009;86 Suppl1:77-92.

Hepatitis C Virus Infection among Drug Injectors in St. Petersburg, Russia: Social and Molecular Epidemiology of an Endemic Infection

Researchers sought to understand the epidemiology and transmission patterns of hepatitis C virus (HCV), the predominant blood borne-pathogen infecting injection drug users (IDUs), in a part of the former Soviet Union. The authors recruited a cross-sectional respondent-driven sample of 387 IDUs in late 2005 through 2006, and administered a survey to collect demographic, medical, and general and dyad-specific drug injection and sexual behavioral data. Blood samples were also collected to detect antibodies to HCV and to amplify viral RNA for molecular analysis. The molecular data, including genotypes, were analyzed spatially and linkage patterns were compared to the social linkages obtained by respondent-driven sampling (RDS) for chains of respondents and among the injection dyads. HCV infection was ubiquitous: 94.6% of IDUs were HCV-seropositive. Among the 209 viral sequences amplified, genotype 3a predominated (n = 119, 56.9%), followed by 1b (n = 61, 29.2%) and 1a (n = 25, 11.9%). There was no significant clustering of genotypes spatially. Neither genotypes nor closely related sequences were clustered within RDS chains. Analysis of HCV sequences from dyads failed to find associations of genotype or sequence homology within pairs. Genotyping reveals that there have been at least five unique introductions of HCV genotypes into the IDU community in St. Petersburg. Analysis of prevalent infections does not appear to correlate with the social networks of IDUs, suggesting that simple approaches to link these networks to prevalent infections, rather than incident transmission, is unlikely to prove meaningful. On a more positive note, the majority of IDUs were infected with 3a genotype, which is associated with sustained virological response to antiviral therapy. Paintsil E, Verevochkin S, Dukhovlinova E, et al. Hepatitis C virus infection among drug injectors in St. Petersburg, Russia: Social and molecular epidemiology of an endemic infection. Addiction 2009;104(111):1881-1890.

Sexual Orientation, Substance Use Behaviors and Substance Dependence in the United States

The research team assessed past-year prevalence rates of substance use behaviors and substance dependence across three major dimensions of sexual orientation (identity, attraction and behavior) in a large national sample of adult women and men in the United States. Data were collected from structured diagnostic face-to-face interviews using the Alcohol Use Disorder and Associated Disabilities Interview Schedule DSM-IV version IV (AUDADIS-IV). Prevalence estimates were based on data collected from the 2004-2005 (wave 2) National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) which was comprised of a sample of 34,653 adults aged 20 years and older. Approximately 2% of the population self-identified as lesbian, gay or bisexual; 4% reported at least one life-time same-sex sexual partner and 6% reported same-sex sexual attraction. Although non-heterosexual orientation was generally associated with a higher risk of substance use and substance dependence, the majority of sexual minority respondents did not report substance use or meet criteria for DSM-IV substance dependence. There was considerable variation in substance use outcomes across sexual orientation dimensions; these variations were more pronounced among women than among men. Results support previous research findings on heightened risk of substance use and substance dependence among some sexual minority groups and point to the need for research that examines the reasons for such differences. Results also highlight important gender differences and question previous findings indicating uniformly higher risk for substance dependence among sexual minorities. Risks appear to vary based on gender and how sexual orientation is defined. Findings have implications for more effective prevention and intervention efforts that target subgroups at greatest risk. McCabe S, Hughes T, Bostwick W, West B, Boyd C. Sexual orientation, substance use behaviors and substance dependence in the United States. Addiction 2009;104(8):1333-1345.

HIV Seroprevalence in a Sample of Tanzanian Intravenous Drug Users

Injection drug use has gradually been emerging in sub-Saharan Africa. The purpose of this study was to assess the factors associated with increased risk of testing HIV-positive in a sample of injection drug users (IDUs) in Dar es Salaam, Tanzania. Participants were recruited by a trained outreach worker or were referred by IDUs who had completed the study. Blood specimens and self-reported socioeconomic and behavioral data were collected from 315 male and 219 female IDUs. Data were analyzed using univariate odds ratios and multivariate logistic regression modeling. Forty-two percent of the sample tested HIV-positive. Several socioeconomic, injection, and sexual factors were found to be associated with increased odds of testing HIV-positive. Multivariate analysis showed that having had sex more than 81 times in past 30 days, earning less than 100,000 shillings (US$76) in the past month, residency in Dar es Salaam for less than 5 years, and injecting for 3 years were independently associated with the greatest risk of infection. The rate of HIV infection in this sample of IDUs was found to be very high, suggesting that injection drug use may be an increasingly important factor in the continuing epidemic in sub-Saharan Africa, especially given the risky needle use practices and sexual networks of IDUs. Williams M, McCurdy S, Bowen A, Kilonzo G, Atkinson J, Ross M, Leshabari M. HIV seroprevalence in a sample of Tanzanian intravenous drug users. AIDS Educ Prev 2009;21(5):474-483.

Correlates of Unsafe Equipment Sharing among Injecting Drug Users in St. Petersburg, Russia

Researchers assessed the urban environment, social norms and individual correlates of unsafe injecting among injecting drug users (IDUs) in St. Petersburg, Russia. Between December 2004 and January 2007, 446 IDUs were interviewed in St. Petersburg, Russia. Prevalence of hepatitis C (HCV) was 96% and HIV 44%; 17% reported receptive syringe sharing after an HIV-infected IDU, 49% distributive syringe sharing, 76% sharing cookers, 73% sharing filters and 71% syringe-mediated drug sharing when not all syringes were new. Urban environmental characteristics correlated with sharing cookers and syringe-mediated sharing, and social norms correlated with receptive and distributive syringe sharing and sharing cookers. Individual correlates included cleaning used syringes (all 5 dependent variables) and self-report of HIV infection (receptive and distributive syringe sharing). These findings show that HIV status disclosure is an unreliable but frequently used HIV prevention method among IDUs in St. Petersburg, who reported alarmingly high levels of injecting equipment sharing. Voluntary counseling and testing should be widely available for this population. Ethnography would help in assessing the effectiveness of the syringe cleaning process and informing development of prevention interventions that incorporate urban environmental factors and social norms, including peer education and social network interventions. Gyarmathy V, Li N, Tobin K, et al. Correlates of unsafe equipment sharing among injecting drug users In St. Petersburg, Russia. Eur Addict Res. 2009;15(3):163-170.

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

Secondary transmission remains a significant concern among HIV-infected youth. Little is known, however, about partner-specific sexual risk behaviors for the secondary transmission of HIV and how they may differ between the 2 largest subgroups of HIV-positive youth, women-who-have-sex-with-men (WSM) and men-who-have-sex-with-men (MSM). During 2003-2004, researchers recruited a convenience sample of HIV-infected youth, 13 to 24 years of age, from 15 Adolescent Medicine Trials Network clinical sites, with approximately 10 to 15 youth recruited at each site. Participants completed an ACASI survey including questions about sex partners in the past year. Cross-sectional data analyses, including bivariate and multivariable regressions using generalized estimating equations, compared recent partner-specific sexual risk behaviors between WSM and MSM. Of 409 participants, 91% (371), including 176 WSM and 195 MSM, were included in the analysis. Ninety-two percent (163 WSM, 177 MSM) provided information on characteristics of their sexual partners. There were significant differences between the 2 groups in recent partner-specific sexual risk behaviors: lower rates of condom use at last sex among WSM (61% WSM vs. 78% MSM; P = 0.0011); a larger proportion of the sex partners of MSM reported as concurrent (56% MSM vs. 36% WSM; P = 0.0001); and greater use of hard drugs at last sex by MSM and/or their partner (18% MSM vs. 4% WSM; P = 0.0008). When measuring risk as a composite measure of sexual risk behaviors known to be associated with HIV transmission, both groups had high rates of risky behaviors, 74.7% among young MSM compared to 68.1% of WSM. These data suggest that recent partner-specific sexual risk behaviors for HIV transmission are high among young infected MSM and WSM, indicating the importance of offering interventions to reduce the secondary transmission of HIV to all HIV-positive youth in care. Moreover, the differences in risk behaviors between young MSM and WSM suggest that population-specific interventions are warranted. Jennings J, Ellen J, Deeds B, et al. Youth living with HIV and partner-specific risk for the secondary transmission of HIV. Sex Transm Dis. 2009;36(7):439-444.

Impulsivity and Later Risky Sexual Behaviors and Drug Abuse

Researchers examined a mediational model of the inter-relationship of drug use, sexual risk, and impulsivity in a longitudinal sample of 89 18-20 year old Minnesotans, recruited at ages 7-11 in 1991, almost half of whom displayed highly disruptive behaviors as children. They chose a mediational model because emerging evidence suggests that impulsivity is an underlying risk factor for many youth health risk problems, including sexual risk behaviors. They found that the three target variables were significantly related to each other, yet the association of drug use and sexual risk was significantly reduced (although not to zero) when controlled by impulsivity, suggesting a partial meditational model. These findings support the view that the association of drug use and sexual risk behaviors is partially mediated by impulsivity, as well as the broader theory that youth with deficits in self-regulatory behavioral systems have a greater likelihood of engaging in risky behaviors. This work adds to previous research on the role of impulsivity in the genesis of substance abuse, and supports the utility of dimensional approaches to understanding risk. Winters KC, Botzet A, Fahnhorst T, Bamuel L, Lee S. Impulsivity and its relationship to risky sexual behaviors and drug abuse. J Child Adolesc Subst Abuse 2009;18(1):43-56.

Calculation of P-values for Genome-Wide Analysis

Linkage analysis in multivariate or longitudinal contexts presents both statistical and computational challenges. The permutation test can be used to avoid some of the statistical challenges, but it substantially adds to the computational burden. Utilizing the distributional dependencies between p (defined as the proportion of alleles at a locus that are identical by descent (IBD) for a pairs of relatives, at a given locus) and the permutation test, this study reports on a new method of efficient permutation. The distribution of p for a sample of relatives at locus x is estimated as a weighted mixture of p drawn from a pool of ''representative'' p distributions observed at other loci. The weighting scheme is then used to sample from the distribution of the permutation tests at the representative loci to obtain an empirical P-value at locus x (which is asymptotically distributed as the permutation test at loci x). This weighted mixture approach greatly reduces the number of permutation tests required for genome-wide scanning, making it suitable for use in multivariate and other computationally intensive linkage analyses. In addition, because the distribution of p is a property of the genotypic data for a given sample and is independent of the phenotypic data, the weighting scheme can be applied to any phenotype (or combination of phenotypes) collected from that sample. The validity of this approach is demonstrated through simulation. Medland S, Schmitt J, Webb B, Kuo P, Neale M. Efficient calculation of empirical p-values for genome-wide linkage analysis through weighted permutation. Behav Genet. 2009;39(1):91-100.

Differences in Sexual Identity, Risk Practices, and Sex Partners between Bisexual Men and Other Men among a Low-Income Drug-Using Sample

Men who have sex with men and women (MSMW) represent an important target population for understanding the spread of HIV because of the inherent bridging aspect of their sexual behavior. Despite their potential to spread HIV between gender groups, relatively little recent data have been reported about this population as a subgroup distinct from men who have sex with men only. This paper analyzes data from the Chicago site of Sexual Acquisition and Transmission of HIV Cooperative Agreement Program to characterize 343 MSMW in terms of their demographics, drug use, sexual risk behavior, sexual identity, and sex partners. Results show the MSMW sample to be extremely disadvantaged; to have high rates of drug use, including injection and crack use; to report more female than male sex partners; to not differ from gay and heterosexual men in rates of condom use; and, for the most part, to report

sexual identities that are consistent with their sex behavior. MSMW represent an important high risk subpopulation in the HIV epidemic that should be targeted for risk reduction interventions. Williams C, Mackesy-Amiti M, McKirnan D, Ouellet L. Differences in sexual identity, risk practices, and sex partners between bisexual men and other men among a low-income drug-using sample. J Urban Health 2009;86 Suppl 1:93-106.

Substance Use Treatment Outcomes in a Sample of Male Serious Juvenile Offenders

This study examined drug-treatment-related reductions in alcohol and marijuana use, cigarette smoking, and nondrug offending among male adolescents who had been adjudicated of a serious (almost exclusively felony) offense. Sample included 429 male adolescent juvenile offenders from an ongoing longitudinal study of desistance from crime (Pathways to Desistance Project). Results indicated that the "real-world" drug treatments that these adolescents experienced had significant effects on substance use, which could not be explained solely by incarceration in controlled environments. However, effects on cigarette smoking and criminal offending were found only for treatments that included family involvement. Results suggest that involving families in adolescents' treatment may be useful for promoting desistence from criminal offending in this population. Chassin L, Knight G, Vargas-Chanes D, Lasoya SH, Naranjo D. Substance use treatment outcomes in a sample of male serious juvenile offenders. J Subst Abuse Treat. 2009;36(2):183-194.

Latina Mother-Daughter Relations Under Influence of Substances

Associations among mother-daughter attachment, mother and daughter substance abuse, and daughter's sexual behavior under the influence of drugs and alcohol were investigated among 158 adult U.S. Latina daughters. Latina daughters were sampled from four mother-daughter dyad types: substance abusing mother and daughter, substance abusing mother only, substance abusing daughter only, and non-substance-abusing mother and daughter. Substance abusing daughters with substance abusing mothers, and daughters who were less strongly attached to their mothers, reported more sex under the influence of drugs. Age, marital status, substance abuse, and mother's substance abuse all influenced the daughter's sex under the influence of alcohol. An unexpected positive association between attachment and sex under the influence of alcohol was found for daughters who were more closely attached to a substance abusing mother. Rosa MD, Dillon FR, Rojas P, Schwartz SJ, Duan R. Latina mother-daughter dyads: Relations between attachment and sexual behavior under the influence of alcohol or drugs. Arch Sex Behav. 2009:1-15.

Predictors of DSM and Fagerstrom-defined Nicotine Dependence in African American and Puerto Rican Young Adults

This study examined the psychosocial predictors of nicotine dependence, as defined by a variant of the criteria employed in the DSM-IV-specifically that of the University of Michigan Composite International Diagnostic Interview (UM-CIDI)-and the Fagerstrom Test for Nicotine Dependence (FTND). The study conducted interviews with a community sample of African American and Puerto Rican young adults (N=475; mean age=26). Predictor variables included physiologically based psychosocial (i.e., depressive symptoms and family problems with smoking) as well as social-behavioral psychosocial (i.e., rebelliousness and partner's problems with smoking) predictors of nicotine dependence. Using multiple regression analyses, UM-CIDI-defined dependence was predicted by each of the four psychosocial variables, while FTND-defined dependence was predicted only by the social-behavioral variables. These

findings bear out the disparate dimensions of nicotine dependence each measure taps. Brook J, Koppel J, Pahl K. Predictors of DSM and Fagerstrom-defined nicotine dependence in African American and Puerto Rican young adults. Subst Use Misuse 2009;44(6):809-822.

Longitudinal Analysis of Movie Exposure to Alcohol Cues and Adolescent Alcohol Problems

The authors tested a theoretical model of how exposure to alcohol cues in movies predicts level of alcohol use (ever use plus ever and recent binge drinking) and alcohol-related problems. A national sample of younger adolescents (baseline N=6,522) was interviewed by telephone with 4 repeated assessments spaced at 8-month intervals. A structural equation modeling analysis performed for ever-drinkers at Time 3 (N=961) indicated that, controlling for a number of covariates, movie alcohol exposure at Time 1 was related to increases in peer alcohol use and adolescent alcohol use at Time 2. Movie exposure had indirect effects to alcohol use and problems at Times 3 and 4 through these pathways, with direct effects to problems from Time 1 rebelliousness and Time 2 movie exposure also found. Prospective risk-promoting effects were also found for alcohol expectancies, peer alcohol use, and availability of alcohol in the home; protective effects were found for mother's responsiveness and for adolescent's school performance and self-control. Theoretical and practical implications are discussed. Wills T, Sargent J, Gibbons F, Gerrard M, Stoolmiller M. Movie exposure to alcohol cues and adolescent alcohol problems: A longitudinal analysis in a national sample. Psychol Addict Behav. 2009;(1):23-35.

Prenatal Smoking, Maternal Mental Health, and Childhood Asthma among Puerto Rican Youth

Childhood asthma is a major public health problem, with mainland and island Puerto Rican children having the highest asthma rates of any ethnic group in the United States. The objective of the study was to examine the relationship between maternal mental health problems, prenatal smoking, and risk of asthma among children in Puerto Rico and the Bronx, New York. A cross-sectional community-based study was conducted in the South Bronx in New York City and the San Juan Standard Metropolitan Area in Puerto Rico. Participants were Puerto Rican children 5 to 13 years of age and their adult caretakers with probability samples of children 5 to 13 years of age and their caregivers drawn at two sites: the South Bronx in New York City (n = 1,135) and San Juan and Caguas, Puerto Rico (n = 1,351). Self-reported maternal mental health problems (vs. none reported) were associated with significantly higher levels of prenatal smoking ($p < 0.0001$). Both maternal mental health problems and prenatal smoking contributed to increased asthma risk; however after adjusting for prenatal smoking, the relationship between maternal mental health problems and childhood asthma was no longer statistically significant. These results suggest that prenatal smoking may partly explain the observed relationship between maternal psychopathology and childhood asthma. Goodwin R, Canino G, Ortega A, Bird H. Maternal mental health and childhood asthma among Puerto Rican youth: The role of prenatal smoking. J Asthma 2009;6(7):726-730.

Intentions to Quit Smoking among Youth in Substance Abuse Treatment Programs

Smoking cessation interventions for adolescents in substance abuse treatment have shown promise. However, a better understanding of the correlates of substance use disordered (SUD) youths' intentions toward smoking cessation will help tailor cessation interventions to this population. The current study

examined tobacco use, smoking-related self-efficacy, substance use and intentions to quit using alcohol and illicit drugs as correlates of intentions to quit smoking among youth in SUD treatment. Participants were 178 adolescents who were in inpatient (n=90) or outpatient (n=88) SUD treatment and had smoked at least once in the past 30 days. The sample was 44% female, 72% non-Hispanic Caucasian, with a mean age of 16.2 years (SD=1.2). Participants rated the likelihood that they would be nonsmokers in the next year (9-point scale). SUD youth intention to quit smoking averaged 4.9 out of 10 (SD=3.2), comparable to intention to quit drinking (M=5.3, SD=3.6), but lower than their intention to quit using drugs (M=6.0, SD=3.4). Teens' intentions to quit smoking were associated with nicotine dependence ($r=-.30$, $p<.01$) and smoking cessation related self-efficacy ($r=.36$, $p<.01$), but not with pretreatment substance use severity ($r=-.15$). Controlling for nicotine dependence, teens' intentions to quit smoking were positively related to smoking cessation self-efficacy ($pr=.26$, $p<.01$) and intention to quit using illicit drugs ($pr=.15$, $p<.05$), but unrelated to intention to quit drinking. Findings highlight the appropriateness of addressing adolescent tobacco use during SUD treatment, but emphasize the importance of assessing intention and other cognitions for each substance, as they may differ markedly. Ramo DE, Prochaska JJ, Myers MG. Intentions to quit smoking among youth in substance abuse treatment. Drug Alcohol Depend. 2009;1-3.

Initial Investigation into Coping with Temptations and Adolescent Smoking Cessation

Although a great deal of research focuses on adolescent cigarette smoking little is known about the process by which adolescents attempt to stop smoking. Resisting temptations to smoke is one of the key challenges encountered by individuals who attempt smoking cessation. A large body of literature has examined coping with temptation among adult smokers, and research on this issue for adolescents is lacking. To further our understanding in this area, the present study reports on an initial examination of the Smoking Temptation Coping Questionnaire (STCQ). The STCQ, which assesses coping in a social pressure situation involving cigarettes, was adapted from the Temptation Coping Questionnaire, a brief self-report measure of adolescent coping with temptations to use alcohol and other drugs. The present study included 109 adolescent participants (aged 14-19 years) in a naturalistic study of smoking self-change. Participants completed baseline and 6-month follow-up interviews. Exploratory factor analysis of the STCQ coping scale yielded a single factor including six strategies for coping with temptations. Analyses provided support for the concurrent, predictive, and construct validity of the STCQ. In particular, the coping scale score significantly predicted prospective duration of abstinence for adolescents who engaged in smoking cessation efforts. These results provide preliminary support for the utility of the STCQ. In addition, findings support the role of temptation coping in the adolescent smoking cessation process. Myers M, Macpherson L. Coping with temptations and adolescent smoking cessation: An initial investigation. Nicotine Tob Res. 2009;11(8):940-944.

Prospective Study of Cigarette Smoking Initiation among Chinese and Korean American Students in College

The present study was a prospective investigation of baseline influences on initial smoking and transition to established smoking among 267 Asian-American college students who had not smoked prior to college. Students of Chinese (52%) or Korean (48%) descent were enrolled during their freshman year in college. Data for the present study were collected during four annual in-person interviews. Two main outcomes were included: initial use of a cigarette, which reflected having first smoked a cigarette (more than a puff) during college, and established smoking, which was defined as having smoked at least

100 cigarettes. Over the course of the study, 25% of baseline never-smokers tried their first cigarette, and 9% became established smokers. Overall, men were significantly more likely to experiment and progress to established smoking. Baseline alcohol and drug use, behavioral undercontrol, and parental smoking predicted smoking experimentation but not established smoking. Students of Korean ethnicity were more likely to become established smokers. However, acculturation was not a significant predictor of experimentation or established smoking after accounting for the effects of other predictors. These findings suggest a need for efforts to prevent smoking uptake among Asian American college students. Myers M, Doran N, Trinidad D, Wall T, Klonoff EA. Prospective study of cigarette smoking initiation during college: Chinese and Korean American students. Health Psychol. 2009;28(4):448-456.

Simultaneous Recruitment of Drug Users and Men Who have Sex with Men in the United States and Russia Using Respondent-Driven sampling: Sampling Methods and Implications

The Sexual Acquisition and Transmission of HIV Cooperative Agreement Program (SATHCAP) examined the role of drug use in the sexual transmission of the human immunodeficiency virus (HIV) from traditional high-risk groups, such as men who have sex with men (MSM) and drug users (DU), to lower risk groups in three US cities and in St. Petersburg, Russia. SATHCAP employed respondent-driven sampling (RDS) and a dual high-risk group sampling approach that relied on peer recruitment for a combined, overlapping sample of MSM and DU. The goal of the sampling approach was to recruit an RDS sample of MSM, DU, and individuals who were both MSM and DU (MSM/DU), as well as a sample of sex partners of MSM, DU, and MSM/DU and sex partners of sex partners. The approach efficiently yielded a sample of 8,355 participants, including sex partners, across all four sites. At the US sites-Los Angeles, Chicago, and Raleigh-Durham-the sample consisted of older (mean age = 41 years), primarily black MSM and DU (both injecting and non-injecting); in St. Petersburg, the sample consisted of primarily younger (mean age = 28 years) MSM and DU (injecting). The US sites recruited a large proportion of men who have sex with men and with women, an important group with high potential for establishing a generalized HIV epidemic involving women. The advantage of using the dual high-risk group approach and RDS was, for the most part, the large, efficiently recruited samples of MSM, DU, and MSM/DU. The disadvantages were a recruitment bias by race/ethnicity and income status (at the US sites) and under-enrollment of MSM samples because of short recruitment chains (at the Russian site). Iguchi M, Ober A, Berry S, et al. Simultaneous recruitment of drug users and Men Who have Sex with Men in the United States and Russia using respondent-driven sampling: Sampling methods and implications. J Urban Health 2009;86Suppl 1:5-31.

Effect of Cigarette Smoking on HIV Acquisition, Progression, and Mortality

Cigarette smoking is more common among those with HIV compared with the general population. However, it remains unclear whether smoking alters the natural history of HIV infection, or if unique health consequences related to smoking occurs in the context of HIV. In this article, researchers review the literature on the effect of smoking on acquisition of HIV, progression of HIV to AIDS, and mortality. Although there was significant heterogeneity in the study populations evaluated, they found little evidence that cigarette smoking increases the risk for acquiring HIV. Two studies observed that smoking was associated with more rapid CD4 cell count declines, but most data suggest that smoking does not accelerate progression to clinical AIDS. The most consistent finding was an increased risk for respiratory infections in smokers. Although no effect of smoking was seen with AIDS-related mortality, findings related to all-cause mortality were inconclusive. Owing to an increase in chronic non-AIDS

outcomes in the post-highly active antiretroviral therapy (HAART) era, smoking is likely an increasingly important contributor to morbidity and mortality in HIV-infected populations. Future investigation of the biological and clinical effects of smoking, and of preventive approaches to reduce the heavy burden among individuals with HIV is warranted. Marshall M, McCormack M, Kirk G. Effect of cigarette smoking on HIV acquisition, progression, and mortality. AIDS Educ Prev. 2009;1(3 Suppl):28-39.

Persistence and Change in Disparities in HIV Infection among Injection Drug Users in New York City after Large-Scale Syringe Exchange Programs

Researchers examined racial/ethnic disparities in HIV infection among injection drug users (IDUs) before and after implementation of large-scale syringe exchange programs in New York City. Participants were recruited from IDUs entering the Beth Israel drug detoxification program in New York City, with n=1203 recruited from 1990 through 1994, prior to large-scale syringe exchange programs (pre-exchange). They were compared with n=1109 participants who began injecting in 1995 or later, who were interviewed 995 through 2008 (post-exchange). There were large differences in HIV prevalence among pre-exchange vs post-exchange participants (African Americans, 57% vs 15%; Hispanics, 53% vs 5%; Whites, 27% vs 3%). Pre- and post-exchange relative disparities of HIV prevalence were similar for African Americans vs Whites (adjusted odds ratio [AOR] = 3.46, 95% confidence interval [CI] = 2.41, 4.96 and AOR = 4.02, 95% CI = 1.67, 9.69, respectively) and Hispanics vs Whites (AOR = 1.76, 95% CI = 1.49, 2.09 and AOR = 1.49, 95% CI = 1.02, 2.17). Racial/ethnic group differences in risk behavior did not explain differences in HIV prevalence. The findings suggest that new interventions are needed to address continuing disparities in HIV infection among IDUs. Self-reported risk behaviors by themselves may not be adequate outcome measures for evaluating interventions to reduce racial/ethnic disparities in HIV infection. Des Jarlais D, Arasteh K, Hagan H, McKnight C, Perlman D, Friedman S. Persistence and change in disparities in HIV infection among injection drug users In New York City after large-scale syringe exchange programs. Am J Public Health 2009;Suppl 2:445-451.

Bridging Sexual Boundaries: Men Who have Sex with Men and Women in a Street-Based Sample in Los Angeles

This study sought to determine the potential contribution of bisexual men to the spread of HIV in Los Angeles. Researchers compared the characteristics and behaviors of men who have sex with men and women (MSMW) to men who have sex with only women (MSW) and men who have sex with only men (MSM) in Los Angeles. Men (N = 1,125) who participated in one of the two waves of data collection from 2005 to 2007 at the Los Angeles site for NIDA's Sexual Acquisition and Transmission of HIV-Cooperative Agreement Program (SATHCAP) were recruited using Respondent Driven Sampling (RDS). Participants completed ACASI and received oral HIV rapid testing with confirmatory blood test by Western Blot. They also provided urine specimens for detection of recent powder cocaine, crack cocaine, methamphetamine, or heroin use. MSM, MSW, or MSMW were defined by the gender of their sex partner/s in the past 6 months. Men were mostly of low income, unemployed, and minority, with many homeless; 66% had been to jail or prison, 29% had ever injected drugs, and 25% had used methamphetamine in the past 30 days. The sample had high HIV prevalence: 12% of MSMW, 65% of MSM, and 4% of MSW. Overall, HIV-positive MSM had more unprotected anal intercourse (UAI) with partners of any HIV status; among HIV-positive MSMW, more had UAI with HIV-negative and HIV status unknown female partners than male partners. Findings highlight the interconnectedness of sexual and drug networks in this sample of men-as most have partners who use drugs and they

use drugs themselves. A concentration of risk was found among impoverished minority men, who were heavily involved in drug use, sex trading, and having sex with either gender. Findings also suggest an embedded core group of drug-using MSMW who, driven by their pressing need for drugs and money, may concentrate the epidemic among men and women like themselves who have few resources. Gorbach P, Murphy R, Weiss R, Hucks-Ortiz C, Shoptaw S. Bridging sexual boundaries: Men Who Have Sex With Men and Women in a street-based sample In Los Angeles. J Urban Health 2009;6 Suppl 1:63-76.

Drug Choice, Spatial Distribution, HIV Risk, and HIV Prevalence among Injection Drug Users in St. Petersburg, Russia

The HIV epidemic in Russia has been driven by the unsafe injection of drugs, predominantly heroin and the ephedrine derived psychostimulants. Understanding differences in HIV risk behaviors among injectors associated with different substances has potentially important implications for prevention programs. Researchers examined behaviors associated with HIV risk among 900 IDUs who inject heroin, psychostimulants, or multiple substances in 2002. Study participants completed screening questionnaires that provided data on sociodemographics, drug use, place of residence and injection- and sex-related HIV risk behaviors. HIV testing was performed and prevalence was modeled using general estimating equation (GEE) analysis. Individuals were clustered by neighborhood and disaggregated into three drug use categories: Heroin Only Users, Stimulant Only Users, and Mixed Drug Users. Among Heroin Only Users, younger age, front/backloading of syringes, sharing cotton and cookers were all significant predictors of HIV infection. In contrast, sharing needles and rinse water were significant among the Stimulant Only Users. The Mixed Drug Use group was similar to the Heroin Only Users with age, front/back loading, and sharing cotton significantly associated with HIV infection. These differences became apparent only when neighborhood of residence was included in models run using GEE. The type of drug injected was associated with distinct behavioral risks. Risks specific to Stimulant Only Users appeared related to direct syringe sharing. The risks specific to the other two groups are common to the process of sharing drugs in preparation to injecting. These findings point to the need for increased efforts in HIV prevention education for IDUs in St. Petersburg that take into account the ways that neighborhood differences may influence risky injecting behaviors and preferences for different drugs. Kruse G, Barbour R, Heimer R, et al. Drug choice, spatial distribution, HIV risk, and HIV prevalence among injection drug users in St. Petersburg, Russia.Harm Reduct J. 2009;6:22-29.

Potential Bridges of Heterosexual HIV Transmission from Drug Users to the General Population in St. Petersburg, Russia: Is it Easy to be a Young Female?

The epidemic of HIV in St. Petersburg is currently concentrated among injection drug users (IDUs) but may be penetrating into the general population. Non-IDUs who have IDU sex partners (SP) could be potential bridges in an expanding epidemic. To investigate potential bridges, researchers recruited a convenience sample of 288 non-IDUs whose HIV diagnosis was attributed to sexual transmission and determined the proportion that had IDUs among their SP (IDU SP ever (lifetime) and IDU SP in the last year were the key variables for this analysis). The interaction of gender and age was found to be a significant predictor of having lifetime IDU SP ($p = 0.006$, chi (2) test) and IDU SP in the last year ($p = 0.05$, chi (2) test): females aged 26 and younger were more likely to have both lifetime IDU SP and IDU SP in the last year. Among the group of young females, 46% reported ever having an IDU SP. Of young women reporting ever having an IDU SP, 85% also reported at least one lifetime non-IDU SP. Among the females aged 26 or younger, a lower level of education (odds ratio [OR] = 2.7, confidence interval [CI] = 1.1-6.7), being

born in St. Petersburg (OR = 2.9, CI = 1.2-7.2), and alcohol use in the last 30 days (OR = 3.5, CI = 1.3-9.6) were significant correlates for ever having had an IDU SP. The findings underscore the need to expand HIV prevention to target this potential bridging population and prevent further transmission. Toussova O, Shcherbakova I, Volkova G, Niccolai L, Heimer R, Kozlov A. Potential bridges of heterosexual HIV transmission from drug users to the general population in St. Petersburg, Russia: Is it easy to be a young female? J Urban Health 2009; 86 Suppl 1:121-130.

The Potential for Bridging of HIV Transmission in the Russian Federation: Sex Risk Behaviors and HIV Prevalence among Drug Users (DUs) and their Non-DU Sex Partners

The HIV epidemic that began in Russia in the mid-1990s has been concentrated mostly among drug users (DUs). Recent evidence of increasing HIV cases among non-DUs attributed to sexual behavior raises potential concern about a more generalized epidemic. This analysis examined the potential for HIV transmission from DUs to their non-DU sex partners, based on data collected during 2005-2008 in St. Petersburg, Russia. A total of 631 DUs were recruited into the sample with an HIV prevalence of 45%. A majority (84%) of DUs reported being sexually active in the past 6 months, and the DU status of their sex partners was reported as: 54% DU, 40% non-DU, and 6% unknown DU status. In 41% of partnerships with an HIV-negative or unknown status partner not known to be DU (potential bridging partnerships), the last reported intercourse was unprotected. Female DUs with potential bridging partnerships were more likely than male DUs to be younger and report homelessness and to have multiple or new sex partners. Many non-DU sex partners of DUs enrolled in the study reported new sex partners in the past 6 months (66%), unprotected intercourse at last sex (60%), and multiple sex partners in the past 6 months (48%). HIV prevalence in this group was 15% (eight out of 53). The high prevalence of HIV among DUs, their sexual contact with non-DUs, and the high-risk sexual behaviors of this potential bridging population together indicate the real potential for an increasingly generalized epidemic. Niccolai L, Shcherbakova I, Toussova O, Kozlov A, Heimer R. The potential for bridging of HIV transmission in the Russian Federation: Sex risk behaviors and HIV prevalence among drug users (DUs) and their non-DU sex partners. J Urban Health 2009; 86 Suppl 1:131-143.

Behaviorally Bisexual Men and their Risk Behaviors with Men and Women

Gay and bisexual men are often treated as a homogenous group; however, there may be important differences between them. In addition, behaviorally bisexual men are a potential source of HIV infection for heterosexual women. In this study, 97 men who use drugs and have sex with men only (MSM) were compared to 175 men who use drugs and have sex with men and women (MSMW). The 175 MSMW were also compared to 772 men who have sex with women only (MSW). Bivariate and multiple logistic regression analyses were performed to assess correlates of MSMW risk behaviors with men and with women as well as whether MSMW, compared with MSW, engaged in more risky behaviors with women. Compared with MSM, MSMW were less likely to be HIV-positive or to engage in unprotected receptive anal intercourse. In contrast, MSMW were more likely than MSW to be HIV-positive and to engage in anal intercourse with their female partners; however, rates of unprotected anal intercourse were similar. The study findings suggest that there may be important differences in HIV risk behaviors and HIV prevalence between MSM and MSMW as well as between MSMW and MSW. Zule W, Bobashev G, Wechsberg W, Costenbader E, Coomes C. Behaviorally bisexual men and their risk behaviors with men and women. J Urban Health 2009; Suppl 1:48-62.

Staphylococcus Aureus in the Community: Colonization versus Infection

Antibiotic-resistant Staphylococcus aureus infections have increased dramatically in the community, yet S. aureus nasal colonization has remained stable. The objectives of this study were to determine if S. aureus colonization is a useful proxy measure to study disease transmission and infection in community settings, and to identify potential community reservoirs. Randomly selected households in Northern Manhattan completed a structured social network questionnaire and provided nasal swabs that were typed by pulsed field gel electrophoresis to identify S. aureus colonizing strains. The main outcome measures were: 1) colonization with S. aureus; and 2) recent serious skin infection. Risk factor analyses were conducted at both the individual and household levels; logistic regression models identified independent risks for household colonization and infection. The 321 surveyed households contained 914 members; S. aureus prevalence was 25% and MRSA was 0.4%. More than 40% of households were colonized. Recent antibiotic use was the only significant correlate for household colonization ($p = .002$). Seventy-eight (24%) households reported serious skin infection. In contrast with colonization, five of the six risk factors that increased the risk of skin infection in the household at the univariate level remained independently significant in multivariable analysis: international travel, sports participation, surgery, antibiotic use and towel sharing. S. aureus colonization was not significantly associated with serious skin infection in any analysis. Among multiperson households with more than one person colonized, 50% carried the same strain. Given the absence of an association between S. aureus nasal colonization and serious skin infection, further exploration is needed to identify the venues or body sites involved in transmission. The magnitude of colonization and infection within the household also suggests that households are an underappreciated and substantial community reservoir. Miller M, Cook H, Furuya E, Bhat M, Lee M, Vavagiakis P, Visintainer P, Vasquez G, Larson E, Lowy F. Staphylococcus aureus in the community: Colonization versus infection. PLoS One 2009; 4(8):6708-6717.

The Impact of Incarceration upon Adherence to HIV Treatment among HIV-Positive Injection Drug Users: A Qualitative Study

HIV-positive injection drug users (IDU) often do not derive the full benefits of highly active antiretroviral therapy (HAART). Among IDU, recent incarceration has been associated with discontinuation of HAART for non-clinical reasons. Researchers sought qualitative information on experiences with HAART among HIV-positive IDU who had been recently incarcerated within provincial prisons in British Columbia to identify factors influencing adherence to treatment. Twelve in-depth qualitative interviews were conducted with males recruited from a cohort study (ACCESS) involving over 450 HIV-positive IDU. All participants had been incarcerated after initiating HAART. Audio-recorded interviews were conducted to examine experiences of taking HAART in prison, with particular attention to adherence and experiences of treatment discontinuation. Participant accounts described situations where adherence to HIV treatment was compromised in custody. A small number of participants reported treatment interruptions that lasted over a week when they were unable to obtain HIV medications through institutional healthcare. Short-term interruptions in treatment were said to be common during intake into the correctional system and at the point of release from custody. High levels of HIV discrimination motivate prisoners to hide the fact that they are HIV-positive by making efforts to take medications discreetly, which may result in missed doses. The current study identified contextual factors within correctional environments that may hinder individuals' ability to adhere to HAART. The findings suggest that improved health services and coordination with community care providers are needed to enhance the quality of HIV treatment

within correctional environments. Small W, Wood E, Betteridge G, Montaner J, Kerr T. The impact of incarceration upon adherence to HIV treatment among HIV-positive injection drug users: a qualitative study. AIDS Care 2009;1(6):708-714.

HIV Testing and Conspiracy Beliefs Regarding the Origins of HIV among African Americans

Conspiracy beliefs regarding the origins of HIV are common among African Americans, and have been associated with engaging in HIV risk behaviors as well as with earlier diagnosis among HIV patients. This study sought to examine the association of HIV serostatus testing with conspiracy beliefs. A total of 1430 African Americans from low-income neighborhoods with high rates of drug use were surveyed in 1997-1999 in face-to-face interviews. Two 4-point items assessed if participants agreed that "AIDS was started by an experiment that went wrong" and "AIDS was created to kill blacks and poor folks." A binary variable indicated if the respondent agreed with the statements. On average, 22.5% of the sample endorsed conspiracy beliefs, 4.0% of whom reported not having had an HIV test, compared to 7.7% of those who did not endorse conspiracy beliefs. In multivariable logistic regression modeling, never having had an HIV test was significantly associated with conspiracy beliefs (adjusted odds ratio [AOR] = 0.43, 95% confidence interval [CI] = 1.3-4.3), having a high school education (AOR = 0.55, CI = 0.35-0.84), having depression (AOR = 1.61, CI = 1.02-2.52), female gender (AOR = 0.54, CI = 0.34-0.86), younger age, and a history of injection drug use (AOR = 0.36, CI = 0.23-0.56), but not sex risk behaviors (multiple partners, irregular condom use). Individuals who have conspiracy beliefs are more likely to have been tested for HIV, however, which may partially explain why HIV-positive individuals who endorsed conspiracy beliefs were more likely to have an earlier diagnosis compared to those who did not endorse such beliefs. Bohnert A, Latkin C. HIV testing and conspiracy beliefs regarding the origins of HIV among African Americans. AIDS Patient Care STDS 2009;23(9):759-763.

Validating the Multidimensional Measure of Cultural Identity for Latinos

The psychometric properties of the Multidimensional Measure of Cultural Identity Scales for Latinos (MMCISL; Félix-Ortiz, Newcomb, & Myers, 1994) have never been examined in an adult Latina sample representing various levels of nativity and nationality. The rationale for the study was to confirm the factor structure and psychometric properties of the MMCISL with a predominantly immigrant sample of Latina mothers and daughters (n = 316). Adequate reliability estimates were found for six of the original ten scales. Confirmatory factor analyses provided evidence of construct validity for the reliable scales. The Preferred Latino Affiliation scale was the only scale to meet strict measurement invariance criteria across mothers and daughters. Criterion validity was evidenced by relations between the Familiarity with Latino Culture scale and all criterion variables. Dillon F, Félix-Ortiz M, Rice C, De La Rosa M, Rojas P, Duan R. Validating the multidimensional measure of cultural identity scales for Latinos among Latina mothers and daughters. Cultur Divers Ethnic Minor Psychol. 2009;15(2):191-201.

Influence of Gender, Sexual Orientation, and Need on Treatment Utilization for Substance Use and Mental Disorders: Findings from the California Quality of Life Survey

Prior research has shown a higher prevalence of substance use and mental disorders among sexual minorities, however, the influence of sexual orientation on treatment seeking has not been widely studied. Researchers used a model

of help-seeking for vulnerable populations to investigate factors related to treatment for alcohol or drug use disorders and mental health disorders, focusing on the contributions of gender, sexual orientation, and need. Survey data were obtained from a population-based probability sample of California residents that oversampled for sexual minorities. Logistic regression was used to model the enabling, predisposing, and need-related factors associated with past-year mental health or substance abuse treatment utilization among adults aged 18-64 (N=2,074). Compared with individuals without a diagnosed disorder, those with any disorder were more likely to receive treatment. After controlling for both presence of disorder and other factors, lesbians and bisexual women were most likely to receive treatment and heterosexual men were the least likely. Moreover, a considerable proportion of sexual orientation minorities without any diagnosable disorder, particularly lesbians and bisexual women, also reported receiving treatment. This study highlights the need to better understand the factors beyond meeting diagnostic criteria that underlie treatment utilization among sexual minorities. Future research should also aim to ascertain the effects of treatment provided to sexual minorities with and without diagnosable disorders, including the possibility that the provision of such treatment may reduce the likelihood of their progression to greater severity of distress, disorders, or impairments in functioning. Grella C, Greenwell L, Mays V, Cochran S. Influence of gender, sexual orientation, and need on treatment utilization for substance use and mental disorders: Findings from the California Quality of Life Survey. BMC Psychiatry 2009; 9(9):52-62.

Longitudinal Prospective Cohort Study on Differences in Substance Abuse in US vs Immigrant Hispanic Adolescents

The current study was conducted to ascertain whether the effects of nativity (i.e., U.S. born vs. immigrant) on Hispanic adolescent substance use is mediated by ecological processes such as family functioning, school connectedness, and perceived peer substance use. The effects of family, peer, and school processes on adolescent substance use were examined in a nationally representative sample of 742 (358 male, 384 female) Hispanic youth (mean age = 15.9; SD = 1.8). Results from a structural equation model indicated that the higher rates of substance use among U.S.-born Hispanics (compared with foreign-born Hispanics) are partially mediated by perceived peer substance use (as measured by the adolescent). The results also showed that perceived peer substance use and school connectedness mediate the relationship between family processes and substance use, suggesting that family processes may offset some of the deleterious effects of negative peer selection on adolescent substance use. These findings imply that public health behavioral interventions to prevent substance use among both U.S.-born and foreign-born Hispanics may need to attend to multiple ecological processes, including family, school, and peers. Prado G, Huang S, Schwartz S, Maldonado-Molina M, Bandiera F, de la Rosa M, Pantin H. What accounts for differences in substance use among U.S.-born and immigrant Hispanic adolescents? : Results from a longitudinal prospective cohort study. J Adolesc Health 2009; 145(2):118-125.

A Prospective Three Generational Study of Fathers' Constructive Parenting

This prospective, intergenerational study considered multiple influences on 102 fathers' constructive parenting of 181 children. Fathers in the 2nd generation (G2) were recruited as boys on the basis of neighborhood risk for delinquency and assessed through early adulthood. The fathers' parents (G1) and the G2 mothers of G3 also participated. A multiagent, multimethod approach was used to measure G1 and G2 constructive parenting (monitoring, discipline, warmth, and involvement), G2 positive adolescent adjustment, and problem behavior in all 3 generations, including G3 difficult temperament and externalizing

problems in early and middle childhood, respectively. Path modeling supported direct transmission of G1 constructive parenting of G2 in late childhood to G2 constructive parenting of G3 in middle childhood. Of note, G1 parenting indirectly influenced G2 parenting through G2 positive adjustment but not through G2 adolescent antisocial behavior. G1 parenting influenced G2 parenting in both early and middle childhood of G3. G2 parenting influenced G3 problem behavior but not vice versa. Intergenerational continuities in parenting persisted, even when additional influences were considered. These findings suggest that transmission pathways are not limited to life-course adversity. Rather, constructive parenting is maintained, in part, by engendering positive adjustment in offspring. Kerr D, Capaldi D, Pears K, Owen L. A prospective three generational study of fathers' constructive parenting: Influences from family of origin, adolescent adjustment, and offspring temperament. Dev Psychol. 2009;(5):1257-1275.

Behavioral Problems and the Occurrence of Tobacco, Cannabis, and Coca Paste Smoking in Chile: Evidence Based on Multivariate Response Models for School Survey Data

In this study the researchers estimate suspected links between youthful behavioral problems and smoking of tobacco, cannabis, and coca paste. In the Republic of Chile, school-attending youths were sampled from all 13 regions of the country, with sample size of 46,907 youths from 8th to 12th grades. A Generalized Estimating Equations (GEE) approach to multiple logistic regression was used to address three interdependent response variables, tobacco smoking, cannabis smoking, and coca paste smoking, and to estimate associations. Drug-specific adjusted slope estimates indicate that youths at the highest levels of behavioral problems are an estimated 1.1 times more likely to have started smoking tobacco, an estimated 1.6 times more likely to have started cannabis smoking, and an estimated 2.0 times more likely to have started coca paste smoking, as compared to youths at the lowest level of behavioral problems ($p<0.001$). In Chile, there is an association linking behavioral problems with onsets of smoking tobacco and cannabis, as well as coca paste; strength of association is modestly greater for coca paste smoking. Caris L, Anthony C, R'os-Bedoya C, Anthony J. Behavioral problems and the occurrence of tobacco, cannabis, and coca paste smoking in Chile: Evidence based on multivariate response models for school survey data. Drug Alcohol Depend. 2009;104(1-2):50-55.

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

Research Findings - Prevention Research

Preventive Intervention Ameliorates Genetic Risk for Problem Behavior

The present research addresses whether participation in an efficacious preventive intervention can ameliorate the risk that a genetic vulnerability factor is hypothesized to confer on increases in risk behaviors across preadolescence. As part of a preventive intervention study, 641 black families in rural Georgia were assigned randomly to a prevention or control condition. The prevention condition participated in the Strong African American Families preventive intervention, consisting of separate, concurrent sessions for parents and youths, followed by a joint parent-youth session in which families practiced skills they learned in the separate sessions. Involvement in risk behaviors was assessed when the youths were 11 (pretest), 12 (posttest), and 14 (long-term follow-up) years of age. A genetic vulnerability factor, that is, a variable-nucleotide repeat polymorphism in the promoter region of the SLC6A4 gene (5HTT), was assessed 2 years after the long-term follow-up assessment. Youths at genetic risk who were assigned to the control condition displayed greater increases in risk behaviors across the 29 months that separated the pretest and long-term follow-up assessments, compared with youths at genetic risk who were assigned to the Strong African American Families condition and youths without genetic risk who were assigned to either condition. This is the first study to demonstrate that participation in an efficacious preventive intervention can ameliorate a genetic risk for increasing involvement in health-compromising risk behaviors across preadolescence. Brody GH, Chen Y, Beach SR, Philibert RA, Kogan SM. Participation in a family-centered prevention program decreases genetic risk for adolescents ' Risky Behaviors. Pediatrics 2009;124(3):911-917.

Effects of the Linking the Interests of Families and Teachers (LIFT) Preventive Intervention

Substance use outcomes were examined for 351 fifth grade children (51% female) who participated in a randomized controlled trial designed to assess the efficacy of a school-based multimodal universal preventive intervention called Linking the Interests of Families and Teachers (LIFT). Twelve randomly chosen public elementary schools within a moderate-sized metropolitan area in the U.S. Pacific Northwest with higher than local median number of police contacts were invited to participate. Schools were randomly assigned to either a "services as usual" control condition or the LIFT intervention condition. Frequency of any use of tobacco, alcohol, and other drugs was assessed via self-report from grades 5 through 12. The LIFT universal preventive intervention is based in a developmental model centered on moment-to-moment social interaction processes thought to be important in initiating and

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continuing youth problem behaviors. The intervention included multiple components, including parent management training, child social and problem solving skills training, the recess Good Behavior Game, as well as parent-teacher communication aids such as a weekly newsletter for parents and the "LIFT Line," which was a dedicated phone line and answering machine within each intervention classroom. Latent variable growth models specified average level, linear growth and accelerated growth of tobacco, alcohol, and other drugs. The LIFT intervention had a significant effect on reducing the rate of growth in use of tobacco and illicit drugs, particularly for girls, and it had an overall impact on average levels of use of tobacco, alcohol, and illicit drugs. Average tobacco use reductions were mediated by increases in family problem solving. The intervention had significant indirect effects on growth in substance use through intervention effects on reduced playground aggression and increased family problem solving. The intervention was also associated with roughly a 10% reduced risk in initiating tobacco and alcohol use. DeGarmo DS, Eddy JM, Reid JB, Fetrow RA. Evaluating mediators of the impact of the Linking The Interests of Families and Teachers (LIFT) Multimodal Preventive Intervention on substance use initiation and growth across adolescence. Prev Sci. 2009;10(3):208-220.

Drug Prevention Intervention Effects Mediated by Delayed Drug Initiation

The authors examine whether delayed substance initiation during adolescence, achieved through universal family-focused interventions conducted in middle school, can reduce problematic substance use during young adulthood. Sixth-grade students enrolled in 33 rural mid-western schools and their families were randomly assigned to 3 experimental conditions. Self-report questionnaires provided data at 7 time points for the Iowa Strengthening Families Program (ISFP), Preparing for the Drug Free Years (PDFY), and control groups through young adulthood. Five young adult substance frequency measures, including drunkenness, alcohol-related problems, cigarettes, illicit drugs, and poly-substance use, were modeled as distal outcomes affected by the average level and rate of increase in substance initiation across the adolescent years in latent growth curve analyses. Results show that the models fit the data and that they were robust across outcomes and interventions, with more robust effects found for ISFP. The addition to the model of direct intervention effects on young adult outcomes was not supported, suggesting long-term effects were primarily indirect. Relative reduction rates calculated to quantify intervention-control differences in the estimated proportion of young adults indicating problematic substance use ranged from 19% to 31% for ISFP and from 9% to 16% for PDFY. Spoth R, Trudeau L, Guyll M, Shin C, Redmond C. Universal intervention effects on substance use among young adults mediated by delayed adolescent substance initiation. J Consult Clin Psychol. 2009;77(4):620-632.

Comprehensive School-Based Program Prevents Early Onset Substance Use, Violence and Sexual Risk Behavior

This research assessed the effectiveness of a 5-year trial of a comprehensive school-based program designed to prevent substance use, violent behaviors, and sexual activity among elementary-school students. The study involved a matched-pair, cluster-randomized, controlled design, with 10 intervention schools and 10 control schools. Fifth-graders (N = 1714) self-reported on lifetime substance use, violence, and voluntary sexual activity. Teachers of participant students reported on student (N = 1225) substance use and violence. Two-level random-effects count models (with students nested within schools) indicated that student-reported substance use (rate ratio [RR] = 0.41; 90% confidence interval [CI] = 0.25, 0.66) and violence (RR = 0.42; 90% CI = 0.24, 0.73) were significantly lower for students attending intervention schools. A 2-level random-effects binary model indicated that sexual activity was lower

(odds ratio = 0.24; 90% CI = 0.08, 0.66) for intervention students. Teacher reports substantiated the effects seen for student-reported data. Dose-response analyses indicated that students exposed to the program for at least 3 years had significantly lower rates of all negative behaviors. Risk-related behaviors were substantially reduced for students who participated in the program, providing evidence that a comprehensive school-based program can have a strong beneficial effect on student behavior. Beets M, Flay B, Vuchinich S, et al. Use of a social and character development program to prevent substance use, violent behaviors, and sexual activity among elementary-school students in Hawaii. Am J Public Health 2009;99(8):1438-1445.

Optimal Performers in Drug Court have Consistently Negative Drug Screens

Graduation rates in drug courts average 50% to 70%, but it is unclear what proportion of graduates responded to the drug court services and what proportion might not have had serious drug problems on entry. This study cluster analyzes urine drug screen results during the first 14 weeks of treatment on 284 participants from three misdemeanor drug courts. A four-cluster solution (R 2 >.75) produced distinct subgroups characterized by (a) optimal performers with consistently drug-negative urine specimens (34% of the sample), (b) non-responders with consistently drug-positive specimens (21%), (c) non-complaints with consistently missed urine specimens (26%), and (d) responders with urine specimens that began as drug positive but became progressively drug negative over time (19%). With regard to longer-term outcomes, optimal performers were more likely to provide a drug-negative urine specimen at the 6-month follow-up. Authors propose adaptive approaches for drug courts. DeMatteo D, Marlowe DB, Festinger DS, Arabia PL. Outcome trajectories in drug court: Do all participants have serious drug problems? Criminal Justice and Behavior. 2009;36(4):354-368.

Community-Based Prevention System Reduces Substance Use and Delinquency in Grades 5 through 8

This study tested whether the Communities That Care (CTC) prevention system reduces adolescent alcohol, tobacco, and other drug use and delinquent behavior community wide. The Community Youth Development Study is the first randomized trial of the CTC prevention system. In 2003, 24 small towns in 7 states, matched within state, were randomly assigned to control or CTC conditions. A panel of 4407 fifth-grade students was surveyed annually through eighth grade. In the intervention condition, a coalition of community stakeholders received training and technical assistance to install the CTC prevention system. Coalitions used epidemiological data to identify elevated risk factors and depressed protective factors in the community, and chose and implemented tested programs to address their community's specific profile from a menu of effective programs for families, schools, and youths aged 10 to 14 years. Outcomes focused on incidence and prevalence of alcohol, tobacco, and other drug use and delinquent behavior by spring of grade 8. Results indicated that the incidences of alcohol, cigarette and smokeless tobacco initiation, and delinquent behavior were significantly lower in CTC than in control communities for students in grades 5 through 8. In grade 8, the prevalence of alcohol and smokeless tobacco use in the last 30 days, binge drinking in the last 2 weeks, and the number of different delinquent behaviors committed in the last year were significantly lower for students in CTC communities. Hawkins J, Oesterle S, Brown E, Arthur M, Abbott R, Fagan A, Catalano R. Results of a Type 2 Translational Research Trial to Prevent adolescent drug use and delinquency: A test of Communities That Care. Arch Pediatr Adolesc Med. 2009;163(9):789-798.

Long-term Effects of Project ALERT on Risky Sexual Behaviors

This study assesses the impact of a school-based drug prevention program, called Project ALERT, on risky sexual behavior among 1901 non-married, sexually active young adults who participated in one of two program variations as adolescents. It also tests for differences in program effect depending on program duration (middle school only vs. a combined middle school and high school program) and participants' gender. Using survey data from a randomized controlled experiment conducted in 45 Midwestern communities (55 schools), the authors assessed program effects on risky sexual behavior at age 21 with three measures: having unprotected sex because of drug use, engaging in inconsistent condom use, and having sex with multiple partners. Compared to control, Project ALERT reduced the likelihood of all risky sex outcomes except inconsistent condom use among these sexually active young adults. Program effects were found 5 and 7 years after program exposure and were partially mediated by reductions in alcohol and drug abuse. There were no significant differences in program effects by gender or by program duration compared to control. Ellickson P, McCaffrey D, Klein D. Long-term effects of drug prevention on risky sexual behavior among young adults. J Adolesc Health 2009;45(2):111-117.

Reduced Rates of Pregnancy Among Juvenile Justice Girls Exposed to Preventive Intervention

Preventing adolescent pregnancy is a national research priority that has had limited success. In the present study, the authors examined whether Multidimensional Treatment Foster Care (MTFC) relative to intervention services as usual (group care [GC]) decreased pregnancy rates among juvenile justice girls mandated to out-of-home care. Girls (13-17 years of age) with histories of criminal referrals (Mdn = 10) were randomly assigned to MTFC (n = 81) or GC (n = 85) as part of 2 randomized controlled trials. Pregnancy histories were assessed from baseline through 24 months. Fewer post baseline pregnancies were reported for MTFC girls (26.9%) than for GC girls (46.9%)--an effect that remained significant after controlling for baseline criminal referrals, pregnancy history, and sexual activity. MTFC has previously been shown to decrease arrest and lock-up rates. The present findings support the long-term preventive effects of MTFC on adolescent girls' pregnancy rates. Findings are consistent with the notion that programs that target delinquency by impacting general risk behavior pathways and contexts may more successfully prevent teen pregnancy than those that directly target sexual behaviors. Kerr D, Leve L, Chamberlain P. Pregnancy rates among juvenile justice girls in two randomized controlled trials of multidimensional treatment foster care. J Consult Clin Psychol. 2009;77(3):588-593.

Peer Health Advocates Function as Multi-Level Change Agents

The Risk Avoidance Partnership (RAP) Project conducted in Hartford, Connecticut, tests a program to train active drug injectors and crack cocaine users as "Peer Health Advocates" (PHAs) to deliver a modular HIV, hepatitis, and STI prevention intervention to hard-to-reach drug users in their networks and others in the city. The intervention was designed to diffuse health promotion and risk-reduction interventions by supporting PHAs to model prevention practices and deliver risk- and harm-reduction materials and information. The study compared change in behaviors and attitudes between baseline and 6-month follow-up of 112 primarily African-American and Latino PHAs, 223 of their drug-user network contact referrals, and 118 other study recruits (total n = 523). Results indicated significant HIV risk reduction among all study participants, associated with significant health advocacy action conducted by PHAs, and a relationship between exposure to the RAP peer-

delivered intervention and risk reduction among all study groups. Findings suggest that active drug users' engagement in peer health advocacy can set in motion a feedback and diffusion process that supports both the continued work of the PHAs and the adoption of harm reduction and mimicking of health advocacy by their peers. Weeks M, Li J, Dickson-Gomez J, Convey M. Outcomes of a peer HIV prevention program with injection drug and crack users: The risk avoidance partnership. Subst Use Misuse 2009;44;251-279.

Two Interventions Reduce Sexual Risks among IDU in Ukraine

A brief human immune-deficiency virus (HIV) testing and counseling intervention was compared to a more time-consuming and expensive street-based intervention with injection drug users (IDUs). A cross-over experimental design was used in which 900 IDUs were recruited, followed by a ''wash-out '' period with no recruitment, a reversal of intervention assignment areas and an additional recruitment of 900 IDUs with baseline and 6-month follow-up assessments. The project was conducted in Kiev, Odessa and Makeevka/Donesk Ukraine with a total of 798 IDUs. HIV testing and ACASI data were collected from all. Participants in both conditions reduced their injection and sex risks significantly; however, there was little difference in outcomes between conditions. IDUs who knew they were HIV-infected at baseline were significantly more likely to practice safe sex than those unaware or HIV-negative; those who first learned that they were infected at baseline changed their safe sex practices significantly more than those who already knew that they were infected at baseline and those who were HIV-negative. Booth R, Lehman W, Dvoryak S, Brewster J, Sinitsyna L. Interventions with injection drug users in Ukraine. Addiction. 2009;104(11):1864-1873.

Variations in Risk Reduction with a Peer Intervention in Thailand & the US

This study assessed the efficacy of a network-oriented peer education intervention promoting HIV risk reduction among injection drug users and their drug and sexual network members in Chiang Mai, Thailand and Philadelphia, USA. A total of 414 networks with 1123 participants were enrolled. The experimental intervention consisted of 6 small group peer educator training sessions and 2 booster sessions delivered to the network index only. All participants in both arms received individual HIV counseling and testing. Follow-up visits occurred every six months for up to 30 months. There were 10 HIV seroconversions, 5 in each arm. The number of participants reporting injection risk behaviors dropped dramatically between baseline and follow-up in both arms at both sites. Index members in the intervention arm engaged in more conversations about HIV risk following the intervention compared to control indexes. There was no evidence of change in sexual risk as a result of the intervention. Reductions in injection risk behaviors were observed: 37%, 20%, and 26% reduction in odds of sharing cottons, rinse water and cookers, respectively, and 24% reduction in using a syringe after someone else. Analysis of the individual sites suggested a pattern of reductions in injection risk behaviors in the Philadelphia site. In both sites, the intervention resulted in index injection drug users engaging in the community role of discussing reduction in HIV injection risk behaviors. Latkin CA, Donnell D, Metzger D, et al. The efficacy of a network intervention to reduce HIV risk behaviors among drug users and risk partners in Chiang Mai, Thailand and Philadelphia, USA. Soc Sci Med. 2009;68(4):740-748.

Brief Motivational Intervention Reduces HIV Risk and Increases HIV Testing among Offenders Under Community Supervision

Risky drug- and sex-related behaviors put criminal offenders at high risk for

HIV. Intervening with this population under supervision can potentially reduce risk. This study reports a randomized trial that examines the efficacy of brief negotiation interviewing (BNI) compared to usual education activities. BNI is a computerized, self-directed intervention that combines a short structured interview with a brief counseling session. The study examined whether BNI could decrease HIV risks and increase testing for HIV in a cohort of criminal-justice-involved clients. The trial randomly assigned 212 participants to experimental (108) and control (104) conditions. Interview data were collected at baseline and at 2-month follow-up. Results indicate that the BNI intervention group had a significantly higher rate of HIV testing and was more likely to consider behavioral changes. Alemagno S, Stephens R, Stephens P, Shaffer-King P, White P. Brief motivational intervention to reduce HIV risk and to increase HIV testing among offenders under community supervision. J Correct Health Care. 2009; 15(3):210-221.

Parenting Interventions for American Indian Communities: A Cultural Approach to Implementation

The current investigation puts forth the authors' conceptualization of a cultural approach to implementing evidence-based practices with American Indian (AI) families. Their approach involves two phases, the motivational phase, which sets an historical context for current difficulties; and the intervention phase, which links evidence-based skills with cultural traditions, beliefs, and values. This report presents preliminary evidence for the efficacy of the intervention phase, overlaid onto the Incredible Years parenting program (Webster-Stratton, 1992). Forty-nine families with American Indian children, ages 3-11 (26 boys), participated in the study; all families participated in the motivational phase and were subsequently randomized to the culturally linked intervention or to a control condition (delayed intervention condition). Significant pre- and post improvements in parenting and child behavior were observed in the intervention group as compared to those in the control group. Moreover, a majority of participants reported high levels of satisfaction with the intervention. Dionne R, Davis B. Initial evaluation of a cultural approach to implementation of evidence-based parenting interventions in American Indian communities. J Community Psychol. 2009;37(7):911-921.

Implementation of Evidence-Based Prevention under Real World Conditions Can Positively Impact Youth, Parent and Family Outcomes

It is becoming increasingly common for community teams or coalitions to implement programming for children and families designed to promote positive youth development and prevent adolescent problem behaviors. However, there has been only limited rigorous study of the effectiveness of community teams' programming efforts to produce positive outcomes. This study employed a community-level randomized control design to examine protective parent and youth skills outcomes of evidence-based preventive interventions selected from a menu and delivered by community teams supported by a community-university partnership model called PROSPER. Twenty-eight rural communities in two states were randomized across intervention and control conditions. Data were collected through written questionnaires that were completed by approximately 12,000 middle school students in the fall of the 6th grade, prior to intervention delivery, and again in the spring of the 7th, 8th, and 9th grades. Positive intervention effects were found for youth, parent, and family outcomes (e.g., association with antisocial peers, child management, parent-child affective quality) at each post-intervention assessment point. Improvements in these family and youth skill outcomes are expected to support long-term reductions of adolescent problem behaviors, such as substance abuse. This study supports the use of research-based models for diffusion of evidence-based prevention interventions, in this case a model for

delivery via community teams. Redmond C, Spoth R, Shin C, Schainker L, Greenberg M, Feinberg M. Long-term protective factor outcomes of evidence-based interventions implemented by community teams through a community-university partnership. J Prim Prev. 2009;30(5):513-530.

Implementing Evidence-Based Prevention in the US and Netherlands

This paper describes the degree to which implementation of the Communities That Care (CTC) prevention operating system, a theoretically based community-based strategic approach to reducing youth involvement in problem behaviors, was reached in 22 communities in 2 countries: the US (12 communities) and the Netherlands (10 communities). Core elements of CTC and results from two implementation measures conducted in both countries are reported here. The implementation process of CTC in the US and the Netherlands was compared. The US data came from a group-randomized trial of CTC, conducted in 24 small to medium communities in seven states, which began implementation in 2002. The Netherlands data came from 10 Dutch cities that implemented CTC between 2000 and 2006. Similarities and differences of the implementation process are discussed. Milestones (goals met by the communities) and benchmarks (actions by community members or conditions put in place to achieve the targeted goals) of the CTC implementation process were assessed along with interviews of coalition board members. Assessment of milestones and benchmarks suggested that the US achieved high implementation of CTC in the 24 communities. Implementation in the Netherlands was similar, but somewhat lower. Both countries were successful at recruiting and engaging key stakeholders and establishing community planning boards. Common challenges to implementation in both countries included the adoption and implementation of tested, effective programs--largely due to concern about uptake of new programs over familiar programs without evidence of effectiveness. Also, while both countries identified key stakeholders and board members, challenges were noted in both countries around these efforts and around specific roles and coordination of CTC planning with other community efforts, with lack of technology for facilitating this identified as a specific issue. Overall, both countries were successful in mobilizing stakeholders and using data to guide the selection and adoption of evidence-based prevention interventions. This cross-national comparison demonstrates potential for a system of implementation for science-based prevention programs. Jonkman HB, Haggerty KP, Steketee M, Fagan A, Hanson K, Hawkins JD. Communities That Care, core elements and context: Research of implementation in two countries. Soc. Dev. Issues. 2009;30(3):42-57.

The Role of Actor and Message Characteristics in Antismoking Public Service Announcements

This study examined whether the appeal of actors (i.e., their likeability and attractiveness) used in antismoking public service announcements (PSAs) interacts with adolescents' risk of future smoking to predict adolescents' smoking resistance self-efficacy and whether the antismoking messages in the PSAs further moderates this relationship. The study design involved a 2 (future smoking risk: low, high) x 2 (actor appeal: low, high) x 3 (PSA antismoking message: tobacco industry manipulation, short-term smoking effects, long-term smoking effects) analysis. A diverse sample of 110 adolescents (55% female, aged 11-17 years), with varying levels of experience with smoking, rated their smoking resistance self-efficacy after viewing each of the PSAs. A total of 22 (18%) of the sample reported smoking at least a puff of a cigarette in the past, but none of the participants were current smokers. Overall, PSAs that used long-term smoking effects messages were associated with the strongest smoking resistance self-efficacy, followed in turn by PSAs that used

short-term smoking effects messages and by tobacco industry manipulation messages. There was a significant interaction between actor appeal and PSA antismoking message. The use of more appealing actors was associated with stronger smoking resistance self-efficacy only in long-term smoking effects PSAs. The use of less appealing actors was associated with stronger smoking resistance self-efficacy for tobacco industry manipulation PSAs and short-term smoking affects PSAs. Future smoking risk did not moderate any of these findings. Antismoking PSAs that emphasize long-term smoking effects are most strongly associated with increased smoking resistance self-efficacy. The effect of these PSAs can be strengthened by using actors whom adolescents perceive to be appealing. Shadel W, Fryer C, Tharp-Taylor S. Uncovering the most effective active ingredients of antismoking public service announcements: The role of actor and message characteristics. Nicotine Tob Res. 2009;11(5):547-552.

International Spanish/English Smoking Cessation Trial Yields 20% Abstinence Rates at One Year

Traditional smoking cessation methods, such as nicotine replacement therapy and smoking cessation groups, yield between 14% and 27% abstinence rates at 6 months. Evidence-based Internet interventions with comparable abstinence rates could be a powerful global tool to reduce tobacco-related morbidity and mortality. This study reports on a randomized control trial in which 500 Spanish-speaking and 500 English-speaking adult Internet users, smoking at least 5 cigarettes a day and intending to quit in the next month, were recruited online from 68 countries. Consenting participants who completed baseline measures, logged cigarettes smoked on 3 days within a week, and set a quit date were randomized to four intervention conditions. Each condition added new elements: Condition 1 was the "Gu'a Para Dejar de Fumar," a static National Cancer Institute evidence-based stop smoking guide; Condition 2 consisted of Condition 1 plus E-mail reminders to return to the site; Condition 3 consisted of Condition 2 plus mood management lessons; and Condition 4 consisted of Condition 3 plus a "virtual group" (an asynchronous bulletin board). Main outcome measures were 7-day point prevalence abstinence at 1, 3, 6, and 12 months after initial quit date. There were no significant differences among the four conditions. The overall 12-month 7-day abstinence rates were 20.2% for Spanish speakers and 21.0% for English speakers when those with missing data were assumed to be smoking. Internet smoking cessation interventions with such abstinence rates that are provided globally could contribute substantially to tobacco control efforts. Mu–oz R, Barrera A, Delucchi K, Penilla C, Torres L, Pérez-Stable E. International Spanish/English internet smoking cessation trial yields 20% abstinence rates at 1 year. Nicotine Tob Res. 2009;11(9):1025-1034.

Mediation Effects for the Aban Aya Drug Abuse Prevention Program

This study illustrates a method to evaluate mediational mechanisms in a longitudinal prevention trial, the Aban Aya Youth Project (AAYP). In previous studies, interventions of AAYP were found to be effective in reducing the growth of violence, substance use and unsafe sex among African American adolescents. In this article, the authors hypothesize that the effects of the intervention in reducing the growth of substance use behavior were achieved through effects in changing intermediate processes such as behavioral intentions, attitudes toward the behavior, estimates of peers' behaviors, best friends' behaviors, and peer group pressure. In evaluating these mediational mechanisms, difficulties arose because the growth trajectories of the substance use outcome variable and some of the mediating variables were curvilinear. In addition, all of the multivariate mediational measures had planned missing data so that a score from the multiple items for a mediator could not be formed

easily. A latent growth modeling (LGM) approach was introduced to address these issues; namely, a two-domain LGM mediation model, in which the growth curves of the outcome and the mediator are simultaneously modeled and the mediation effects are evaluated. Results showed that the AAYP intervention effects on adolescent drug use were mediated by normative beliefs of prevalence estimates, friends' drug use behavior, perceived friends' encouragement to use, and attitudes toward the behavior. Liu L, Flay B. Evaluating mediation in longitudinal multivariate data: Mediation effects for the Aban Aya youth project drug prevention program. Prev Sci. 2009;10(3):197-207.

Drug Use Among Patrons of Electronic Music Dance Events

The prevalence of drug and alcohol use among patrons of clubs featuring electronic music dance events was determined by using biological assays at entrance and exit. Using a portal methodology that randomly selects groups of patrons on arrival at clubs, oral assays for determining level and type of drug use and level of alcohol use were obtained anonymously. Patrons provided self-reported data on their personal characteristics. A total of 362 patrons were interviewed at entrance and provided oral assay data, and 277 provided data at both entrance and exit. Overall, one quarter of all patrons surveyed at entrance were positive for some type of drug use. Based on the authors' exit sample, one quarter of the sample were positive at exit. Individual drugs most prevalent at entrance or exit included cocaine, marijuana, and amphetamines/stimulants. Only the amphetamine/stimulant category increased significantly from entrance to exit. Drug-using patrons arrive at the club already using drugs; few patrons arrive with no drug use and leave with detectable levels of drug use. Clubs vary widely in drug-user prevalence at entrance and exit, suggesting that both events and club policies and practices may attract different types of patrons. Approximately one half of the total entrance sample arrived with detectable alcohol use, and nearly one fifth arrived with an estimated blood alcohol concentration of .08 or greater. Based on our exit sample data, one third of patrons were intoxicated, and slightly less than one fifth were using both drugs and alcohol at exit. Clubs attract a wide array of emerging adults, with both genders and all ethnicities well represented. Clubs also attract emerging adults who are not in college and who are working full time. Thus, these clubs present a potentially important location for prevention strategies designed to reduce the risks associated with drug and alcohol use for young people. Miller B, Furr-Holden D, Johnson M, Holder H, Voas R, Keagy C. Biological markers of drug use in the club setting. J Stud Alcohol Drugs 2009;70(2):261-268.

Racial/Ethnic Differences in Parental Concern about Their Child's Drug Use in a Nationally Representative Sample in the United States

Parental concern and negative attitudes toward drug use may prevent youth from being involved in drug use. However, few studies have addressed parental concern about children's drug use and its possible variation by race/ethnicity. This study examined the potential racial/ethnic differences in parental concern about their children's drug use with a nationally representative sample. The data were from the 2003 National Survey of Children's Health, a random household telephone survey of parents of children up to age 17 (n = 102,353). The sample for this study was restricted to parents of children aged 6 to 17 years (n = 61,046). Multivariate logistic regression models were performed while controlling for children's age, gender, family structure, and family poverty level, and simultaneously accommodating the complex survey design. Parents of African American and Hispanic children expressed more concern about drug use than parents of white children, even after controlling for potential confounders (adjusted odds ratio (AOR), 1.9; 95% CI, 1.8-2.1 and AOR, 1.9;

95% CI, 1.7-2.1, respectively). The finding that level of parental concern about adolescent drug use was different across race/ethnicity groups may have implications for parental participation in school-based adolescent prevention programs. Zhu S, Wang Y, Browne DC, Wagner FA. Racial/ethnic differences in parental concern about their child's drug use in a nationally representative sample in the United States. J Natl Med Assoc. 2009;101(9):915-919.

Executive Functions in Children: Associations with Aggressive Behavior and Appraisal Processing

This study investigated whether and how deficits in executive functioning and distortions in appraisal processing are related to subtypes of aggressive behavior. The sample included 83 boys assessed using multi-informant reports and performance measures. Deficits in two executive functions, response inhibition and planning ability were related primarily to reactive aggression. Hostile attributional biases moderated relations between planning ability and proactive and reactive aggression subtypes, with minimal relations between planning deficits and aggression at low levels of hostile attributional bias. As the level of hostile attributional bias increased, the relation between planning deficits and reactive aggression became increasingly large in a positive direction whereas the relation between planning deficits and proactive aggression became increasingly negative. Additionally, hostile encoding moderated the relation between behavioral inhibition and reactive aggressive behavior. Results also suggested a mediational role for response inhibition in the relation between planning ability and reactive aggression. Ellis M, Weiss B, Lochman J. Executive functions in children: Associations with aggressive behavior and appraisal processing. J Abnorm Child Psychol. 2009;37(7):945-956.

Abuse and Distress among Sex Workers on the US-Mexico Border

This study examined histories of past emotional, physical, and sexual abuse as correlates of current psychological distress using data from 916 female sex workers (FSWs) who were enrolled in a safer-sex behavioral intervention in Tijuana and Ciudad (Cd.) Juarez, Mexico. It was hypothesized that histories of abuse would be associated with higher symptom levels of depression and somatization and that social support would moderate the relationship. Nonparametric correlations and a series of hierarchical regression analyses revealed that all forms of past abuse predicted higher levels of depressive symptoms, and physical and sexual abuse were significantly associated with higher levels of somatic symptoms. Social support was also significantly associated with fewer symptoms of distress; however, it was not shown to moderate the relationship between abuse history and distress. Ulibarri M, Semple S, Rao S, et al. History of abuse and psychological distress symptoms among female sex workers in two Mexico-U.S. border cities. Violence Vict. 2009; 24(3):399-413.

Links between Perceived Racism, Low Academic Control, and Depression among African American Youth

Experiences with racism are a common occurrence for African American youth and may result in negative self perceptions relevant for the experience of depressive symptoms. This study examined the longitudinal association between perceptions of racism and depressive symptoms, and whether perceived academic or social control mediated this association, in a community epidemiologically-defined sample of urban African American adolescents. Participants were 500 African American middle school students (46.4% female) who were initially assessed in the fall of first grade as part of an evaluation of two school-based preventive interventions whose immediate targets were early

learning and aggressive behavior in first grade. The original sample consisted of 678 children and families, representative of students entering first grade in nine Baltimore City public elementary schools, who were recruited for participation in the intervention trials. Structural equation modeling revealed that experiences with racism were associated with low perceived academic control, which in turn was associated with increased depressive symptoms. Findings suggest that experiences with racism can have long lasting effects for African American youth's depressive symptoms, and highlight the detrimental effects of experiences with racism for perceptions of control in the academic domain. Lambert S, Herman K, Bynum M, Ialongo N. Perceptions of racism and depressive symptoms in African American adolescents: The role of perceived academic and social control. J Youth Adolesc. 2009;38(4):519-531.

Adolescent Substance Use May Increase in Reaction to Exposure to Natural Disasters

Little systematic research attention has been devoted to the impact of natural disasters on adolescent substance use. The present study examined relationships among exposure to Hurricane Rita, post-traumatic stress (PTS) symptoms, and changes in adolescent substance use from 13 months pre-disaster to seven and 19 months post-disaster. Subjects were 280 high school students in southwestern Louisiana who participated in a drug abuse prevention intervention trial prior to the hurricane. Two-thirds of participants were female and 68% were white. Students completed surveys at baseline (13 months pre-hurricane) and two follow-ups (seven and 19 months post-hurricane). Results indicated objective exposure to the hurricane predicted increases in marijuana use, and post-hurricane negative life events predicted increases in alcohol, marijuana, and cigarette use (ps < .10). These findings suggest that increased substance use may be one of the behaviors that adolescents exhibit in reaction to exposure to hurricanes. Rohrbach L, Grana R, Vernberg E, Sussman S, Sun P. Impact of Hurricane Rita on adolescent substance use. Psychiatry. 2009;72(3):222-237.

Assessment of HIV Risks among Male Clients of Female Sex Workers on the US-Mexico Border

Research rarely has directly assessed male clients of female sex workers (FSW). A total of 400 men aged 18 years or older who had paid or traded for sex with a FSW in Tijuana during the past 4 months were recruited in Tijuana's "zone of tolerance," where prostitution is practiced openly under a municipal permit system. Efforts were made to balance the sample between residents of the United States (San Diego County) and of Mexico (Tijuana). Participants underwent interviews and testing for HIV, syphilis, gonorrhea, and Chlamydia. Logistic regression identified correlates of HIV infection. Mean age was 36.6 years. One-quarter had injected drugs within the previous 4 months. Lifetime use of heroin, cocaine, and methamphetamine was 36%, 50%, and 64%, respectively. Men had frequented FSWs for an average of 11 years, visiting FSWs an average of 26 times last year. In the past 4 months, one-half reported having unprotected sex with a FSW; 46% reported being high fairly or very often when having sex with a FSW. Prevalence of HIV, syphilis, gonorrhea, and Chlamydia was 4%, 2%, 2.5%, and 7.5%; 14.2% were positive for at least one infection. Factors independently associated with HIV infection were living in Mexico, ever using methamphetamine, living alone, and testing positive for syphilis. Male clients of FSWs in Tijuana had a high sex and drug risk profile. Although sexually transmitted infection prevalence was lower than among FSWs, HIV prevalence was comparable suggesting the need for interventions among clients to prevent spread of HIV and sexually transmitted infections. Patterson T, Goldenberg S, Gallardo M, et al. Correlates of HIV, sexually transmitted infections, and associated high-risk behaviors among male clients of female sex workers In Tijuana, Mexico. AIDS 2009;23(13):1765-

1771.

HIV Risk among IDU on the US-Mexico Border

Tijuana is situated on the Mexico-USA border adjacent to San Diego, CA, on a major drug trafficking route. Increased methamphetamine trafficking in recent years has created a local consumption market. Factors associated with methamphetamine use and routes of administration by gender among injection drug users (IDUs) were examined. From 2006-2007, IDUs > or =18 years old in Tijuana were recruited using respondent-driven sampling, interviewed, and tested for HIV, syphilis, and TB. Logistic regression was used to assess associations with methamphetamine use (past 6 months), stratified by gender. Among 1,056 participants, methamphetamine use was more commonly reported among females compared to males (80% vs. 68%, $p < 0.01$), particularly, methamphetamine smoking (57% vs. 34%; $p < 0.01$). Among females (N = 158), being aged >35 years (AOR, 0.2; 95% CI, 0.1-0.6) was associated with methamphetamine use. Among males (N = 898), being aged >35 years (AOR, 0.5; 95% CI, 0.3-0.6), homeless (AOR, 1.4 (0.9-2.2)), and ever reporting sex with another male (MSM; AOR, 1.9; 95% CI, 1.4-2.7) were associated with methamphetamine use. Among males, a history of MSM was associated with injection, while sex trade and >2 casual sex partners were associated with multiple routes of administration. HIV was higher among both males and females reporting injection as the only route of methamphetamine administration. Methamphetamine use is highly prevalent among IDUs in Tijuana, especially among females. Routes of administration differed by gender and subgroup which has important implications for tailoring harm reduction interventions and drug abuse treatment. Rusch M, Lozada R, Pollini R, Vera A, Patterson T, Case P, Strathdee S. Polydrug use among IDUs in Tijuana, Mexico: Correlates of methamphetamine use and route of administration by gender. J Urban Health 2009;86(5):760-775.

Drug Use and Associated Factors in the Mortality of HIV+ Women

Deaths were studied over a 10-year period among participants in the Women's Interagency HIV Study. Deaths were ascertained by National Death Index Plus match, and causes of death determined by death certificate. From 1995 through 2004, 710 of 2,792 HIV-infected participants died. During this interval, the standardized mortality ratio fell from a high of 24.7 in 1996 to a plateau with a mean of 10.3 from 2001 to 2004. Over the decade, deaths from non-AIDS causes increased and accounted for the majority of deaths by 2001-2004. The most common non-AIDS causes of death were trauma or overdose, liver disease, cardiovascular disease, and malignancy. Independent predictors of mortality besides HIV-associated variables were depressive symptoms and active Hepatitis B or C. Women who were overweight or obese were significantly less likely to die of AIDS than women of normal weight. French A, Gawel S, Hershow R, et al. Trends in mortality and causes of death among women with HIV in the United States: A 10-year study. J Acquir Immune Defic Syndr. 2009;51(4):399-406.

Isolated Antibody to Hepatitis B Core Antigen (Anti-HBc) among HIV+ and HIV- Women

Isolated antibody to hepatitis B core antigen (anti-HBc) is a common serologic finding in persons infected with human immunodeficiency virus (HIV), but the outcome and clinical significance are uncertain. Repeated hepatitis B virus (HBV) serologic tests were performed on women who participated in the Women's Interagency HIV Study and who had isolated anti-HBc at study entry. Tests were performed for 322 women (282 HIV-infected and 40 HIV-uninfected) at a median of 7.5 years after study entry, of whom 71% women

retained isolated anti-HBc serologic status, 20% acquired antibody to hepatitis B surface antigen (anti-HBs), and 2% acquired hepatitis B surface antigen (HBsAg). In unadjusted analysis, increasing age, injection drug use, and hepatitis C viremia were negatively associated with acquisition of anti-HBs. Among HIV-infected women, predictors of acquisition of anti-HBs were an increase in CD4 cell count and the use of highly active antiretroviral therapy (HAART). Receipt of drugs with activity against HBV and self-reported HBV vaccination did not predict anti-HBs acquisition. In the multivariable regression model, HAART use remained a significant predictor of anti-HBs acquisition, whereas women with hepatitis C viremia were more likely to retain isolated anti-HBc serologic status. Isolated anti-HBc status remained stable over time for the majority of women, especially women with chronic hepatitis C virus infection. Development of anti-HBs was predicted by HAART use and an increase in CD4 cell count. The authors conclude that a proportion of HIV-infected women with isolated anti-HBc have prior natural HBV infection with anti-HBs that is at an undetectable level because of immune dysfunction. Isolated anti-HBc in the presence of chronic hepatitis C virus infection may be attributable to a different phenomenon, such as dysfunctional antibody production. French A, Lin M, Evans C, et al. Long-term serologic follow-up of isolated Hepatitis B core antibody in HIV-infected and HIV-uninfected women. Clin Infect Dis. 2009;49(1):48-154.

Factors Associated with STI Incidence among Thai Methamphetamine Users

Methamphetamine users aged 18 to 25 years were enrolled in a 12-month randomized behavioral intervention trial in Chiang Mai, Thailand in 2005. Behavioral questionnaires were administered at visits every 3 months, and biologic specimens were collected at baseline and 12 months to test for common STIs (chlamydia, gonorrhea, HSV-2, and HIV). Poisson regression with robust variance was used to determine risk factors for incident STIs. Overall, 12.7% of 519 participants acquired at least 1 STI. Chlamydia was the most common (10.6%), followed by HSV-2 (4.0%), gonorrhea (2.9%), and HIV (0.6%). Risk factors for both men and women included self-reported incarceration, having a casual sex partner during follow-up, and having a prevalent STI at baseline. Additionally, among women, having 2 or more heterosexual partners, and among men, having a greater frequency of drunkenness were risk factors for STI acquisition. Although HIV incidence was low in this population, incidence of other STIs is high compared with previous studies of young Thai adults. Sutcliffe C, Aramrattana A, Sherman S, Sirirojn B, German D, Wongworapat K, Quan V, Keawvichit R, Celentano D. Incidence of HIV and sexually transmitted infections and risk factors for acquisition among young methamphetamine users in northern Thailand. Sex Transm Dis. 2009;36(5):284-289.

Correlates of Incarceration among Thai Methamphetamine Users

Correlates of incarceration among young methamphetamine users in Chiang Mai, Thailand were observed in cross-sectional data collected from 2005 to 2006 among 1189 young methamphetamine users, of whom 22% reported ever having been incarcerated. Participants were surveyed about their recent drug use, sexual behaviors, and incarceration. Biological samples were obtained to test for sexually transmitted and viral infections. In multivariate analysis, incarceration history was associated with frequent public drunkenness, starting to use illicit drugs at an early age, involvement in the drug economy, tattooing, injecting drugs, and unprotected sex. HIV, HCV, and herpes simplex virus type 2 (HSV-2) infections also were correlated with incarceration. Thomson N, Sutcliffe CG, Sirirojn B, Kaewvichit R, Wongworapat K, Sintupat K, Aramrattana A, Celentano DD. Correlates of incarceration among methamphetamine users in Chiang Mai, Thailand. Am J Public Health

2009;99(7);1232-1238.

Transactional Sex among Street Children in Pakistan

The study examined HIV risk behaviors and factors associated with exchanging sex among male street children in Lahore, Pakistan with a survey that was conducted from August 2003 to March 2004 among 565 registrants, ages 5-19, of Project Smile, a program that aimed to enhance the lives of street children in Lahore. Multivariate log-binomial regression was used to evaluate the independent effect of covariates on exchange of sex for money, goods, or drugs. Approximately 40% of participants reported having exchanged sex during the past 3 months. In multivariate analysis, the factors associated with exchanging sex were living on the street for longer than 48 months (Prevalence Ratio [PR]=1.36, 95% Confidence Interval [CI]: 0.99-1.85), reporting ever having used drugs (PR=1.87, 1.10-3.16), cutting ones self (PR=1.66, 95% CI: 1.26-2.19), and having heard of HIV/AIDS (PR=1.36, 95% CI: 1.03-1.80) after adjusting for demographic and street life variables. The finding that children who have heard about HIV/AIDS are more likely to exchange sex suggests that children at HIV risk talk about HIV, but accuracy of their conversations is unclear. Street children in Pakistan are in great need of HIV education and safe alternatives for generating income. Towe V, ul Hasan S, Zafar S, Sherman S. Street life and drug risk behaviors associated with exchanging sex among male street children in Lahore, Pakistan. J Adolesc Health 2009;44(3):222-228.

Risk Behavior in Sociocentric Network of Eastern European MSM

This study recruited four sociocentric networks (n = 156) of men who have sex with men in Budapest, Hungary, and St. Petersburg, Russia. The sampling approach was based on identifying an initial "seed" in the community for each network, and then recruiting three successive friendship group waves out from the seed. HIV prevalence in the networks was 9%, and the composite rate of other sexually transmitted diseases was 6%. Fifty-seven percent of participants reported both main and casual male partners, and 2/3 reported unprotected anal intercourse in the past 3 months. Fifty-five percent of men's most recent anal intercourse acts were with nonexclusive partners, and 56% of most recent anal intercourse acts were unprotected. Sexual risk was associated with more often talking with friends about AIDS, higher ecstasy use, and less often drinking. Amirkhanian Y, Kelly J, Takacs J, Kuznetsova A, DiFranceisco W, Mocsonaki L, McAuliffe T, Khoursine R, Toth T. HIV/STD prevalence, risk behavior, and substance use patterns and predictors in Russian and Hungarian sociocentric social networks of Men Who Have Sex With Men. AIDS Educ. Prev. 2009;21(3):266-279.

Sexual HIV Risk Behavior among IDU in Baltimore

This study compared male and female injection drug users (IDUs) on perceived risk of contracting HIV and examined the associations between risk perceptions and sharing injection drugs or equipment, engaging in casual sex, and engaging in commercial sex. Baseline data from 271 IDUs recruited between 2000 and 2005 from the Baltimore, Maryland site of the International Neurobehavioral HIV Study was analyzed. Although there was no significant difference in levels of perceived risk between males and females, males reported significantly more casual sex, whereas females reported more commercial sex. Logistic regression analyses with the entire sample indicated that sharing of injection drugs or equipment was consistently associated with greater perceived risk. There was also a significant interaction between gender and having had casual sex, such that females who had engaged in casual sex were significantly more likely to perceive that they were at greater risk for contracting HIV. Results suggest that male IDUs should be targeted for HIV

risk-reduction programs focusing on casual and commercial sex. Mitchell M, Latimer W. Gender differences in high risk sexual behaviors and injection practices associated with perceived HIV risk among injection drug users. AIDS Educ. Prev. 2009;21(4):384-394.

Characteristics of Hospitalized HIV+ Crack Users

A total of 1038 HIV+ inpatients were interviewed in public hospitals in Miami, Florida, and Atlanta, Georgia, to examine patient factors associated with use of HIV care, use of antiretroviral therapy, and unprotected sexual intercourse. Multivariate analyses and multiple logistic regression models showed that use of crack cocaine and heavy drinking were associated with never having had an HIV-care provider, high-risk sexual behavior, and not receiving antiretroviral therapy. Inpatient interventions that link and retain HIV-positive persons in primary care services could prevent HIV transmission and unnecessary hospitalizations. Metsch LR, Bell C, Cardenas G, et al. Hospitalized HIV-infected patients in the era of highly active antiretroviral therapy. Am J Public Health 2009;99(6):1045-1049.

Global Reach of an Internet Smoking Cessation Intervention among Spanish- and English-Speaking Smokers

This investigation is a secondary analysis of demographic, smoking, and depression information in a global sample of Spanish- and English-speaking smokers who participated in a series of randomized controlled smoking cessation trials conducted via the Internet. The final sample consisted of 17,579 smokers from 157 countries. Smoking profiles were similar across languages and world regions and consistent with characteristics of participants in traditional smoking cessation studies. Participants were predominantly Spanish-speakers, evenly divided between men and women and relatively few indicated using traditional smoking cessation methods (e.g., groups or medication). This study demonstrates that substantial numbers of smokers from numerous countries seek Web-based smoking cessation resources, and adds to the growing support for Web-assisted tobacco interventions as an additional tool to address the need for global smoking cessation efforts. Barrera A, Pérez-Stable E, Delucchi K, Mu–oz R. Global reach of an internet smoking cessation intervention among Spanish- and English-speaking smokers from 157 countries. Int J Environ Res Public Health 2009;6(3):927-940.

Higher Rates of Current Smoking in Indigenous and Mixed Ethnicity Youth in Jujuy, Argentina

Latin America is the world region with the highest rates of youth tobacco use and widest socioeconomic gaps, yet no data are available on smoking among Indigenous people, the largest disadvantaged group in the region. A self-administered survey of 3,131 8th grade youth enrolled in a random sample of 27 urban and rural schools was administered in 2004 in Jujuy, Argentina. Standard questions adapted from global surveys were used. Compared with youth of European background, Indigenous and Mixed ethnicity youth had higher prevalence of current smoking. The odds of current smoking remained significantly elevated for Indigenous (OR 1.9; 95% CI = 1.1 - 3.3) and Mixed youth (OR 2.0; 95% CI = 1.2 - 3.4) after controlling for confounders. Other risk factors that were associated with current smoking included: having any friends who smoke, repeating a grade in school, depressive symptoms in previous year, drinking any alcohol in the previous week and thrill seeking orientation. These results underscore the importance of social and cultural diversity aspects of the global tobacco epidemic. Alderete E, Kaplan C, Gregorich S, Mej'a R, Pérez-Stable E. Smoking behavior and ethnicity in Jujuy, Argentina: Evidence from a low-income youth sample. Subst Use Misuse

2009;44(5):632-646.

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

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

A Randomized Trial of Contingency Management for Adolescent Marijuana Abuse and Dependence

Dr. Stanger and colleagues from the University of Arkansas for Medical Sciences examined an initial efficacy test of an innovative behavioral outpatient treatment model for adolescents with problematic use of marijuana. Specifically, sixty-nine adolescents, aged 14-18, were enrolled and randomly assigned to one of two treatment conditions. Both conditions received individualized Motivational Enhancement and Cognitive Behavioral Therapy (MET/CBT) and a twice-weekly drug-testing program. The experimental contingency management condition involved a clinic-delivered, abstinence-based incentive program, and weekly behavioral parent training sessions that included a parent-delivered, abstinence-based, substance monitoring contract. The comparison condition included an attendance-based incentive program, and weekly psychoeducational parent sessions. Follow-up assessments were performed at 3, 6, and 9 months post-treatment. The experimental condition showed greater marijuana abstinence during treatment, e.g., 7.6 vs. 5.1 continuous weeks and 50% vs. 18% achieved > or = 10 weeks of abstinence. Improvements were found in parenting and youth psychopathology across treatment conditions, and improvements in negative parenting uniquely predicted post-treatment abstinence. The outcomes observed in the experimental condition are consistent with adult substance-dependence treatment literature, and suggest that integrating CM abstinence-based approaches with other empirically based outpatient interventions provides an alternative and efficacious treatment model for adolescent substance abuse/dependence. Replication and continued development of more potent interventions remain needed to further advance the development of effective substance abuse treatments for adolescents. Stanger C, Budney AJ, Kamon JL, Thostensen J. A randomized trial of contingency management for adolescent marijuana abuse and dependence. Drug Alcohol Depend. 2009 Dec 1;105(3):240-247.

Comparable Efficacy of Contingency Management for Cocaine Dependence among African American, Hispanic, and White Methadone Maintenance Clients

Cocaine use is a significant problem among methadone maintenance clients. Contingency management (CM) is a reinforcement-based approach with demonstrated efficacy for reducing cocaine use. This study examines whether the efficacy of CM treatment for cocaine-dependent individuals receiving methadone maintenance for opioid dependence differs by ethnicity. Participants were 191 African American, Hispanic, and White cocaine-dependent methadone

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maintenance clients, randomly assigned to standard methadone treatment or standard methadone treatment plus CM for 12 weeks. Hispanic participants were younger, less educated, and reported fewer years of cocaine use than did African American and White participants and reported fewer years of heroin use than did African American participants. African American participants were less likely to report a history of psychiatric symptoms or treatment in comparison with Hispanic and White participants. While CM was associated with longer duration of continuous cocaine abstinence and a greater proportion of submitted urine samples negative for cocaine, ethnicity was not related to treatment outcomes, and there was no significant interaction between treatment and ethnicity. CM appears to be an efficacious treatment for cocaine dependence among methadone maintenance clients, regardless of ethnicity. Barry D, Sullivan B, Petry NM. Comparable efficacy of contingency management for cocaine dependence among African American, Hispanic, and White methadone maintenance clients. Psychol Addict Behav. 2009 Mar;23(1):168-174.

Income Does Not Affect Response to Contingency Management Treatments among Community Substance Abuse Treatment-Seekers

The present study examined a commonly held belief that contingency management (CM) may be less effective for substance abusers with relatively more economic resources compared to those with relatively few resources. Using a combined sample of 393 treatment-seeking cocaine abusers from three clinical trials involving randomization to standard care or standard care plus CM conditions, this study assessed the impact of past year income, alone and in combination with treatment condition, as well as income type (i.e., earned, illegal, unstable) on the longest duration of continuous verified abstinence (LDA) achieved during treatment. Results suggested that income had no effect on LDA in either condition, and that CM's effectiveness did not deteriorate among those with better economic resources in the present sample. This finding may be of value to clinicians and administrators who are considering the addition of CM to standard care treatments in community outpatient substance abuse clinics and have concerns about the generalizability of CM across clients with various economic resources. Rash CJ, Olmstead TA, Petry NM. Income does not affect response to contingency management treatments among community substance abuse treatment-seekers. Drug Alcohol Depend. 2009 Oct 1;104(3):249-253.

Mindfulness Training May be Promising for Treating Stress in Drug Abusers

Stress has been shown to relate to relapse in drug abusers. This study was designed to address whether mindfulness training for drug abusers is feasible and whether it can impact stress related coping in drug abusers better than standard cognitive behavioral therapy (CBT). Thirty-six cocaine or alcohol dependent individuals were randomly assigned to receive CBT or mindfulness treatment. Drug use and treatment satisfaction did not differ between groups. However, a laboratory assessment showed reduced signs of physiological stress in the mindfulness condition. Although this was a small pilot study it suggests that mindfulness treatment meaningfully impacts stress and is feasible with this population. Brewer JA, Sinha R, Chen JA, et al. Mindfulness training and stress reactivity in substance abuse: Results from a randomized, controlled stage I pilot study. Subst Abuse 2009 Oct-Dec;30(4):306-317.

External Pressure Associated with Decreased Risk of Addiction Treatment Dropout for Pregnant Women

Although programs now offer treatment in lieu of incarceration, how much legal pressure to enter treatment actually influences pregnant drug abusers actual levels of drug use or facilitates treatment retention is not clear. Researchers examined a sample of 200 pregnant women entering community based addiction treatment to determine the role of external pressure on these outcomes. Analyses suggested baseline external pressure was related to decreased dropout risk as well as better odds of having a low number of positive urine tests during treatment and after 12 weeks. Research suggests that pressure not only increases engagement but also impacts treatment performance. Ondersma SJ, Winhusen T, Lewis DF. External pressure, motivation, and treatment outcome among pregnant substance-using women. Drug Alcohol Depend. 2009 Nov 16.

Pregnant Drug Dependent Women with Post-Traumatic Stress Experience More Severe Problems

Clinicians routinely report difficulty treating patients with comorbid substance use disorder (SUD) and posttraumatic stress disorder (PTSD), but it is not known whether these patients experience more severe problems than women with other comorbid problems and whether these problems relate to poor outcomes in this group. Researchers examined a group of pregnant opioid and/or cocaine dependent pregnant women experiencing SUD treatment and examined whether comorbidity impacted outcome and whether women with PTSD had other problems which might account for their difficulties. All three groups had similar levels of SUD severity. However, women with PTSD and SUD were more likely to report suicidality, aggression and impairment from psychosocial problems than women with other co-morbidities or SUD alone. These results suggest new treatments for comorbid SUD and PTSD are needed and that these should address a broader array of severe concerns than what is commonly addressed in treatments for SUD or SUD with other comorbidities. Eggleston AM, Calhoun PS, Svikis DS, Tuten M, Chisolm MS, Jones HE. Suicidality, aggression, and other treatment considerations among pregnant, substance-dependent women with posttraumatic stress disorder. Compr Psychiatry 2009 Sep-Oct;50(5):415-423.

Pain: A Factor in Many Methadone Patients

Chronic pain is highly prevalent in opioid dependent patients receiving methadone maintenance therapy with more than 60% reporting some chronic pain and approximately 37% reporting severe chronic pain. Despite methadone maintenance, this patient population is often difficult to treat and exhibits low rates of employment. Currently methadone treatment fails to address pain, and it is not known to what extent pain influences relapse during treatment. This is important because treatment of pain has been shown to improve treatment outcomes for other psychopathologies. Assessment of pain and co-morbid conditions was performed at three outpatient programs over the course of a year. Methadone-maintained patients with severe chronic pain (MM-SCP) showed similar levels of substance use to methadone-maintained patients without pain (MM) but also showed higher levels of depression, anxiety and other co-morbid psychopathology. Results suggest that monitoring and addressing clinical needs related to pain in this population may be worthwhile because of its association with psychopathology. New interventions that address pain may offer ways to improve outcomes further in this group. Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. J Clin Psychiatry 2009 Sep;70(9):1213-1218.

A Test of Motivational Plus Nicotine Replacement Interventions for HIV-Positive Smokers

This study was conducted to test the acceptability and feasibility and preliminary effectiveness of two delivery formats of combined motivational plus pharmacological interventions for smoking cessation targeting HIV positive smokers. Forty participants receiving care for HIV were randomly assigned to motivational interviewing plus nicotine patch or self-guided reading plus nicotine patch. Measures were administered at baseline, 1-month, and 3-month follow-ups. Results indicated that groups did not differ at 3-months on biochemically-verified abstinence. Both interventions led to significant reductions in number of cigarettes smoked per day and CO expiration at 3-month follow-up. Twenty-two percent of the participants were abstinent at the 3-month follow-up. Compliance with the patch was poor and declined over time. The authors conclude that smoking cessation interventions for people with HIV can be helpful and should include components that encourage some smoke-free days, increase self-efficacy, and attend to adherence to nicotine replacement treatment. Ingersoll KS, Cropsey KL, Heckman CJ. A test of motivational plus nicotine replacement interventions for HIV positive smokers. AIDS Behav. 2009 Jun;13(3):545-554.

Reasons for Quitting Smoking among Smokers with and without Psychopathology

Dr. Zvolensky and colleagues at the University of Vermont conducted the present investigation to examine intrinsic and extrinsic reasons for quitting among daily cigarette smokers with posttraumatic stress disorder (PTSD) as compared to clinical daily smokers with other anxiety and mood disorders (AM) and daily smokers with no current Axis I psychopathology (C) prior to a self-guided quit attempt. Participants were 143 daily cigarette smokers. It was expected that the PTSD group would report greater intrinsic reasons for quitting smoking and among those with PTSD, anxiety sensitivity would predict greater intrinsic reasons for quitting. Partially consistent with prediction, the PTSD group reported significantly greater self-control intrinsic reasons for quitting, but not health concern intrinsic reasons, than the C group. The PTSD group also reported greater immediate reinforcement extrinsic reasons for quitting than the C group. The PTSD and AM groups did not significantly differ on any reasons for quitting. Also partially consistent with hypotheses, higher levels of anxiety sensitivity in daily smokers with Axis I psychopathology (both PTSD and AM groups) significantly predicted greater self-control intrinsic reasons for quitting. The current findings suggest that individuals with PTSD and other psychopathology may have unique motivations for quitting smoking that could be usefully explored within smoking cessation treatment programs. Marshall EC, Vujanovic AA, Kutz A, Gibson L, Leyro T, Zvolensky MJ. Reasons for quitting smoking prior to a self-quit attempt among smokers with and without posttraumatic stress disorder or other anxiety/mood psychopathology. Am J Addict. 2009 Jul-Aug;18(4):309-315.

Patterns of Cortisol and Craving by Menstrual Phase in Women Attempting to Quit Smoking

This study's goal was to investigate how menstrual phase, stress and craving interact during ad libitum smoking and during cessation (time to relapse). Five assessments of cortisol concentrations and craving levels were collected the day before smoking cessation in female smokers (n=38) during either the follicular or luteal phase. Craving at wake-up was significantly greater in the F phase than the L phase. Decreased levels of morning cortisol concentrations and a greater decline from morning to the nadir levels in cortisol were associated with increased craving at bedtime in the L, but not in the F phase. Craving at wake-up was a significant predictor of time to relapse. The results indicate that menstrual phase may play a role in the relationship among craving, cortisol concentrations, and risk for relapse. Allen AM, Allen SS,

Widenmier J, Al'absi, M. Patterns of cortisol and craving by menstrual phase in women attempting to quit smoking. Addictive Behaviors, 2009 Aug;34(8):632-635.

Rationale, Design, and Sample Characteristics of a Randomized Controlled Trial of Directly Observed Antiretroviral

Therapy Delivered in Methadone Clinics Directly observed therapy (DOT) programs for HIV treatment have demonstrated feasibility, acceptability, and improved viral suppression, but few have been rigorously tested. In this article, the authors describe a randomized controlled trial testing the efficacy of an antiretroviral DOT program in methadone maintenance clinics. Their objective was to determine if DOT is more efficacious than self-administered antiretroviral therapy for reducing HIV viral load, improving adherence, and reducing drug resistance among opioid dependent drug users receiving methadone treatment. In this trial, participants were randomized to treatment as usual (TAU) or antiretroviral DOT for the 24-week intervention. TAU participants received standard adherence counseling, and DOT participants received standard adherence counseling plus directly observed antiretroviral therapy, which was delivered at the same time as they received daily methadone. Assessments occurred at baseline, weekly for 8 weeks, and then monthly for 4 months. The primary outcomes were between-group changes from baseline to the end of the intervention in: HIV viral load, antiretroviral adherence, and number of viral mutations. Between June 2004 and August 2007, the authors screened 3,231 methadone-maintained patients and enrolled 77; 39 participants were randomized to DOT and 38 to TAU. 65 completed the 24-week intervention. When completed, the trial will allow rigorous evaluation of the efficacy of directly observed antiretroviral therapy delivered in methadone clinics for improving adherence and clinical outcomes. This detailed description of trial methodology can serve as a template for the development of future DOT programs and can guide protocols for studies among HIV-infected drug users receiving methadone for opioid dependence. Berg KM, Mouriz J, Li X, Duggan E, Goldberg U, Arnsten JH. Rationale, design, and sample characteristics of a randomized controlled trial of directly observed antiretroviral therapy delivered in methadone clinics. Contemporary Clinical Trials 2009;30:481-489.

Contributors to Neuropsychological Impairment in HIV-Infected and HIV-Uninfected Opiate-Dependent Patients

Neuropsychological (NP) impairment is multiply determined among HIV-infected and HIV-uninfected individuals who are also dually diagnosed with depression and who use illicit substances. In the present study, the authors assess the impact of HIV status, depression, and problematic substance use on NP performance. A total of 160 opiate-dependent outpatients undergoing methadone maintenance (80 HIV-infected, 80 HIV uninfected) completed diagnostic and NP evaluations. Raw scores from individual NP tests were converted to Z scores relative to standard norms and were averaged to form a composite score. The results indicate that HIV infected participants had significantly lower overall NP performance than HIV-uninfected participants. In multiple regression analyses considering the role of depression and substance use, only HIV status emerged as a significant predictor of NP impairment. These findings confirm NP impairment in HIV-infected substance abusing patients independent of comorbid depression and severity of substance use. Applebaum AJ, Otto, MW, Richardson, MA, Safren, SA. Contributors to neuropsychological impairment in HIV-infected and HIV-uninfected opiate-dependent patients. J Clin Exp Neuropsychol. 2009 Nov 4;1-11.

A Placebo-Controlled Trial of Buspirone for the Treatment of

Marijuana Dependence

The present study investigated the potential efficacy of buspirone for treating marijuana dependence. Participants received either buspirone (maximum 60 mg/day) (n = 23) or matching placebo (n = 27) for 12 weeks, each in conjunction with motivational interviewing. In the modified intention-to-treat analysis, the percentage of negative results in the buspirone-treatment group was 18 percentage points higher than the placebo-treatment group (95% CI: -2% to 37%, p = 0.071). On self-report, participants receiving buspirone reported not using marijuana 45.2% of days and participants receiving placebo reported not using 51.4% of days (p = 0.55). An analysis of participants that completed the 12-week trial showed a significant difference in the percentage negative (95% CI: 7-63%, p = 0.014) and a trend for participants randomized to the buspirone-treatment group who completed treatment to achieve the first negative result sooner than those participants treated with placebo (p = 0.054). Further study with buspirone in this population may be warranted; however, strategies to enhance study retention and improve outcome measurement should be considered in future trials. McRae-Clarka AL, Carter RE, Killeen TK, et al. A placebo-controlled trial of buspirone for the treatment of marijuana dependence. Drug and Alcohol Dependence 2009;105:132-138.

Non-Treatment Laboratory Stress- and Cue-Reactivity Studies are Associated with Decreased Substance Use Among Drug-Dependent Individuals

Human laboratory paradigms for examining stress- or cue-reactivity in substance dependent individuals often involve exposure to pharmacological, psychosocial or physical laboratory procedures or drug paraphernalia. In this study, the authors examine whether participation in such studies alters drug-seeking behavior and which patient attributes contribute to increased use. In two separate studies, the relationship between participation and drug use post-study were examined. Cocaine-dependent participants received corticotropin releasing hormone intravenously, underwent the Trier Social Stress Task, and were exposed to drug cues and various measures obtained. Cocaine use for 90 days prior and 28 days following the study was assessed. Methamphetamine-dependent participants were exposed to drug cues and various measures obtained. Methamphetamine use for 90 days prior and 14 days following the study was assessed. Results indicate that participation decreased the odds of remaining in or transitioning to the high use state (cocaine study: OR= 0.04 [CI = 0.01, 0.11]; methamphetamine study: OR= 0.39 [CI = 0.07, 1.70]). In the cocaine study, older age increased the odds of remaining in or transitioning into the high use state (1.66 [CI = 0.99, 2.96]). In the methamphetamine study, male gender increased the odds (2.70 [CI = 1.10, 6.17]). These findings suggest that stress and cue exposure paradigms were associated with decreased odds of drug use following participation. DeSantisa SM, Bandyopadhyaya D, Back, SE, Brady KT. Non-treatment laboratory stress- and cue-reactivity studies are associated with decreased substance use among drug-dependent individuals. Drug and Alcohol Depend. 2009;105: 227-233.

Reactivity to Laboratory Stress Provocation Predicts Relapse to Cocaine

Cocaine dependence is a chronic relapsing disorder characterized by periods of abstinence and high rates of return to drug using behavior. Elevated levels of stress have been associated with relapse to cocaine; however, the nature of this association is not well understood. In this study, the relationship between reactivity to three human laboratory provocations and relapse to cocaine was investigated. Participants were 53 cocaine-dependent individuals who were admitted for a 2-day inpatient stay during which a psychosocial provocation

(i.e., the Trier Social Stress Task), a pharmacological provocation (i.e., administration of corticotrophin releasing hormone; CRH), and a drug cue exposure paradigm were completed. Adrenocorticotrophic hormone (ACTH), cortisol, heart rate, and subjective cocaine craving and stress were assessed at baseline and at multiple time points post-task. Participants' cocaine use was monitored for approximately 1 month following testing. The majority (72.3%) of participants relapsed to cocaine during the follow-up period. In response to the CRH and drug cue exposure, elevated subjective craving and stress were significant predictors of cocaine use during follow-up. In response to the Trier, attenuated neuroendocrine responses were significant predictors of cocaine use. The findings provide further evidence of the ability of laboratory paradigms to predict relapse. The observed associations between stress reactivity and subsequent cocaine use highlight the clinical importance of the findings. Predictors of relapse may vary based on the type of provocation utilized. Interventions aimed at normalizing stress response, as measured using laboratory paradigms, may prove useful in relapse prevention. Back SE, Hartwell K, DeSantisa SM, et al. Reactivity to laboratory stress provocation predicts relapse to cocaine. Drug and Alcohol Dependence 2009 Aug 31.

Buprenorphine Medication versus Voucher Contingencies in Promoting Abstinence from Opioids and Cocaine

Dr. Bickel and colleagues at the University of Arkansas for Medical Sciences examined two contingency-based interventions for their ability to improve treatment outcomes of buprenorphine-maintained opioid abusers (N = 120) over those abusers treated with standard care. Specifically, during a 12-week intervention, participants maintained on thrice-a-week (M, W, F) buprenorphine plus therapist and computer-based counseling were randomized to receive: (1) medication contingencies (MC = thrice weekly dosing schedule vs. daily attendance and single-day 50% dose reduction imposed upon submission of an opioid and/or cocaine positive urine sample); (2) voucher contingency (VC = escalating schedule for opioid and/or cocaine negative samples with reset for drug-positive samples); or (3) standard care (SC), with no programmed consequences for urinalysis results. The primary finding was that both voucher reinforcement and the medication-based intervention improved outcomes compared with standard-care, with effects primarily in opioid rather than cocaine test results. This study is the first to simultaneously compare buprenorphine medication and voucher-based contingencies with standard care using incentive magnitudes with previously demonstrated efficacy. Chopra MP, Landes RD, Gatchalian KM, et al. Buprenorphine medication versus voucher contingencies in promoting abstinence from opioids and cocaine. Exp Clin Psychopharmacol. 2009 Aug;17(4):226-236.

Impact of Bupropion and Cognitive-Behavioral Treatment for Depression on Positive Affect, Negative Affect, and Urges to Smoke during Cessation Treatment

Bupropion and cognitive-behavioral treatment (CBT) for depression have been used as components of treatments designed to alleviate affective disturbance during smoking cessation. Studies of treatment-related changes in pre-cessation affect or urges to smoke are needed to evaluate the proposed mechanisms of these treatments. Dr. Strong from the Warren Alpert Medical School of Brown University examined affective trajectories and urges to smoke prior to, on quit day, and after quitting in a sample of 524 smokers randomized to receive bupropion versus placebo and CBT versus standard smoking cessation CBT. Results suggested that Bupropion and/or CBT did not affect the observed decreases in positive affect and increases in negative affect prior to cessation. However, on quit day, observed levels of negative affect and urges to smoke were diminished significantly among individuals receiving bupropion. Decreases in positive affect prior to quitting, lower levels of positive affect, and

increased levels of negative affect and urges to smoke on quit day were each related to higher risk of smoking lapse. Depression proneness was an independent predictor of lower positive affect and higher negative affect but did not moderate the effects of bupropion on outcomes. In mediational analyses, the effect of bupropion was accounted for in part by lower negative affect and urges to smoke on quit day. These data support the efficacy of bupropion in reducing relapse risk associated with urges to smoke and negative affect and suggest the need to better understand the role of low positive affect as a risk factor for early lapse. Strong DR, Kahler CW, Leventhal AM, et al. Impact of bupropion and cognitive-behavioral treatment for depression on positive affect, negative affect, and urges to smoke during cessation treatment. Nicotine Tob Res. 2009 Oct;11(10):1142-1153.

Behavioral Family Counseling for Substance Abuse: A Treatment Development Pilot Study

Substance-dependent patients (N=29) living with a family member other than a spouse were randomly assigned to equally intensive treatments consisting of either (a) Behavioral Family Counseling (BFC) plus Individual-Based Treatment (IBT) or (b) IBT alone. Outcome data were collected at baseline, post-treatment, and at 3- and 6-month follow-up. BFC patients remained in treatment significantly longer than IBT patients. BFC patients improved significantly from baseline at all time periods on all outcomes studied, and had a medium effect size reflecting better primary outcomes of increased abstinence and reduced substance use than IBT patients. For secondary outcomes of reduced negative consequences and improved relationship adjustment, both BFC and IBT patients improved significantly and to an equivalent extent. The present results show BFC is a promising method for retaining patients in treatment, increasing abstinence, and reducing substance use. These results also provide support for larger scale, randomized trials examining the efficacy of behavioral family counseling for patients living with family members beyond spouses. O'Farrell TJ, Murphy M, Alter J, Fals-Stewart W. Behavioral family counseling for substance abuse: A treatment development pilot study. Addict Behav. 2010 Jan;35(1):1-6.

Contingency Management and Motivational Enhancement: A Randomized Clinical Trial for College Student Smokers

Gwaltney and colleagues proposed to test the efficacy of contingency-management (CM) and motivational enhancement therapy (MET) for college student smoking cessation. Non treatment-seeking daily smokers (N = 110) were randomly assigned to 3 weeks of CM versus noncontingent reinforcement (NR) and to three individual sessions of MET versus a relaxation control in a 2 x 2 experimental design. Expired carbon monoxide (CO) samples were collected twice daily for 3 weeks. Participants earned 5 US dollars for providing each sample; additionally, those randomized to CM earned escalating monetary rewards based on CO reductions (Week 1) and smoking abstinence (Weeks 2-3). They found that compared with NR, CM resulted in significantly lower CO levels and greater total and consecutive abstinence during the intervention. Those in the CM and MET groups reported greater interest in quitting smoking post-treatment, but rates of confirmed abstinence at follow-up were very low (4% at 6-month follow-up) and did not differ by group. Findings support the short-term efficacy of CM for reducing smoking among college students. Future research should explore enhancements to CM in this population, including a longer intervention period and the recruitment of smokers who are motivated to quit. Tevyaw TO, Colby SM, Tidey JW, et al. Contingency management and motivational enhancement: A randomized clinical trial for college student smokers. Nicotine Tob Res. 2009 Jun;11(6):739-749.

Screening Adolescents for Substance Use-Related High-Risk Sexual Behaviors

Dr. Levy and colleagues sought to determine whether adolescents who screened positive for high-risk substance use with the CRAFFT questions were also more likely to engage in risky sexual behaviors than their peers, and to determine the test-retest reliability of a substance use-related sexual risk behaviors inventory. In this study, clinic patients 12-18 years old completed a multi-part questionnaire that included eight demographic items, the CRAFFT substance use screen, and a 14-item scale assessing sexual behaviors associated with substance use. Participants were invited to return 1 week later to complete an identical assessment battery. Of the 305 study participants, 49 (16.1%) had a positive CRAFFT screen result (score of 2 or greater, indicating high risk for substance abuse/dependence) and 101 (33.9%) reported sexual contact during the past 90 days. After controlling for gender, age, race/ethnicity, and number of parents in household, adolescents with a positive CRAFFT screen had significantly greater odds of having sexual contact after using alcohol or other drugs, of having a sexual partner who used alcohol or other drugs, of having sex without a condom, and of having multiple sexual partners within the past year, compared to their CRAFFT negative peers. The substance use-related sexual risk behaviors inventory has acceptable test-retest reliability, and the 10 frequency questions have scale-like properties with acceptable internal consistency (standardized Cronbach's alpha=.79). The authors suggest that clinicians should pay special attention to counseling CRAFFT-positive adolescents regarding use of condoms and the risks associated with sexual activity with multiple partners, while intoxicated, or with an intoxicated partner. Levy S, Sherritt L, Gabrielli J, Shrier LA, Knight JR. Screening adolescents for substance use-related high-risk sexual behaviors. J Adolesc Health. 2009 Nov;45(5):473-477.

Delay Discounting as a Mediator of the Relationship between Perceived Stress and Cigarette Smoking Status in Adolescents

Little is known about possible behavioral mechanisms by which stress exerts its influence on the decision to smoke. This study by Reynolds and colleagues sought to examine one such behavioral characteristic, delay discounting, that may mediate the relationship between stress and cigarette smoking. Delay discounting generally refers to the discounting of value for outcomes because they are delayed; and high rates of delay discounting have been linked to impulsive behavior. For the current research, adolescent smokers (n = 50) and nonsmokers (n = 50) were compared using a self-report measure of perceived stress and a laboratory assessment of delay discounting. Smokers tended to report higher levels of stress and to discount more by delay, and there was a significant association between reported stress and delay discounting. In addition, delay discounting mediated the relationship between stress and cigarette smoking status. These results suggest that discounting by delay may be a behavior through which stress exerts influence on an adolescent's decision to smoke. Fields S, Leraas K, Collins C, Reynolds B. Delay discounting as a mediator of the relationship between perceived stress and cigarette smoking status in adolescents. Behav Pharmacol. 2009 Sep;20(5-6):455-460.

Feasibility of an Exercise Counseling Intervention for Depressed Women Smokers

In a pilot study, Patten and colleaguesinvestigated the feasibility of an exercise intervention to boost mood and promote smoking abstinence in depressed female smokers Participants (M = 41 years, 98% White) were randomized to 10 weeks of individually delivered exercise counseling (n = 30) or a health education contact control condition (n = 30). All participants received nicotine

patch therapy and behavioral counseling for smoking cessation. The authors found that the intervention was feasible as indicated by ability to recruit participants, exercise counseling session attendance (M = 7.6 of 10 sessions attended), and significant increase in exercise frequency and stage of change from baseline to end of treatment (EOT) (Week 10). Participant attrition rate was 35% by Week 10 but did not differ significantly between groups. Smoking abstinence rates at Week 10, using intention-to-treat analysis, were not significant: 17% for exercise counseling participants and 23% for health education participants. They conclude that an exercise counseling intervention was found to be feasible for depressed women smokers. More intensive intervention may be needed to increase smoking abstinence rates, and methods should be refined to reduce participant burden and attrition. Vickers KS, Patten CA, Lewis BA, et al. Feasibility of an exercise counseling intervention for depressed women smokers. Nicotine Tob Res. 2009 Aug;11(8):985-995.

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

Research Findings - Research on Pharmacotherapies for Drug Abuse

Lasting Reduction of Cocaine Action in Neostriatum - A Hydrolase Gene Therapy Approach

The authors previously found that a quadruple mutant cocaine hydrolase derived from human butyrylcholinesterase [termed cocaine esterase (CocE)] can suppress or reverse cocaine toxicity and abolish drug-primed reinstatement in rats. Here, the authors examined whether gene transfer of CocE reduces cocaine actions in brain reward centers. Early experiments used a standard, early region 1-deleted adenoviral vector, which, after intravenous delivery of 1010 plaque-forming units, caused plasma cocaine hydrolase activity to rise 25,000-fold between day 4 and day 7. During this period, under a protocol that typically induces FosB expression in the caudate nucleus, these rats and unprotected controls given only empty vector or saline were subjected to repeated twice-daily injections of cocaine (30 mg/kg i.p.). Immunohistochemistry of the neostriatum on day 7 showed many FosB-reactive nuclei in unprotected rats but few if any in rats pretreated with active vector, which resembled rats never exposed to cocaine. Western blots confirmed this result. In contrast there was a more localized protection against cocaine-elicited FosB induction when hydrolase vector was injected directly into the ventral striatum, which generated high transgene expression in many neurons of the target area. Similar results were obtained with systemic and local injection of a more efficient helper-dependent adenoviral vector, which transduced high levels of hydrolase for at least 2 months, with lesser expression continued up to 1 year. Behavioral tests are now warranted to determine whether such effects can reduce drug-seeking behavior and lower the probability of relapse. Gao Y, Brimijoin S J. Pharmacol Exp Ther. 2009 Aug 330:449-457.

Cocaine Esterase Prevents Cocaine-Induced Toxicity and the Ongoing Intravenous Self-Administration of Cocaine in Rats

Cocaine esterase (CocE), a naturally occurring bacterial enzyme, is a very efficient protein catalyst for the hydrolysis of cocaine, and has previously been shown to protect rodents from the lethal effects of cocaine. The current studies were aimed at evaluating the capacity of a longer acting mutant form (CocE T172R/G173Q; DM CocE) of CocE to protect against the lethal effects of cocaine, and alter ongoing intravenous cocaine self-administration in rats. A dose-response analysis revealed a dose-dependent suppression of cocaine-reinforced responding with 1.0 mg of CocE T172R/G173Q producing saline-like rates of responding. The effects of 1.0 mg of CocE T172R/G173Q on cocaine-reinforced responding were then compared with responding when saline was available for injection, whereas the selectivity of CocE T172R/G173Q's effects

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was assessed by evaluating the effects of 1.0 mg of CocE T172R/G173Q on (-)-2β-carbomethoxy-3β-phenyltropane (WIN-35065-2)- and food-reinforced responding. Although 1.0 mg of CocE T172R/G173Q suppressed responding maintained by 0.1 mg/kg/injection cocaine, a significant increase in responding was observed when responding was maintained by 1.0 mg/kg/injection cocaine, resulting in a 10-fold rightward shift in the dose-response curve for cocaine self-administration at a dose that did not significantly alter responding maintained by either WIN-35065-2 or food. These findings demonstrate that a long-acting form of CocE is effective at abruptly reducing the ongoing self-administration of low doses of cocaine, and provides a robust antagonism of cocaine's reinforcing effects. Furthermore, these studies provide strong evidence for the potential usefulness of a suitable, stable, and long-acting form of CocE as a pharmacotherapy for cocaine abuse in humans. Collins GT, Brim RL, Narasimhan D, Ko MC, Sunahara RK, Zhan CG, Woods JH. J Pharmacol Exp Ther. 2009 Nov 331(2):445-455.

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

Enhancing cocaine metabolism by administration of cocaine esterase (CocE) has been recognized as a promising treatment strategy for cocaine overdose and addiction, because CocE is the most efficient native enzyme for metabolizing the naturally occurring cocaine yet identified. A major obstacle to the clinical application of CocE is the thermoinstability of native CocE with a half-life of only a few minutes at physiological temperature (37¡C). Here the investigators report thermostable variants of CocE developed through rational design using a novel computational approach followed by in vitro and in vivo studies. This integrated computational-experimental effort has yielded a CocE variant with a 30-fold increase in plasma half-life both in vitro and in vivo. The novel design strategy can be used to develop thermostable mutants of any protein. Gao D, Narasimhan DL, Macdonald J, et al. Mol Pharmacol. 2009 Feb 75(2):318-323.

Cocaine Vaccine (TA-CD) for the Treatment of Cocaine Dependence in Methadone-Maintained Patients

The purpose of this phase 2b, randomized, double-blind, placebo-controlled, 24-week clinical trial in 115 cocaine- and opioid-dependent persons was to evaluate the immunogenicity, safety, and efficacy of a novel cocaine vaccine to treat cocaine dependence. The study did not achieve a significant difference in complete abstinence with immunization; however, there was a significant reduction in cocaine use in patients who attained high IgG levels. Twenty-one vaccinated subjects (38%) who attained serum IgG anticocaine antibody levels of 43 µg/ml or higher had significantly more cocaine-free urines than those with levels less than 43 µg/ml and the placebo-receiving subjects during weeks 9 to 16 (45% vs. 35% cocaine-free urine samples, respectively). The proportion of subjects having a 50% reduction in cocaine use was significantly greater in the subjects with a high IgG level than in subjects with a low IgG level (53% of subjects vs. 23% of subjects, respectively). There were no treatment-related serious adverse events. The reported conclusion is that attaining high (³ 43 µg/ml) IgG anticocaine antibody levels was associated with significantly reduced cocaine use, but only 38% of the vaccinated subjects attained those IgG levels and they had only 2 months of adequate cocaine blockade. Martell BA, Orson FM, Poling J, Mitchell E, Rossen RD, Gardner T, Kosten T. Arch Gen Psychiatry. 2009 66(10):1116-1123.

Cocaine-Specific Antibodies Blunt the Subjective Effects of Smoked Cocaine in Humans

Clinical data demonstrate that a cocaine vaccine (TA-CD) produces selective anticocaine antibodies, yet the impact of these antibodies on cocaine's direct effects is unknown. The objective of this human laboratory study was to measure the relationship between antibody titers and the effects of smoked cocaine on ratings of intoxication, craving, and cardiovascular effects. Ten cocaine-dependent men not seeking drug treatment spent 2 nights per week for 13 weeks inpatient where the effects of cocaine (0 mg, 25 mg, 50 mg) were determined before vaccination and at weekly intervals thereafter. Two doses of TA-CD (82 µg, n = 4; 360 µg, n = 6) were administered at weeks 1, 3, 5, and 9. The results showed that peak plasma antibody levels, which were highly variable, significantly predicted cocaine's effects. Those individuals in the upper half of antibody production had an immediate (within 4 minutes of cocaine smoking) and robust (55%-81%) reduction in ratings of good drug effect and cocaine quality, while those in the lower half showed only a nonsignificant attenuation (6%-26%). Self-reported cocaine use while participants were outpatient tended to decrease as a function of antibody titer ($p < .12$). By contrast, higher antibody levels predicted significantly greater cocaine-induced tachycardia. The investigators concluded that TA-CD vaccine substantially decreased smoked cocaine's intoxicating effects in those generating sufficient antibody. These data support further testing of cocaine immunotherapy as a treatment for cocaine dependence. Haney M, Gunderson EW, Jiang H, Collins ED, Foltin RW. Biol Psychiatry. 2010 Jan 1;67(1):59-65.

Cocaine Abuse Reduces White Matter Volume and Myelination Levels, Which Were Correlated With Diminished Motor and Executive Function

Recent studies demonstrated that diffusion tensor imaging (DTI) can provide information regarding white matter integrity of the corpus callosum (CC). In this study, DTI parameters were compared between cocaine dependent subjects (CDs) and non-drug using controls (NCs) in midsagittal CC. DTI images were acquired from19 CDs and 18 age-matched NCs. The midsagittal CC was segmented into: genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium. Linear mixed models analyses showed that, relative to NCs, CDs had lower fractional anisotropy (FA), higher radial diffusivity ($\lambda\perp$), and higher mean diffusivity (Dav) in the isthmus; higher $\lambda\perp$ and Dav in the rostral body; and lower FA in the splenium. After including mass of lifetime alcohol use in the mixed model analysis of covariance (ANCOVA) as a covariate, significant between group differences in $\lambda\perp$ in the rostral body and isthmus remained. These results suggest that alterations in $\lambda\perp$ in the rostral body and isthmus were mainly due to cocaine use, consistent with previous studies showing that cocaine may alter myelin integrity. Between group differences in FA in the isthmus and splenium, and Dav in the rostral body and isthmus became non-significant after inclusion of alcohol use as a covariate. This is suggestive of alcohol influencing these values, or may be related to the decreased degrees of freedom for these effects. Consistent with clinical data of greater severity of drug use in smoked versus intranasal cocaine, subjects who smoked cocaine showed lower FA and higher $\lambda\perp$ compared to intranasal CDs. Diffusion tensor imaging in cocaine dependence: regional effects of cocaine on corpus callosum and effect of cocaine administration route. Ma L, Hasan KM, Steinberg JL, et al. Drug Alcohol Depend. 2009 Oct 104(3): 262-267.

Diminished Brain Activity in Motor, Reward, and Cognitive Brain Regions of Cocaine-Dependent Subjects Versus Controls

Functional magnetic resonance imaging (fMRI) studies of early abstinence cocaine users offer information about the state of the brain when most cocaine users seek treatment. This study examined the relationship between pretreatment brain function and subsequent treatment response in 19 treatment-seeking early abstinence cocaine dependent (CD) subjects. These

subjects and 14 non-drug using control subjects underwent fMRI while performing a working memory task with three levels of difficulty. CD subjects were then randomized to treatment studies. Results showed CD subjects had significantly lower (random effects, corrected for multiple 28 comparisons) brain activation in caudate, putamen, cingulate gyrus, middle and superior frontal gyri, inferior frontal gyrus pars triangularis and pars opercularis, precentral gyrus, and thalamus compared to non-drug using controls. Within CD subjects, thalamic activation significantly correlated with treatment response. This study shows CD subjects in early abstinence have alteration of brain function in frontal, striatal, and thalamic brain regions known to be part of a circuit associated with motor control, reward, and cognition. Subjects with pretreatment thalamic deactivation showed the poorest treatment response, possibly related to thalamic involvement in mesocortical and mesolimbic dopamine projections. Moeller FG, Steinberg JL, Schmitz JM, Ma L, Liu S, Kjome KL, Rathnayaka N, Kramer LA, Narayana PA. Psych Res: Neuroimaging.2010 Jan;175(1).

Influence of Verbal Recall of a Recent Stress Experience on Anxiety and Desire for Cocaine In Non-Treatment Seeking, Cocaine-Addicted Volunteers

It has long been postulated that stress increases the risk of drug abuse and relapse. The principal goal of this project was to evaluate the effects of verbal recall of a recent stress experience (specifically meaningful to each individual) on physiological and subjective measures in cocaine-addicted participants. Subjects described a recent stressful non-drug-related experience and a neutral non-stressful experience, and then completed mood and drug effect questionnaires, while heart rate and blood pressure were recorded. Participants (N = 25) were predominantly African American and male. As a group, participants used cocaine for more than 15 years and approximately 18 of the last 30 days, and a majority reported use of nicotine and/or alcohol. All participants were evaluated during a time in which they tested positive for cocaine metabolite. On a scale of 1-10, participants reported their verbal recall of a recent stress event as highly stressful and their verbal recall of a recent neutral event as non-stressful. The self-reported vividness of this recall was high (>8 out of 10) for both the stress and neutral events. Heart rate and systolic and diastolic blood pressure did not differ after verbal recall of either stress or neutral events. Similarly, self-reported subjective effects (including ratings of anxiety and craving for cocaine) did not differ after verbal recall of either stress or neutral events. In summary, despite the fact that participants recounted highly stressful and vivid memories, this experience did not elicit significant changes in cardiovascular or subjective effects. These data suggest that simply recalling a stressful event may not be a sufficient enough stimulus to contribute to craving or relapse in cocaine-addicted individuals. De La Garza R, Ashbrook LH, Evans SE, Jacobsen CA, Kalechstein AD, Newton TF. Am J Addict. 2009 Nov-Dec 18(6):481-487.

Mesocorticolimbic Activation of Cholinergic Receptors Appears Useful for the Treatment of Stimulant Addiction

Acetylcholine, the first neurotransmitter discovered, participates in many CNS functions, including sensory and motor processing, sleep, nociception, mood, stress response, attention, arousal, memory, motivation and reward. These diverse cholinergic effects are mediated by nicotinic- and muscarinic-type cholinergic receptors (nAChR and mAChR, respectively). The goal of this review is to synthesize a growing literature that supports the potential role of acetylcholine as a treatment target for stimulant addiction. Acetylcholine interacts with the dopaminergic reward system in the ventral tegmental area, nucleus accumbens and prefrontal cortex. In the ventral tegmental area, both nAChR and mAChR stimulate the dopaminergic system. In the nucleus

accumbens, cholinergic interneurons integrate cortical and subcortical information related to reward. In the prefrontal cortex, the cholinergic system contributes to the cognitive aspects of addiction. Preclinical studies support a facilitative role of nicotinic receptor agonists in the development of stimulant addiction. In contrast, nonselective muscarinic receptor agonists seem to have an inhibitory role. In human studies, acetylcholinesterase inhibitors, which increase synaptic acetylcholine levels, have shown promise for the treatment of stimulant addiction. Further studies testing the efficacy of cholinergic medications for stimulant addiction are warranted. Sofuoglu M, Mooney M. CNS Drugs. 2009 Nov 23(11):939-952.

Atomoxetine Attenuates Dextroamphetamine Effects in Humans

The objectives of this study were to examine the effects of atomoxetine, a norepinephrine transporter inhibitor, on subjective, physiological, and plasma cortisol responses to dextroamphetamine in 10 healthy volunteers. Subjects were randomly assigned to a sequence of atomoxetine (40 mg/day) or placebo treatments, each lasting for 4 days. On day 4, responses to a single 20 mg/70 kg dose of dextroamphetamine were assessed. Atomoxetine treatment attenuated dextroamphetamine-induced increases in systolic and diastolic blood pressure and plasma cortisol as well as the self-report ratings of Ôstimulated', 'high', and Ôgood drug effects'. These findings are consistent with previous preclinical studies supporting the role of the noradrenergic system in mediating acute amphetamine responses, and support the potential use of atomoxetine as a treatment for stimulant addiction. Sofuoglu M, Poling J, Hill K, Kosten T. Am J Drug and Alcohol Abuse. 2009 35:412-416.

How Long Does Craving Predict Use of Methamphetamine?

This study lays the foundation for a clinical prediction model based on methamphetamine craving intensity and its ability to predict the presence or absence of within-treatment methamphetamine use. The study used a random effects logistic approach for estimating repeated-measures, generalized linear mixed models (GLMM) using craving as the sole predictor of methamphetamine. The study investigated whether methamphetamine craving predicted subsequent use more accurately at intervals more proximal to versus those more distal to assessment, examining one-week periods ending one to seven weeks after assessment of craving. Analyses were based on data from 691 methamphetamine dependent outpatients enrolled in the MTP. Craving was assessed by self-report on a 0-100 scale. Self-reported methamphetamine use was toxicologically verified. Craving and drug use were assessed weekly for 8 weeks. Findings showed that in the univariate analysis craving predicted methamphetamine use in the week immediately following the craving report, with subject-specific use increasing 0.38% for each 1-point increase in craving on a 0-100 scale. In the multivariate analysis the probability of use decreased significantly by 2.45% for each week in treatment and increased significantly by 33.11% for previous methamphetamine use, the probability of methamphetamine use still increased significantly, rising 0.28% for each one-point increase in craving score. Predictive accuracy was strongest at the one-week time-lag and declined in magnitude the more distal the assessment period. The authors conclude that craving is a predictor of within-treatment methamphetamine use. Intensity of craving is appropriate for use as a surrogate marker in methamphetamine dependence. Galloway GP, Singleton EG. Subst Abuse 2009 Aug 26;1:63-79.

The Effects of Inhaled L-Methamphetamine on Athletic Performance While Riding a Stationary Bike: A Randomized Placebo-Controlled Trial

L-methamphetamine is banned in athletic competition because it may improve athletic performance, but there are no studies assessing its effects on performance. In the United States L-methamphetamine is formulated in the non-prescription Vick's Vapor Inhaler (VVI) nasal decongestant. VVIs sold elsewhere contain similar inactive ingredients but no L-methamphetamine. This study tested the effects of inhaled L-methamphetamine delivered from a widely available non-prescription product on athletic performance. In a 2-session double-blind placebo-controlled study 12 participants (ages 14-17) were dosed with 4 (session 1) and 12 (session 2) inhalations from VVIs with (USA) or without (UK) L-methamphetamine and then performed two 20 minute rides on a stationary bike with rides separated by a 30 minute rest. The main outcome measure was miles travelled during each 20 minute ride. Secondary outcome measures included postride urine toxicology; heart rate and blood pressure before, 1, 5 and 10 minutes postride; energy, performance, endurance, and ability to breathe; and VVI preference. Data were analysed using Excel statistical macros. After approximately 16 microg L-methamphetamine distance travelled was 5.26 vs. 5.30 miles with placebo. After approximately 48 microg L-methamphetamine distance travelled was 5.30 vs. 5.35 miles with placebo. The approximately 16 microg dose increased systolic blood pressure from 72.6 to 79.6 mm Hg at 5 minutes postride but there were no other differences in outcome. The authors conclude that modest doses of inhaled L-methamphetamine probably do not improve athletic performance but do minimally raise diastolic blood pressure. Dufka F, Galloway G, Baggott M, Mendelson J. Br J Sports Med. 2009 Nov 43(11):832-835.

Evaluation of Modafinil Effects on Cardiovascular, Subjective, and Reinforcing Effects of Methamphetamine In Methamphetamine-Dependent Volunteers

Methamphetamine is a highly addictive stimulant and long-term exposure leads to reductions in dopamine. One therapeutic strategy is to develop and test compounds that normalize dopamine. The primary aim of this study was to determine the safety of modafinil treatment during methamphetamine exposure in a controlled clinical setting. Methamphetamine-dependent volunteers (N=13), who were not seeking treatment, were randomized to receive either modafinil (200mg, PO) or matching placebo over three days (Days 1-3 or Days 8-10). On Day 1, subjects were randomized to modafinil or placebo in the morning, and then 3 and 6h later received infusions of methamphetamine (0 and 30mg, i.v.), after which cardiovascular and subjective effects were assessed. On Day 3, participants completed i.v. self-administration sessions during which they made 10 choices for low doses of methamphetamine (3mg, i.v.) or saline. Days 4-7 were used as a washout period. On Day 8 participants were assigned to the alternate study medication (placebo or modafinil), and the same testing procedures were repeated through Day 10. The data reveal that modafinil treatment was well-tolerated and not associated with increased incidence of adverse events. In general, modafinil reduced, by approximately 25%, ratings of methamphetamine-induced "Any Drug Effect", "High", and "Want Methamphetamine", and reduced total number of choices for methamphetamine and monetary value of methamphetamine, though none of these measures reached statistical significance. Given these encouraging, though non-significant trends, the primary conclusion is that it appears safe to proceed with modafinil in further clinical evaluations of therapeutic efficacy. De La Garza R, Zorick T, London ED, Newton TF. Drug Alcohol Depend. 2009 E-pub Sep 23.

Depression, More Than Marijuana Use Per Se, Leads Abusers To Seek Treatment

A post hoc analysis examined depressive symptoms in regular marijuana smokers interested in non-treatment, laboratory studies, and marijuana-

dependent treatment-seekers considering clinical trial participation. Among marijuana-dependent treatment-seeking patients screened for a clinical trial, the mean Beck Depression Inventory Score (BDI) was significantly higher than for marijuana-using volunteers screened for non-treatment laboratory studies. Mean self-reported baseline marijuana use was not significantly different between groups, and BDI score was not correlated with use. Although the methods by which the two groups were selected influenced their characteristics (i.e., treatment-seekers are more likely to be experiencing some degree of clinical distress), it is notable that treatment-seeking, and not marijuana use per se, is associated with significantly higher rates of depression. Mariani JJ, Haney M, Hart CL, Vosburg SK, Levin FR. J Subst Abuse Treat. 2009;37(4): 431-434.

Buspirone-Treated Subjects Tended To Have Fewer Positive Marijuana Urine Drug Screens Than Controls

The present study investigated the potential efficacy of buspirone for treating marijuana dependence. Participants received either buspirone (maximum 60mg/day) (n=23) or matching placebo (n=27) for 12 weeks, each in conjunction with motivational interviewing. In the modified intention-to-treat analysis, the percentage of negative UDS results in the buspirone-treatment group was 18 percentage points higher than the placebo-treatment group (95% CI: -2% to 37%, p=0.071). On self-report, participants receiving buspirone reported not using marijuana 45.2% of days and participants receiving placebo reported not using 51.4% of days (p=0.55). An analysis of participants that completed the 12-week trial showed a significant difference in the percentage negative UDS (95% CI: 7-63%, p=0.014) and a trend for participants randomized to the buspirone-treatment group who completed treatment to achieve the first negative UDS result sooner than those participants treated with placebo (p=0.054). Further study with buspirone in this population may be warranted; however, strategies to enhance study retention and improve outcome measurement should be considered in future trials. McRae-Clark AL, Carter RE, Killeen TK, Carpenter MJ, Wahlquist AE, Simpson SA, Brady KT. Drug Alcohol Depend. 2009 Nov 105(1-2): 132-138.

Medications, Particularly In Combination With Evidence-Based Psychosocial Treatments, Are Needed To Achieve Sustained Abstinence From Marijuana

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

Varenicline Attenuates Some of the Subjective and Physiological Responses To Nicotine In Smokers

Varenicline, a partial nicotinic acetylcholine receptor (nAChR) agonist, is approved for smoking cessation. A few preclinical studies examined the pharmacological effects of varenicline, alone or in combination with nicotine. How varenicline affects the pharmacological effects of pure nicotine has not been examined in humans. The goal of this study was to characterize varenicline's actions on nicotine's dose-dependent effects in abstinent smokers. Six male and six female smokers participated in a double-blind, placebo-controlled, crossover study. Smokers had two 4-day treatment periods, assigned in random sequence, to varenicline (1 mg/day) or placebo treatment. On day 4 of each treatment phase, smokers had an experimental session, where they received three escalating doses of intravenous (IV) nicotine (0.1, 0.4, and 0.7 mg/70 kg), in 30-min intervals. Varenicline's effects were assessed through subjective, physiological, and cognitive performance outcomes to nicotine administered via IV route. In response to IV nicotine, varenicline treatment attenuated the rating of drug strength, high, head rush, and stimulated. Varenicline also attenuated nicotine-induced increases in heart rate. Varenicline had mixed effects on cognitive performance. Smokers under varenicline treatment, compared with placebo, reported enhanced positive mood measured with the Positive and Negative Affect Schedule. These findings provide new insights into the mechanisms of action of varenicline in smoking cessation. Sofuoglu M, Herman AI, Mooney M, Waters AJ. Psychopharmacology. 2009 Nov 207(1):153-162.

Along With Individual Measures, A Better Understanding of Impulsivity and Compulsion Are Critical For Improved Addiction Treatment

Addictions are among the most costly disorders, estimated at over $500 billion annually. The multidimensional construct of impulsivity has received increased attention recently as a potential endophenotype for addictions. As questions relating to how best to define and categorize addictions are being discussed in anticipation of DSM-V, a growing role for empirical, neurobiological understandings of addictions exists. Given that this process involves gathering, analyzing, and synthesizing data from multiple lines of investigation, the importance of translational, interdisciplinary research has never been greater. Here, the investigators highlight how the manuscripts in this issue inform a translational neurobiological understanding of impulsivity in addiction and identify existing challenges that await future investigation. Potenza MN, Taylor JR. Found in translation: Understanding impulsivity and related constructs through integrative preclinical and clinical research. Biol Psychiatry. 2009 Oct 66(8): 714-716.

Oral Progesterone Enhanced the Negative Effects of Nicotine and Diminished the Urge to Smoke Cigarettes In Smokers

Previous studies suggest possible modulatory effects of progesterone on nicotine addiction. The goal of this study was to determine the effects of progesterone, on acute physiological and subjective responses to intravenous (IV) nicotine in overnight abstinent male and female smokers. Twelve smokers, six males and six females, participated in a double-blind, placebo-controlled, crossover study, which consisted of two experimental sessions. Before each session, subjects were treated orally with a single dose of either 200 mg progesterone or placebo. Starting 2 h following the medication treatment, subjects received an IV saline injection, followed by 0.5 and 1.0 mg/70 kg IV nicotine. Progesterone treatment, compared to placebo, enhanced the ratings

of "bad effects," from IV nicotine and attenuated the rating of "drug liking." Progesterone also enhanced suppression of smoking urges by nicotine as assessed by the Brief Questionnaire on Smoking Urges (BQSU). These results suggest that progesterone may alter the subjective effects of nicotine as well as urges to smoke cigarettes. Further studies are warranted to examine the modulation of nicotine's effects by gonadal hormones. Sofuoglu M, Mitchell E, Mooney M. Progesterone effects on subjective and physiological responses to intravenous nicotine in male and female smokers. Hum Psychopharmacol. 2009 Oct 24(7): 559-564.

Treatment of Depression With Bupropion and CBT Reduces the Relapse Risk To Smoking

Bupropion and cognitive-behavioral treatment (CBT) for depression have been used as components of treatments designed to alleviate affective disturbance during smoking cessation. Studies of treatment-related changes in pre-cessation affect or urges to smoke are needed to evaluate the proposed mechanisms of these treatments. The present report examines affective trajectories and urges to smoke prior to, on quit day, and after quitting in a sample of 524 smokers randomized to receive bupropion versus placebo and CBT versus standard smoking cessation CBT. Bupropion and/or CBT did not affect the observed decreases in positive affect and increases in negative affect prior to cessation. However, on quit day, observed levels of negative affect and urges to smoke were diminished significantly among individuals receiving bupropion. Decreases in positive affect prior to quitting, lower levels of positive affect, and increased levels of negative affect and urges to smoke on quit day were each related to higher risk of smoking lapse. Depression proneness was an independent predictor of lower positive affect and higher negative affect but did not moderate the effects of bupropion on outcomes. In mediational analyses, the effect of bupropion was accounted for in part by lower negative affect and urges to smoke on quit day. Results support the efficacy of bupropion in reducing relapse risk associated with urges to smoke and negative affect and suggest the need to better understand the role of low positive affect as a risk factor for early lapse. Strong DR, Kahler CW, Leventhal AM, et al. Nicotine Tob Res. 2009 Oct 11(10):1142-1153.

Relationship Between Cigarette Use and Mood/Anxiety Disorders Among Pregnant Methadone-Maintained Patients

This study investigates the association between cigarette use and current mood/anxiety disorders among pregnant opioid-dependent patients. Pregnant methadone-maintained women (N = 122) completed the Addiction Severity Index and Structured Clinical Interview for DSM-IV. Participants were categorized based on past 30 days cigarette use: no (n = 15) and any smoking (n = 107); this latter group was then subdivided into light (one to ten cigarettes/day; n = 55), and heavy smokers (11+ cigarettes/day; n = 52). Any smoking was significantly associated with any current mood/anxiety disorder, any current mood disorder, and any current anxiety disorder. No significant association was found between specific level of cigarette use and mood/anxiety disorders. This association between smoking and psychiatric disorders has implications for the mental and physical health of methadone-maintained women and their children, and may contribute to the understanding of the physiological mechanisms underlying smoking and nicotine dependence. Chisolm MS, Tuten M, Brigham EC, Strain EC, Jones HE. Am J Addict. 2009 Sep-Oct 18(5):422-429.

Suicidality, Aggression, and Other Treatment Considerations Among Pregnant, Substance-Dependent Women With Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) and other Axis I comorbidity among women with substance use disorders (SUDs) appear similarly prevalent and are associated with comparable negative clinical profiles and treatment outcomes. The relative contribution of comorbid PTSD vs other Axis I psychiatric disorders to clinical characteristics is largely unexamined, however, despite theory and empirical data indicating that PTSD and SUDs may have a unique relationship that confers specific risk for clinical severity and poor treatment outcome. In a sample of pregnant, opioid- and/or cocaine-dependent women entering substance abuse treatment, women with PTSD (SUD-PTSD; n = 23) were compared to those with other Axis I comorbidity (SUD-PSY; n = 45) and those without Axis I comorbidity (SUD-only; n = 37). Data were collected via face-to-face interviews and urinalysis drug assays. Although the study groups had similar substance use severity, the SUD-PTSD group was more likely to report suicidality, aggression, and psychosocial impairment than both the SUD-PSY and SUD-only groups. Findings indicate treatment considerations for substance-dependent women with PTSD are broader and more severe than those with other Axis I conditions or substance dependence alone. Eggleston AM, Calhoun PS, Svikis DS, Tuten M, Chisolm MS, Jones HE. Compr Psychiatry. 2009 Sep-Oct 50(5):415-423.

PTSD Contributes To Teen and Young Adult Cannabis Use Disorders

Previous studies involving adults suggest that Post Traumatic Stress Disorder (PTSD) increases the prevalence of cannabis use disorders (CUD) (cannabis dependence and cannabis abuse). However, little work with PTSD and CUD has been conducted involving adolescents, despite the fact that CUD typically have their onset during adolescence. This study addresses the effect of PTSD on CUD among teenagers transitioning to young adulthood. The subjects in this study were the offspring of adult men with a lifetime history of a substance use disorder (SUD) (SUD+probands, N=343) vs those with no lifetime history of a SUD (SUD-probands, N=350). The participants were initially recruited when the index sons of these fathers were 10-12 years of age, and subsequent assessments were conducted at age 12-14, 16, 19, 22, and 25. Other variables examined were an index of behavioral undercontrol associated with future risk for developing SUD, known as the Transmissible Liability Index, or TLI, and affiliation with deviant peers. Multivariate logistic regression and path analyses were conducted. Of these 693 subjects, 31 subjects were diagnosed with PTSD, and 161 were diagnosed with a CUD. The CUD subjects included 136 male participants and 25 female participants, including 103 (64%) Caucasian participants and 58 (36%) participants of other races. Logistic regression demonstrated that the development of a CUD was associated with deviance of peers (Wald=63.4, p=0.000), the TLI (Wald=28.8, p=0.000), African American race (Wald=14.2, p=0.000), PTSD (Wald=12.7, p=0.000), male gender (Wald=12.0, p=0.001), household SES (Wald=9.2, p=0.002), and being an offspring of a SUD+proband (Wald=6.9, p=0.009). Path analyses demonstrated that PTSD is directly associated with the presence of a CUD and with peer deviance, that higher peer deviance is associated with the presence of a CUD, and that PTSD mediated the association between peer deviance and CUD. These findings suggest that PTSD contributes to the etiology of CUD among teenagers making the transition to young adulthood beyond the effects of deviant peers, the TLI (Transmissible Liability Index, a measure of risk for SUD), and demographic factors. Cornelius JR, Kirisci L, Reynolds M, Clark DB, Hayes J, Tarter R. Addict Behav. 2010 Feb;35(2):91-94. Epub 2009 Sep 11.

Smoking Expectancies and Intention To Quit In Smokers With Schizophrenia, Schizoaffective Disorder and Non-Psychiatric Controls

Cigarette smoking expectancies are systematically related to intention to quit smoking in adult smokers without psychiatric illness, but little is known about these relationships in smokers with serious mental illness. In this study, the investigators compared positive and negative smoking expectancies, and examined relationships between expectancies and intention to quit smoking, in smokers with schizophrenia (n=46), smokers with schizoaffective disorder (n=35), and smokers without psychiatric illness (n=71). In all three groups, reduction of negative affect was rated as the most important smoking expectancy and intention to quit smoking was systematically related to concerns about the health effects and social consequences of smoking. Compared to the other groups of smokers, those with schizoaffective disorder were more concerned with social expectancies and with the immediate negative physical effects of smoking. Results of this study suggest that challenging positive smoking expectancies and providing more tailored information about the negative consequences of smoking might increase motivation to quit smoking in smokers with schizophrenia and schizoaffective disorder, as has been found with non-psychiatric smokers. Tidey JW, Rohsenow DJ. Schizophr Res. 2009 Dec;115(2-3):310-316.

Predicting Adherence To Treatment For Methamphetamine Dependence From Neuropsychological and Drug Use Variables

Although some individuals who abuse methamphetamine have considerable cognitive deficits, no prior studies have examined whether neurocognitive functioning is associated with outcome of treatment for methamphetamine dependence. In an outpatient clinical trial of bupropion combined with cognitive behavioral therapy and contingency management (Shoptaw, S., Heinzerling, K.G., Rotheram-Fuller, E., Steward, T., Wang, J., Swanson, A.N., De La Garza, R., Newton, T., Ling, W., 2008. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. Drug Alcohol Depend 96, 222-232.), 60 methamphetamine-dependent adults completed three tests of reaction time and working memory at baseline. Other variables that were collected at baseline included measures of drug use, mood/psychiatric functioning, employment, social context, legal status, and medical status. The investigators evaluated the relative predictive value of all baseline measures for treatment outcome using Classification and Regression Trees (CART; Breiman, L., Friedman, J.H., Olshen, R.A., Stone, C.J., 1984.

Classification and Regression Trees

Wadsworth, Belmont, CA.), a nonparametric statistical technique that produces easily interpretable decision rules for classifying subjects that are particularly useful in clinical settings. Outcome measures were whether or not a participant completed the trial and whether or not most urine tests showed abstinence from methamphetamine abuse. Urine-verified methamphetamine abuse at the beginning of the study was the strongest predictor of treatment outcome; two psychosocial measures (e.g., nicotine dependence and Global Assessment of Functioning) also offered some predictive value. A few reaction time and working memory variables were related to treatment outcome, but these cognitive measures did not significantly aid prediction after adjusting for methamphetamine usage at the beginning of the study. On the basis of these findings, the investigators recommend that research groups seeking to identify new predictors of treatment outcome compare the predictors to methamphetamine usage variables to assure that unique predictive power is attained. Dean AC, London ED, Sugar CA, Kitchen CM, et al. Drug Alcohol Depend. 2009 Nov 1;105(1-2):48-55.

Concurrent Validation of the Clinical Opiate Withdrawal Scale (COWS) and Single-Item Indices Against the Clinical Institute

Narcotic Assessment (CINA) Opioid Withdrawal Instrument

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item clinician-administered scale assessing opioid withdrawal. Though commonly used in clinical practice, it has not been systematically validated. The present study validated the COWS in comparison to the validated Clinical Institute Narcotic Assessment (CINA) scale. Opioid-dependent volunteers were enrolled in a residential trial and stabilized on morphine 30 mg given subcutaneously four times daily. Subjects then underwent double-blind, randomized challenges of intramuscularly administered placebo and naloxone (0.4 mg) on separate days, during which the COWS, CINA, and visual analog scale (VAS) assessments were concurrently obtained. Subjects completing both challenges were included (N=46). Correlations between mean peak COWS and CINA scores as well as self-report VAS questions were calculated. Mean peak COWS and CINA scores of 7.6 and 24.4, respectively, occurred on average 30 min post-injection of naloxone. Mean COWS and CINA scores 30 min after placebo injection were 1.3 and 18.9, respectively. The Pearson's correlation coefficient for peak COWS and CINA scores during the naloxone challenge session was 0.85 ($p<0.001$). Peak COWS scores also correlated well with peak VAS self-report scores of bad drug effect ($r=0.57$, $p<0.001$) and feeling sick ($r=0.57$, $p<0.001$), providing additional evidence of concurrent validity. Placebo was not associated with any significant elevation of COWS, CINA, or VAS scores, indicating discriminant validity. Cronbach's alpha for the COWS was 0.78, indicating good internal consistency (reliability). COWS, CINA, and certain VAS items are all valid measurement tools for acute opiate withdrawal. Tompkins DA, Bigelow GE, Harrison JA, et al. Drug Alcohol Depend. 2009 Nov 1;105(1-2):154-159.

The Cardiovascular and Subjective Effects of Methamphetamine Combined With Gamma-Vinyl-Gamma-Aminobutyric Acid (GVG) In Non-Treatment Seeking Methamphetamine-Dependent Volunteers

Gamma-vinyl-gamma-aminobutyric acid (GVG) elevates central nervous system gamma-aminobutyric acid (GABA) levels by irreversibly inhibiting GABA transaminase. An open-label clinical trial in humans suggested that GVG may reduce cocaine and methamphetamine use. To test safety and to obtain preliminary data on efficacy of GVG for treating methamphetamine dependence, the investigators conducted a double-blind, placebo-controlled, parallel group study of GVG interaction with the cardiovascular and subjective effects produced by methamphetamine. Non-treatment seeking methamphetamine-dependent volunteers received either GVG (N=8) or placebo (N=9) by random assignment. GVG treatment was initiated at 1 g/day and increased to 5 g/day. After reaching the target dose of 5 g/day, participants received methamphetamine (15+30 mg, IV), and cardiovascular and subjective effects were assessed. No serious adverse events were noted, and the total number of adverse events was similar between the treatment groups. Considering the full time course and peak effects independently, no significant differences were detected between the groups for systolic or diastolic blood pressures, or heart rate, following methamphetamine exposure. Some methamphetamine-induced cardiovascular changes approached significance ($p<0.10$) and may warrant attention in future trials. Methamphetamine-induced subjective effects ("any drug effect", "high", "crave methamphetamine") were statistically similar between GVG and placebo treatment groups. Pharmacokinetic data indicate that GVG treatment did not alter methamphetamine or amphetamine plasma levels, and there was no association between methamphetamine or amphetamine plasma levels and peak cardiovascular effects. Taken together, the data indicate that GVG treatment is generally well tolerated but not efficacious in attenuating the positive subjective effects of methamphetamine in the laboratory. De La Garza R 2nd, Zorick T, Heinzerling KG, et al. Pharmacol Biochem Behav. 2009 Nov;94(1):186-193.

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

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

Pharmacokinetic Interactions Between Buprenorphine/Naloxone and Tipranavir/Ritonavir In HIV-Negative Subjects Chronically Receiving Buprenorphine/Naloxone

HIV-infected patients with opioid dependence often require opioid replacement therapy. Pharmacokinetic interactions between HIV therapy and opioid dependence treatment medications can occur. HIV-seronegative subjects stabilized on at least 3 weeks of buprenorphine/naloxone (BUP/NLX) therapy sequentially underwent baseline and steady-state pharmacokinetic evaluation of open-label, twice daily tipranavir 500 mg co-administered with ritonavir 200 mg (TPV/r). Twelve subjects were enrolled and 10 completed the study. Prior to starting TPV/r, the geometric mean BUP AUC(0-24h) and C(max) were 43.9 ng h/mL and 5.61 ng/mL, respectively. After achieving steady-state with TPV/r (> or = 7 days), these values were similar at 43.7 ng h/mL and 4.84 ng/mL, respectively. Similar analyses for norBUP, the primary metabolite of BUP, demonstrated a reduction in geometric mean for AUC(0-24h) [68.7-14.7 ng h/mL; ratio=0.21 (90% CI 0.19-0.25)] and C(max) [4.75-0.94 ng/mL; ratio=0.20 (90% CI 0.17-0.23)]. The last measurable NLX concentration (C(last)) in the concentration-time profile, never measured in previous BUP/NLX interaction studies with antiretroviral medications, was decreased by 20%. Despite these pharmacokinetic effects on BUP metabolites and NLX, no clinical opioid withdrawal symptoms were noted. TPV steady-state AUC(0-12h) and C(max) decreased 19% and 25%, respectively, and C(min) was relatively unchanged when compared to historical control subjects receiving TPV/r alone. No dosage modification of BUP/NLX is required when co-administered with TPV/r. Though mechanistically unclear, it is likely that decreased plasma RTV levels while on BUP/NLX contributed substantially to the decrease in TPV levels. BUP/NLX and TPV/r should therefore be used cautiously to avoid decreased efficacy of TPV in patients taking these agents concomitantly. Bruce RD, Altice FL, Moody DE, et al. Drug Alcohol Depend. 2009 Dec 1;105(3):234-9. Epub 2009 Sep 1.

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

Drug use and HIV/AIDS are global public health issues. The World Health Organization (WHO) estimates that up to 30% of HIV infections are related to drug use and associated behaviors. The intersection of the twin epidemics of HIV and drug/alcohol use, results in difficult medical management issues for the health care providers and researchers who work in the expanding global HIV prevention and treatment fields. Access to care and treatment, medication adherence to multiple therapeutic regimens, and concomitant drug -drug

Planned Meetings

Publications

Staff Highlights

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interactions of prescribed treatments are difficult barriers for drug users to overcome without directed interventions. Injection drug users are frequently disenfranchised from medical care and suffer sigma and discrimination creating additional barriers to care and treatment for their drug abuse and dependence as well as HIV infection. In an increasing number of studies, medication assisted treatment of drug abuse and dependence has been shown to be an important HIV prevention intervention. Controlling the global transmission of HIV will require further investment in evidence-based interventions and programs to enhance access to care and treatment of individuals who abuse illicit drugs and alcohol. In this review, the investigators present the cumulative evidence of the importance of medication assisted treatment in the prevention, care, and treatment of HIV infected individuals who also abuse drugs and alcohol. Kresina TF, Bruce RD, McCance-Katz EF. Curr HIV Res. 2009 Jul 7(4):354-364.

Long-Term Combination Antiretroviral Therapy Is Associated With the Risk of Coronary Plaques In African Americans With HIV Infection

The aim of the study was to assess whether long-term antiretroviral therapy (ART) is associated with the risk of coronary plaques in HIV-infected cardiovascularly asymptomatic African Americans. Between August 2003 and December 2007, 176 HIV-infected cardiovascularly asymptomatic African Americans were consecutively enrolled in an observational study investigating the effects of ART on subclinical atherosclerosis in Baltimore, Maryland. Computed tomography coronary angiography was performed to detect coronary plaques. The overall prevalence rate of coronary plaques was 30%. After adjusting for gender, total cholesterol, and cocaine use, logistic regression analysis revealed that exposure to ART for more than 18 months (adjusted odds ratio [OR]: 2.20, 95% confidence interval [CI]: 1.01, 4.79) was independently associated with the presence of coronary plaques. A higher HIV viral load was univariately associated with the presence of noncalcified plaques. Use of ART (>18 months) was independently associated with the presence of noncalcified plaques (adjusted OR: 7.61, 95% CI: 1.67, 34.7), whereas cocaine use (>15 years) was independently associated with the presence of calcified plaques (adjusted OR: 2.51, 95% CI: 1.11, 5.67). This study suggests that long-term exposure to ART may be associated with coronary plaques. Because long-term use of ART and HIV replication may be associated with the presence of noncalcified plaques, some of which may be more vulnerable to rupture, an intensive lifestyle intervention to reduce traditional risk factors for coronary artery disease (CAD) is ultimately vital to those who are on ART. This study also suggests that cocaine cessation is the single most effective strategy to prevent CAD in HIV-infected cocaine users. Lai S, Bartlett J, Lai H, Moore R, Cofrancesco J Jr, Pannu H, Tong W, Meng W, Sun H, Fishman EK. AIDS Patient Care STDS. 2009 Oct 23(10):815-824.

HIV Infection and Abnormal Regional Ventricular Function

The goal of this study was to examine the effect of HIV infection on regional left ventricular dysfunction in cardiovascularly asymptomatic individuals. Nineteen HIV-negative and 27 HIV-positive cardiovascularly asymptomatic study participants in Baltimore, Maryland were selected and underwent tagged cardiac magnetic resonance imaging. Regional left ventricular myocardial mid-wall peak systolic circumferential strain (Ecc) and early diastolic strain rate (SRE) of the left ventricle were assessed with the use of the harmonic phase analysis. The average Ecc and SRE measurements were compared between HIV-negative and HIV-positive individuals. Compared with the HIV-negatives, the HIV-positives had lower average Ecc and SRE measurements in 90% of the 16 standard left ventricular segments. Of the 14 segments with decreased Ecc strain, 3 were statistically significant and of 14 with decreased strain rate

(SRE), 6 were statistically significant. HIV infection may be associated with subclinical regional left ventricular systolic and diastolic dysfunction in individuals free of overt cardiovascular disease. Lai H, Redheuil A, Tong W, Bluemke DA, Lima JA, Ren S, Lai S. Int J Cardiovasc Imaging. 2009 Sep 11. [Epub ahead of print]

Differential Regulation of Indoleamine-2,3-Dioxygenase (IDO) By HIV Type 1 Clade B and C at Protein

Previous studies have demonstrated that infection with HIV-1 clades might differentially contribute to the neuropathogenesis of HIV-1-associated dementia (HAD). HIV-1 transactivator regulatory protein (Tat) plays a major role in the process of disruption of neuronal function. It is not well understood how these HIV-1 subtypes exert different neuropathogenic effects. Activation of indoleamine-2,3-dioxygenase (IDO), the rate-limiting enzyme of the kynurenine pathway, leads to increased tryptophan catabolism and the generation of neurotoxins such as kynurenine (KYN). It is known that KYN plays a crucial role in the neuropathogenesis of HAD. It was hypothesized that HIV-1 clade B and C Tat proteins might exert differential effects on human primary astrocytes by the upregulation of the IDO gene and protein expression as well as its activity and production of the neurotoxin KYN. RNA extracted from human primary astrocytes treated with either HIV-1 clade B and C Tat proteins was reverse transcribed and analyzed by quantitative real-time PCR to determine IDO gene expression. In addition, the enzymatic activity of IDO and the concentration of KYN were measured in cell lysates and culture supernatants. These results indicate that HIV-1 clade B Tat protein significantly upregulated the IDO gene and protein expression, IDO enzyme activity, as well as KYN concentration compared to HIV-1 clade C Tat protein. Thus, these studies for the first time demonstrate that HIV-1 clade B Tat protein in human primary astrocytes appears to increase the level of neuropathogenic agents, such as IDO and KYN, as compared to HIV-1 clade C Tat protein. These results provide further evidence that the prevalence of HAD may be correlated with the difference in clades of HIV-1. Samikkannu T, Saiyed ZM, Rao KV, Babu DK, Rodriguez JW, Papuashvili MN, Nair MP. AIDS Res Hum Retroviruses. 2009 Mar 25(3):329-335.

Differential Effects of HIV Type 1 Clade B and Clade C Tat Protein on Expression of Proinflammatory and Antiinflammatory Cytokines By Primary Monocytes

The existence of multiple subtypes of HIV-1 worldwide has created new challenges to control HIV-1 infection and associated neuropathogenesis. Previous studies indicate a difference in neuropathogenic manifestations of HIV-1-associated neuroAIDS between clade B- and clade C-infected subjects with clade B being more neuropathogenic than clade C. However, the exact mechanism underlying the differences in the neuropathogenesis by both the subtypes remains elusive. Development of neuroAIDS is associated with a complex interplay between proinflammatory and antiinflammatory cytokines and chemokines. In the current study, the investigators hypothesize that HIV-1 clade B and C Tat protein exert differential effects on human primary monocytes leading to differences in gene and protein expression of cytokines implicated in neuroAIDS. Primary human monocytes were treated with clade B and clade C Tat protein and quantitative real time PCR was performed to determine gene expression of proinflammatory cytokines (IL-6 and TNF-alpha) and antiinflammatory cytokines (IL-4 and IL-10). Further, cytokine secretion was measured in culture supernatants by ELISA, whereas intracellular cytokine expression was detected by flow cytometry. Results indicate that monocytes treated with Tat B showed significant upregulation of proinflammatory cytokines, IL-6 and TNF-alpha, as compared to Tat C-treated cultures. However, expression of antiinflammatory molecules and IL-4 and IL-10 was

found to be higher in Tat C-treated compared to Tat B-treated cultures. Thus, this result shows for the first time that Tat B and Tat C differentially modulate expression of neuropathogenic molecules that may be correlated with the differences in neuroAIDS manifestation induced by clade-specific infections. Gandhi N, Saiyed Z, Thangavel S, Rodriguez J, Rao KV, Nair MP. AIDS Res Hum Retroviruses. 2009 Jul 25(7):691-699.

Kupffer Cells are Depleted With HIV Immunodeficiency and Partially Recovered With Antiretroviral Immune Reconstitution

HIV-related enhancement of gut microbial translocation is associated with progression of hepatic fibrosis. Although hepatic macrophages (Kupffer cells) clear most microbial translocation products and can be infected by HIV, their fate in HIV progression has not been carefully investigated. Kupffer cell density (KCD) was studied in 76 HIV-hepatitis C virus coinfected patients investigated at various stages of liver disease and CD4(+) lymphocyte depletion (and restoration). KCD averaged 23 cells per high-powered field (range 4.4-52.2) and was highest in portal and periportal regions as compared with centrilobular regions ($P < 0.001$). No differences were detected in KCD by age, liver fibrosis stage, or hepatic inflammatory score. Compared with individuals without apparent HIV-related immunosuppression, however, KCD was substantially lower in persons with lower peripheral blood CD4(+) lymphocyte counts ($P = 0.027$) and lowest among those with deepest CD4(+) lymphocyte nadir ($P = 0.006$). After the initial liver biopsy, eight patients began antiretroviral therapy and had immune restoration (> or = 2-fold increase in peripheral CD4(+) lymphocyte count) and a second histologic evaluation with a median of 36.8 months later (range 28.1-58.4 months); KCD increased in all ($P = 0.007$). Given the central role of Kupffer cells in controlling microbial translocation, these data suggest Kupffer cell loss needs to be considered in the pathogenesis of liver fibrosis in HIV-hepatitis C virus coinfected persons. The abundance of portal and periportal Kupffer cells is suggestive of their contribution to fibrosis in periportal regions in chronic viral hepatitis. Balagopal A, Ray SC, De Oca RM, et al. AIDS. 2009 Nov 27;23(18):2397-2404.

Genetic Variation In IL28B and Spontaneous Clearance of Hepatitis C Virus

Hepatitis C virus (HCV) infection is the most common blood-borne infection in the United States, with estimates of 4 million HCV-infected individuals in the United States and 170 million worldwide. Most (70-80%) HCV infections persist and about 30% of individuals with persistent infection develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Epidemiological, viral and host factors have been associated with the differences in HCV clearance or persistence, and studies have demonstrated that a strong host immune response against HCV favours viral clearance. Thus, variation in genes involved in the immune response may contribute to the ability to clear the virus. In a recent genome-wide association study, a single nucleotide polymorphism (rs12979860) 3 kilobases upstream of the IL28B gene, which encodes the type III interferon IFN-3, was shown to associate strongly with more than a twofold difference in response to HCV drug treatment. To determine the potential effect of rs12979860 variation on outcome to HCV infection in a natural history setting, the investigators genotyped this variant in HCV cohorts comprised of individuals who spontaneously cleared the virus (n = 388) or had persistent infection (n = 620). The C/C genotype was shown to strongly enhance resolution of HCV infection among individuals of both European and African ancestry. To the author's knowledge, this is the strongest and most significant genetic effect associated with natural clearance of HCV, and these results implicate a primary role for IL28B in resolution of HCV infection. Thomas DL, Thio CL, Martin MP, et al. Nature. 2009 Oct 8;461(7265):798-801.

Spontaneous Control of Primary Hepatitis C Virus Infection and Immunity Against Persistent Reinfection

Patients with ongoing hepatitis C virus (HCV) exposure following control of an initial HCV infection to determine whether primary control conferred protection against future persistent infections were followed. Twenty-two active injection drug users (IDU) who had cleared a primary hepatitis C viremia for at least 60 days were monitored monthly. Reinfection was defined as the detection of a new HCV infection. Protection was assessed based on the magnitude and duration of viremia following reinfection and generation of T-cell and neutralizing antibody (nAb) responses. Reinfection occurred in 11 IDU (50%) who previously spontaneously controlled primary HCV infection. Although viral clearance occurs in approximately 25% of patients with primary infections, spontaneous viral clearance was observed in 83% of reinfected patients. The duration and maximum level of viremia during subsequent episodes of reinfection were significantly decreased compared with those of the primary infection in the same subjects. In contrast to chronic infection, reinfection was associated with a significant increase in the breadth of T-cell responses. During acute infection, nAbs against heterologous viral pseudoparticles were detected in 60% of reinfected subjects; cross-reactive nAbs are rarely detected in patients who progress to chronic infection. HCV reinfection is associated with a reduction in the magnitude and duration of viremia (compared with the initial infection), broadened cellular immune responses, and generation of cross-reactive humoral responses. These findings are consistent with development of adaptive immunity that is not sterilizing but protects against chronic disease. Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. Osburn WO, Fisher BE, Dowd KA, et al. Gastroenterology. 2009 Sep 24. [Epub ahead of print]

Factors Associated With Serum Retinol, Alpha-Tocopherol, Carotenoids, and Selenium In Hispanics With Problems of HIV, Chronic Hepatitis C, and Drug Use

The effects of hepatitis and drug use on nutritional problems in HIV infection have rarely been examined despite the importance of drug use in the global HIV pandemic. The effects of HIV, hepatitis C, and drug use on serum micronutrients in 300 US Hispanic adults were examined. Chronic hepatitis C infection was associated with lower serum retinol (-8.2 microg/dl, $P < 0.0001$), alpha-tocopherol (-0.10 ln microg/dl, $P = 0.024$), and carotenoids (-19.8 microg/dl, $P < 0.0001$). HIV infection was associated with lower selenium (-6.1 microg/l, $P = 0.028$). Elevated triglycerides in HIV infection were associated with higher serum retinol and alpha-tocopherol. Drug use was not independently associated with micronutrient alterations. It was concluded that hepatitis C is an important determinant of low serum micronutrients, and should be considered in any nutritional assessment of HIV infected populations. As the safety of micronutrient supplementation is not established, policy for appropriate HIV clinical care should distinguish between populations with and without hepatitis coinfection. Forrester JE, Wang XD, Knox TA, et al. J Public Health Policy. 2009 Sep 30(3):285-992.

Hepatitis B and Long-Term HIV Outcomes In Coinfected HAART Recipients

Chronic hepatitis B (CH-B) is common among HIV-infected individuals and increases liver-related mortality in the absence of HAART. The impact of CH-B on long-term HAART outcomes has not been fully characterized. To address this question, HAART initiators enrolled in the Multicenter AIDS Cohort Study were retrospectively analyzed. Patients were classified by hepatitis B category based on serology at the time of HAART initiation. The association of CH-B with

mortality, AIDS-defining illnesses, CD4 cell rise, and HIV suppression was assessed using regression analysis. Of 816 men followed for a median of 7 years on HAART, 350 were never hepatitis B virus (HBV) infected, 357 had past infection, 45 had CH-B, and 64 were only core-antibody positive. Despite HAART, AIDS-related mortality was the most common cause of death [8.3/1000 person-years (PYs)]. It was highest in those with CH-B (17/1000 PYs, 95% confidence interval 7.3, 42) and lowest among never HBV infected (2.9/1000 PYs, 95% confidence interval 1.4, 6.4). In a multivariable model, patients with CH-B had a 2.7-fold higher incidence of AIDS-related mortality compared with those never infected (P = 0.08). Non-AIDS-related mortality was also highest among those with CH-B (22/1000 PYs), primarily due to liver disease (compared to never infected, adjusted hazard ratio 4.1, P = 0.04). There was no significant difference in AIDS-defining events, HIV RNA suppression, and CD4 cell increase. In HIV-infected patients receiving long-term HAART, HBV status did not influence HIV suppression or CD4 cell increase. However, mortality was highest among those with CH-B and was mostly due to liver disease despite HBV-active HAART. Hoffmann CJ, Seaberg EC, Young S, et al. AIDS. 2009 Sep 10;23(14): 1881-1889.

Health-Related Quality of Life In Methadone Maintenance Patients With Untreated Hepatitis C Virus Infection

To assess health-related quality of life (HRQOL) in methadone maintenance treatment (MMT) patients with untreated chronic HCV infection and to determine the clinical factors that predict HRQOL. HRQOL was measured in 100 MMT patients entering an HCV treatment trial. Subjects were mostly male (61%) and white (81%) with a mean age of 43 (+/-10). 57% had a current non-substance use psychiatric disorder. 55% had a current (past 12 months) substance use disorder, including 44% with current opioid or cocaine abuse/dependence. HRQOL in our sample was compared to published reports for the general population as well as for non-MMT HCV patients. To assess predictors of SF-36 HRQOL, hierarchical multiple regression techniques were used to assess model improvement with four blocks of baseline predictors: Demographics, Medical Severity, Addiction Severity, and Depression Severity. HRQOL scores were significantly lower than scores for the general population and were also lower than scores reported for untreated HCV patients not in MMT. Regression analysis demonstrated a consistent pattern whereby Depression Severity increased predictive accuracy for HRQOL measures over simpler models. Beck Depression Inventory scores significantly predicted quality of life across both the mental and physical composite scores and all eight sub-scales of the SF-36. Untreated HCV patients in MMT had lower HRQOL than HCV patients not in MMT. Depression Severity was associated with significantly lower quality of life measures, suggesting that psychiatric evaluation and intervention prior to the start of HCV treatment may improve overall quality of life and could influence HCV treatment outcomes in MMT patients. Batki SL, Canfield KM, Smyth E, Ploutz-Snyder R. Drug Alcohol Depend. 2009 May 1;101(3):176-182.

Antiviral Activity of Geneticin Against Dengue Virus

The aminoglycoside, geneticin (G418), was recently shown to have antiviral activity against bovine viral diarrhea virus (BVDV). Since BVDV, dengue virus (DENV) and yellow fever virus (YFV) all belong to the Flaviviridae family, it seemed possible that a common step in their life cycle might be affected by this aminoglycoside. Here it is shown that geneticin prevented the cytopathic effect (CPE) resulting from DENV-2 infection of BHK cells, in a dose-dependent manner with an 50% effective concentration (EC(50)) value of 3+/-0.4microg/ml. Geneticin had no detectable effect on CPE caused by YFV in BHK cells. Geneticin also inhibited DENV-2 viral yield with an EC(50) value of 2+/-0.1microg/ml and an EC(90) value of 20+/-2microg/ml. With a CC(50)

value of 165+/-5microg/ml, the selectivity index of anti-DENV activity of geneticin in BHK cells was established to be 66. Furthermore, 25microg/ml of geneticin nearly completely blocked plaque formation induced by DENV-2, but not YFV. In addition, geneticin, inhibited DENV-2 viral RNA replication and viral translation. Gentamicin, kanamycin, and the guanidinylated geneticin showed no anti-DENV activity. Neomycin and paromomycin demonstrated weak antiviral activity at high concentrations. Finally, aminoglycoside-3'-phosphotransferase activity of neomycin-resistant gene abolished antiviral activity of geneticin. Zhang XG, Mason PW, Dubovi EJ, et al. Antiviral Res. 2009 Jul 83(1):21-27.

Morningness/Eveningness and Menstrual Symptoms in Adolescent Females

Two types of sleep preference have been supported in the literature. Morning types awaken early and are refreshed upon waking, whereas Evening types rise later and have more erratic sleep schedules. Sleep affects menstrual functioning in adult women. However, there is scant research on the association between sleep preference and menstrual functioning in adolescents. Thus, the present study examined the asso-ciation between sleep preference and menstrual functioning in 210 adolescent girls (11-17 years old). Data represent baseline measures from a longitudinal study examining the association of psychological functioning and smoking with reproductive and bone health. Measures included the Menstrual Symptom Questionnaire (MSQ), regularity and duration of menstrual cycles, and the Morningness/ Eveningness scale (measuring sleep preference).MSQ factor scores were used in analyses: abdominal pain, negative affect/somatic complaints, back pain, and anxiety/fatigue. The results from hierarchical linear regression analyses showed significant associations between Evening preference and more symptoms of abdominal pain (P<.01), negative affect/somatic complaints (P<.01), anxiety/fatig ue (P<.01), and shorter menses (P<.05). Adolescent girls with Evening preference experience more menstrual symptoms than those with Morning preference. Future research should include sleep preference in studies of health and behavior particularly in adolescence when there is a normative shift toward Evening preference. Negriff S, Dorn LD. J Psychosom Res. 2009;67(2):169-172.

Toxic Effect of Methamphetamine on the Retina of CD1 Mice

The goal of this study was to investigate whether systemic administration of methamphetamine (METH) induces retinal damage in CD1 mice. Eighteen male CD1 mice were randomly assigned to three groups, six mice per group: Group 1 receiving a single dose of 40 mg/kg METH, Group 2 receiving four doses of 10 mg/kg METH, and Group 3 (control) receiving 40 mg/kg 0.9% NaCl solution. METH and NaCl were administered by intraperitoneal injection. Immunostaining of glial fibrillary acidic protein (GFAP), S-100 for astrocytes and Muller cells, CD11b for microglia, and tyrosine hydroxylase (TH) and TUNEL labeling for apoptotic cell death were performed on the retinal sections on day 1 and day 7 post-exposure. GFAP and S-100 immunoreactivity was observed in Group 1 mice. CD11b+ cells in Group 1 mice showed more intensely stained shorter and thicker cellular processes than Groups 2 and 3, indicating activated microglia in the mice exposed to large-dose METH. No significant difference in TH level was seen among the three groups. TUNEL labeling did not reveal positive cells in the retinas of any of the 18 CD1 mice. A single large dose of METH induces an increase in short-term protein expression of GFAP and S-100 and in microglial activation. The results suggest that METH has a neurotoxic effect on CD1 mouse retina. Lai H, Zeng H, Zhang C, et al.Curr Eye Res. 2009 Sep 34(9):785-790.

Determination of Relative Timing of Pubertal Maturation through Ordinal Logistic Modeling: Evaluation of Growth and Timing Parameters

The purpose of this study is (1) To propose a new method using statistical modeling to determine relative timing of pubertal maturation; (2) to validate the new method by evaluating its relationship with pubertal growth and timing parameters, including age at menarche, age onset of areolar maturation, age of peak height velocity, age at attainment of adult height, adult height, peak height velocity, body mass index, and percent body fat; and (3) to contrast the new method with relative timing of menarche on these pubertal parameters. The timing of puberty has a well-known impact on anthropometric and psychosocial outcomes. Multiple methods have been used to determine pubertal timing, but all with limitations. A uniformly applicable method is needed for different study designs and study populations. Using the National Heart Lung and Blood Institute Growth and Health Study data, an ordinal logistic modeling was used to assess relative timing of pubertal maturation. The proposed method demonstrated good reliability and strong associations with all pubertal timing parameters, also body mass index and percent body fat. Timing was not significantly associated with adult height and peak height velocity. The proposed method is highly feasible, easy to implement, and valid. The study demonstrated important differences between the relationships of relative timing of secondary sexual characteristics and the timing of menarche on pubertal parameters and also demonstrates that individuals with early or late timing at one point of time are likely to maintain the same relative timing throughout puberty. Huang B, Biro FM, Dorn LD. J Adolesc Health. 2009 Oct 5(4):383-388.

Upregulation of Serotonin Transporter By Alcohol In Human Dendritic Cells: Possible Implication In Neuroimmune Deregulation

Alcohol is the most widely abused substance and its chronic consumption causes neurobehavioral disorders. It has been shown that alcohol affects the function of immune cells. Dendritic cells (DC) serve as the first line of defense against infections and are known to accumulate neurotransmitters such as 5-hydroxytryptamine (5-HT). The enzyme monoamine oxidase-A (MAO-A) degrades 5-HT that is associated with clinical depression and other neurological disorders. 5-HT is selectively transported into neurons through the serotonin transporter (SERT), which is a member of the sodium- and chloride-dependent neurotr ansmitter transporter (SLC6) family. SERT also serves as a receptor for psychostimulant recreational drugs. It has been demonstrated that several drugs of abuse such as amphetamine and cocaine inhibit the SERT expression; however, the role of alcohol is yet to be elucidated. The author's hypothesize that alcohol can modulate SERT and MAO-A expression in DC, leading to reciprocal downregulation of 5-HT in extracellular medium. Dendritic cells were treated with different concentrations (0.05% to 0.2%v/v) of alcohol for 24-72 hours and processed for SERT and MAO-A expression using Q-PCR and Western blots analysis. In addition, SERT function in DC treated with alcohol both in the presence and absence of imipramine, a SERT inhibitor was measured using 4-[4-(dimethylamino)styryl]-1-methylpyridinium iodide uptake assay. 5-HT levels in culture supernatant and intracellular 5-hydroxy indole acetic acid (5-HIAA) and cyclic AMP were also quantitated using ELISA. Dendritic cells treated with 0.1% alcohol for 24 hours showed significant upregulation of SERT and MAO-A expression compared with untreated DC. It was observed that 0.1% alcohol enhanced the function of SERT and decreased extracellular 5-HT levels compared with untreated DC cultures, and this was associated with the elevation of intracellular 5-HIAA and cyclic AMP levels. This study suggests that alcohol upregulates SERT and MAO-A by elevating cyclic AMP, which may lead to decreased concentration of 5-HT in the extracellular medium. As 5-HT is a

major neurotransmitter and an inflammatory mediator, its alcohol-mediated depletion may cause both neurological and immunological deregulation. Babu DK, Diaz A, Samikkannu T, et al. Alcohol Clin Exp Res. 2009 Oct 33(10):1731-1738. Epub 2009 Jul 1.

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

Research Findings - Services Research

Randomized Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies

Little direct evidence exists on the relative efficacies of different smoking cessation pharmacotherapies, yet such evidence is needed to make informed decisions about their clinical use. The purpose of this study is to assess the relative efficacies of 5 smoking cessation pharmacotherapy interventions using placebo-controlled, head-to-head comparisons. 1504 adults from 2 urban research sites who smoked at least 10 cigarettes per day during the last 6 months were studied. Participants were excluded if they reported using any form of tobacco other than cigarettes; current use of bupropion; having a current psychosis or schizophrenia diagnosis; or having medical contraindications for any of the study medications. Participants were randomized to 1 of 6 treatment conditions: nicotine lozenge, nicotine patch, sustained-release bupropion, nicotine patch plus nicotine lozenge, bupropion plus nicotine lozenge, or placebo. In addition, all participants received 6 individual counseling sessions. The main outcome measures were biochemically confirmed 7-day point-prevalence abstinence assessed at 1 week after the quit date (post-quit), end of treatment (8 weeks post-quit), and 6 months post-quit. Other outcomes were initial cessation, number of days to lapse, number of days to relapse, and latency to relapse after the first lapse. All pharmacotherapies differed from placebo when examined without protection for multiple comparisons (odds ratios, 1.63-2.34). With such protection, only the nicotine patch plus nicotine lozenge (odds ratio, 2.34, $P < .001$) produced significantly higher abstinence rates at 6-month post-quit than did placebo. While the nicotine lozenge, bupropion, and bupropion plus lozenge produced effects that were comparable with those reported in previous research, the nicotine patch plus lozenge produced the greatest benefit relative to placebo for smoking cessation. Piper ME, Smith SS, Schlam TR, Fiore MC, Fraser D, Baker TB. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch Gen Psychiatry 2009; 66(11):1253-1262.

A Randomized Clinical Trial of Methadone Maintenance for Prisoners: Results at 12 months Post-release

This study examined the impact of prison-initiated methadone maintenance at 12 months post-release. Males with pre-incarceration heroin dependence (N = 204) were randomly assigned to (a) Counseling Only: counseling in prison, with passive referral to treatment upon release; (b) Counseling + Transfer: counseling in prison with transfer to methadone maintenance treatment upon release; and (c) Counseling + Methadone: counseling and methadone maintenance in prison, continued in the community upon release. The mean number of days in community-based drug abuse treatment were, respectively,

Planned Meetings

Publications

Staff Highlights

Grantee Honors

Counseling Only, 23.1; Counseling + Transfer, 91.3; and Counseling + Methadone, 166.0 ($p < .01$); all pairwise comparisons were statistically significant (all ps < .01). Counseling + Methadone participants were also significantly less likely than participants in each of the other two groups to be opioid-positive or cocaine-positive according to urine drug testing. These results support the effectiveness of prison-initiated methadone for males in the United States. Kinlock TW, Gordon MS, Schwartz RP, Fitzgerald TT, O'Grady KE. A randomized clinical trial of methadone maintenance for prisoners: Results at 12 months post-release. J Subst Abuse Treat. 2009;37(3):277-285.

Addiction Treatment is Costly to Patients Even if They Receive Free Care

A study of 302 individuals in treatment in Dayton, Ohio assessed the cost to the patient of attending addiction treatment. It found that patients in outpatient treatment paid approximately $28.50 for each visit including $23.50 in time costs, $3.69 in transportation costs, $0.45 in cash or in-kind payments, and $0.84 in miscellaneous costs. For an average treatment episode this amounts to $571. Episode costs for patients receiving methadone were approximately $1,853 per episode and those for patients in inpatient treatment were $10,749. Although patients with other health conditions pay time, transportation and other costs as well, the nature of treatments for addiction, which can require multiple visits over several weeks, months, or years, makes these costs potentially more burdensome than those for many other diseases. McCollister K, French M, Pyne J, Booth B, Rapp R, Carr C. The cost of treating addiction from the client's perspective: Results from a multi-modality application of the client DATCAP. Drug Alcohol Depend. 2009;104(3):241-248.

Pharmacokinetic Interactions Between Buprenorphine/Naloxone and Tipranavir/Ritonavir in HIV-negative Subjects

HIV-infected patients with opioid dependence often require opioid replacement therapy. Pharmacokinetic interactions between HIV therapy and opioid dependence treatment medications can occur. HIV-seronegative subjects stabilized on at least 3 weeks of buprenorphine/naloxone (BUP/NLX) therapy sequentially underwent baseline and steady-state pharmacokinetic evaluation of open-label, twice daily tipranavir 500 mg co-administered with ritonavir 200 mg (TPV/r). Twelve subjects were enrolled and 10 completed the study. Prior to starting TPV/r, the geometric mean BUP AUC(0-24h) and C(max) were 43.9 ng h/mL and 5.61 ng/mL, respectively. After achieving steady-state with TPV/r (> or = 7 days), these values were similar at 43.7 ng h/mL and 4.84 ng/mL, respectively. Similar analyses for norBUP, the primary metabolite of BUP, demonstrated a reduction in geometric mean for AUC(0-24h) [68.7-14.7 ng h/mL; ratio=0.21 (90% CI 0.19-0.25)] and C(max) [4.75-0.94 ng/mL; ratio=0.20 (90% CI 0.17-0.23)]. The last measurable NLX concentration (C(last)) in the concentration-time profile, never measured in previous BUP/NLX interaction studies with antiretroviral medications, was decreased by 20%. Despite these pharmacokinetic effects on BUP metabolites and NLX, no clinical opioid withdrawal symptoms were noted. TPV steady-state AUC(0-12h) and C(max) decreased 19% and 25%, respectively, and C(min) was relatively unchanged when compared to historical control subjects receiving TPV/r alone. No dosage modification of BUP/NLX is required when co-administered with TPV/r. Though mechanistically unclear, it is likely that decreased plasma Ritonavir levels while on BUP/NLX contributed substantially to the decrease in TPV levels. BUP/NLX and TPV/r should therefore be used cautiously to avoid decreased efficacy of TPV in patients taking these agents concomitantly. Bruce R, Altice F, Moody D, et al. Pharmacokinetic interactions between buprenorphine/naloxone and tipranavir/ritonavir in HIV-negative subjects chronically receiving buprenorphine/naloxone. Drug Alcohol Depend. 2009;105(3):234-239.

Trends in Prescribed Opioid Therapy for Non-Cancer Pain for Individuals with Prior Substance Use Disorders

Long-term opioid therapy for non-cancer pain has increased. Caution is advised in prescribing for persons with substance use disorders, but little is known about actual health plan practices. This paper reports trends and characteristics of long-term opioid use in persons with non-cancer pain and a substance abuse history. Using health plan data (1997-2005), the study compared age-sex-standardized rates of incident, incident long-term and prevalent long-term prescription opioid use, and medication use profiles in those with and without substance use disorder histories. The CONsortium to Study Opioid Risks and Trends study included over one million adult enrollees of two health plans, Kaiser Permanente of Northern California (KPNC) and Group Health Cooperative (GH) of Seattle, Washington. At KPNC (1999-2005), prevalence of long-term use increased from 11.6% to 17.0% for those with substance use disorder histories and from 2.6% to 3.9% for those without substance use disorder histories. Respective GH rates (1997-2005), increased from 7.6% to 18.6% and from 2.7% to 4.2%. Among persons with an opioid disorder, KPNC rates increased from 44.1% to 51.1%, and GH rates increased from 15.7% to 52.4%. Long-term opioid users with a prior substance abuse diagnosis received higher dosage levels, were more likely to use Schedule II and long-acting opioids, and were more often frequent users of sedative-hypnotic medications in addition to their opioid use. Since these patients are viewed as higher risk, the increased use of long-term opioid therapy suggests the importance of improved understanding of the benefits and risks of opioid therapy among persons with a history of substance abuse, and the need for more careful screening for substance abuse history than is the usual practice. Weisner C, Campbell C, Ray G, et al. Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. Pain 2009;145(3):287-293.

Interim Methadone Reduces Arrests

This study examined the frequency and severity of arrest charges among heroin addicts randomly assigned to either interim methadone (IM) maintenance or to remain on a waiting list for methadone treatment. It was hypothesized that IM participants would have a: (1) lower number of arrests at 6 and 12 months and (2) lower mean crime severity scores at 6 and 12 months post-baseline. Available official arrest data for all 319 study participants for the 2 years before and after study enrollment showed that participants randomly assigned to IM as compared to those on a waiting list had significantly fewer arrests at 6 but not at 12 months from study enrollment. Additional post hoc analyses revealed that those participants not in treatment at 4 and 10-month follow-up assessment points were significantly more likely to be arrested and to have a higher mean crime severity rating at 12 and 24 months post-baseline assessment. Schwartz R, Jaffe J, O 'Grady K, Kinlock T, Gordon M, Kelly S, Wilson M, Ahmed A. Interim methadone treatment: Impact on arrests. Drug Alcohol Depend. 2009;103(3):148-154.

HIV Patients with Psychiatric Disorders are Less Likely to Discontinue HAART

This study examined whether having a psychiatric disorder among HIV-infected individuals is associated with differential rates of discontinuation of HAART and whether the number of mental health visits impact these rates. This longitudinal study (fiscal year: 2000-2005) used discrete time survival analysis to evaluate time to discontinuation of HAART. The predictor variable was presence of a psychiatric diagnosis (serious mental illness versus depressive

disorders versus none). The setting was five United States outpatient HIV sites affiliated with the HIV Research Network. The sample consisted of 4989 patients; the majority was nonwhite (74.0%) and men (71.3%); 24.8% were diagnosed with a depressive disorder, and 9% were diagnosed with serious mental illness. The main outcome measure was time to discontinuation of HAART adjusting for demographic factors, injection drug use history, and nadir CD4 cell count. Relative to those with no psychiatric disorders, the hazard probability for discontinuation of HAART was significantly lower in the first and second years among those with SMI [adjusted odds ratio: first year, 0.57 (0.47-0.69); second year, 0.68 (0.52-0.89)] and in the first year among those with depressive disorders [adjusted odds ratio: first year, 0.61 (0.54-0.69)]. The hazard probabilities did not significantly differ among diagnostic groups in subsequent years. Among those with psychiatric diagnoses, those with six or more mental health visits in a year were significantly less likely to discontinue HAART compared with patients with no mental health visits. Individuals with psychiatric disorders were significantly less likely to discontinue HAART in the first and second years of treatment. Mental health visits are associated with decreased risk of discontinuing HAART. Himelhoch S, Brown C, Walkup J, Chander G., Korthius P., Afful J., Gebo K. HIV patients with psychiatric disorders are less likely to discontinue HAART. AIDS 2009;23(13):1735-1742.

Trends in Long-Term Opioid Therapy for Chronic Non-Cancer Pain

The authors report trends and characteristics of long-term opioid use for non-cancer pain. CONSORT (CONsortium to Study Opioid Risks and Trends) data base which includes adult enrollees of two health plans serving over 1 per cent of the US population was used. Using automated data, authors constructed episodes of opioid use between 1997 and 2005. Age-sex standardized rates of opioid use episodes were estimated beginning in each year (incident) and on-going in each year (prevalent), and the per cent change in rates annualized (PCA) over the 9-year period. Long-term episodes were defined as > 90 days with 120+ days supply or 10+ opioid prescriptions in a given year. It was found that over the study period, incident long-term use increased from 8.5 to 12.1 per 1000 at Group Health (GH) (6.0% PCA), and 6.3 to 8.6 per 1000 at Kaiser Permanente of Northern California (KPNC) (5.5% PCA). Prevalent long-term use doubled from 23.9 to 46.8 per 1000 at GH (8.5% PCA), and 21.5 to 39.2 per 1000 at KPNC (8.1% PCA). Non-Schedule II opioids were the most commonly used opioid among patients engaged in long-term opioid therapy, particularly at KPNC. Long-term use of Schedule II opioids also increased substantially at both health plans. Among prevalent long-term users in 2005, 28.6% at GH and 30.2% at KPNC were also regular users of sedative hypnotics. Long-term opioid therapy for non-cancer pain is increasingly prevalent, but the benefits and risks associated with such therapy are inadequately understood. Concurrent use of opioids and sedative-hypnotics was unexpectedly common and deserves further study. Von Korff M, Boudreau D, Rutter CM, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepi Drug Saf. 2009:1-10.

Correlates of Alcohol Use Among Methadone-Maintained Adults

This prospective study (n = 190) examined correlates of alcohol use from baseline data of a longitudinal trial conducted among moderate and heavy alcohol users receiving methadone maintenance therapy (MMT). The sample included MMT clients who were 18-55 years of age, and were receiving MMT from five large methadone maintenance clinics in the Los Angeles area. Half of the sample was heavy drinkers and nearly half (46%) reported heroin use. Using a structured questionnaire, correlates of heavy alcohol use included White and Hispanic ethnicity, and fair or poor physical health combined with older age (³50 years). We also found that MMT clients who were younger than 50 years, regardless of health status, were more likely to be heavy drinkers.

Compared with moderate alcohol consumers, a greater number of heavy alcohol users also experienced recent victimization. To optimize MMT, alcohol screening should be part of routine assessment and alcohol treatment should be made available within MMT programs. Moreover, special consideration should be provided to the most vulnerable clients, such as the younger user, those with a long-term and current history of heavy drug use, and those victimized and reporting fair or poor health. In addition, promoting attention to general physical and mental health problems within MMT programs may be beneficial in enhancing health outcomes of this population. Nyamathi A, Cohen A, Marfisee M, et al. Correlates of alcohol use among methadone-maintained adults. Drug Alcohol Depend. 2009;101:124-127.

Important Sex Differences in Aberrant Prescription Drug Use Behaviors

Patients who are prescribed opioids often display one or more aberrant prescription use behaviors (e.g., requesting early refills, borrowing medication from family), which raise concern among healthcare professionals. Little is known about the sex differences in specific types of aberrant behaviors or sex-specific predictors of such behaviors. A battery of anonymous, self-report assessments was administered to 121 (49 men, 72 women) chronic pain patients enrolled in an outpatient pain management clinic. Most of the participants were white women with an average age of 51.6 years (SD=13.2). Significantly more men than women were taking a prescribed opioid (91.7% vs. 77.8%, P=0.05). Women were significantly more likely than men to hoard unused medication (67.6% vs. 47.7%, P=0.04) and to use additional medications to enhance the effectiveness of pain medication (38.8% vs. 20.0%, P=0.04). A trend toward men using alternative routes of administration (eg, crushing and snorting pills) more often than women was observed (8.9% vs. 1.5%, P=0.08). Among men, high rates of aberrant prescription use behaviors were associated with current alcohol use and the use of oxycodone and morphine. Among women, use of hydrocodone was associated with high rates of aberrant prescription use behaviors. Some aberrant prescription use behaviors are common among chronic pain patients and may be sex-specific. Predictors of aberrant prescription use behaviors may also differ by sex. The authors note that additional research may be needed to help identify aberrant prescription use behaviors that best predict sex-specific risk for developing opioid abuse or dependence. Back S, Payne R, Waldrop A, Smith A, Reeves S, Brady K. Prescription opioid aberrant behaviors: A pilot study of sex differences. Clin J Pain 2009;25(6):477-484.

Prescription Opioid Abuse and Diversion in an Urban Community

Prescription-drug diversion is a topic about which comparatively little is known, and systematic information garnered from prescription-drug abusers and dealers on the specific mechanisms of diversion is extremely limited. A pilot ultrarapid assessment was carried out in Wilmington, Delaware, during December 2006 to better understand the scope and dynamics of prescription-drug abuse and diversion. This involved focus groups with prescription-drug abusers and key informant interviews with police, regulatory officials, prescription-drug dealers, and pill brokers. The research team recruited focus group participants from the two residential substance abuse treatment programs in Wilmington reporting the highest proportions of prescription drug abusing clients. A total of six focus groups were conducted with 32 patients in these two programs. Dealers were recruited from the same treatment facilities, and three in-depth interviews were completed. In-depth interviews were also conducted with two prescription pill brokers recruited through the authors' existing contacts in the drug abusing community. Six in-depth interviews were conducted with representatives from a number of Delaware agencies-the Attorney General's Office, the Department of Professional Regulation, the State

Police, the Wilmington Police Department, and the Newark Police Department. In-depth interview and focus group guides were developed for each of the target populations. The in-depth interviews with police and regulatory officials focused on the extent of prescription drug abuse and diversion in the community, the types of drugs most commonly diverted, and mechanisms being used to channel the drugs to the illicit market. The focus group areas of inquiry with prescription drug abusers included general perceptions of the prescription drug problem in Delaware, sources and mechanisms of access to prescription drugs, popularity and prices of prescription medications on the street, as well as the initiation and progression of prescription and illicit drug abuse. The primary sources of prescription drugs on the street were the elderly, patients with pain, and doctor shoppers, as well as pill brokers and dealers who work with all of the former. The popularity of prescription drugs in the street market was rooted in the abusers' perceptions of these drugs as 1) less stigmatizing; 2) less dangerous; and, 3) less subject to legal consequences than illicit drugs. For many, the abuse of prescription opioids also appeared to serve as a gateway to heroin use. The diversion of prescription opioids might be reduced through physician education focusing on 1) recognizing that a patient is misusing and/or diverting prescribed medications; 2) considering a patient's risk for opioid misuse before initiating opioid therapy; and 3) understanding the variation in the abuse potential of different opioid medications currently on the market. Patient education also appears appropriate in the areas of safeguarding medications, disposal of unused medications, and understanding the consequences of manipulating physicians and selling their medications. Inciardi J, Surratt H, Cicero T, Beard R. Prescription opioid abuse and diversion in an urban community: The results of an ultrarapid assessment. Pain Med. 2009;10(3):537-548.

Correlates of the Provision of Detoxification Services and Medication-Based Treatments for Substance Abuse in Correctional Institutions

In recent years, there has been an increased examination of organizational-level innovation adoption in substance abuse treatment organizations. However, the majority of these studies have focused on community-based treatment centers. One understudied area of the substance abuse treatment system is correctional institutions. This study uses the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) cooperative's National Criminal Justice Treatment Practices (NCJTP) survey to examine the adoption of detoxification services and pharmacotherapies for the treatment of substance abuse across a nationally representative sample of correctional institutions (n = 198). There were significant differences between jails and prisons in the percentage of organizations offering detoxification services and medications. Specifically, detoxification services were offered by 5% of prisons and 34% of jails; and, medications were offered by 6% of prisons and 32% of jails. Binary logistic regression models were used to examine the associations between these services and organizational characteristics, including context, resources, previously introduced practices, culture, and systems integration. Variables measuring organizational context and previously introduced practices were significant correlates of the provision of both detoxification services and medications. Multivariate results indicated that the differences between jails and prisons remained significant after controlling for other organizational factors. Although the adoption of detoxification services and pharmacotherapies may be a controversial topic for correctional institutions, these services have the potential to improve offender well-being and reduce public health risks associated with substance abuse. Oser CB, Knudsenb HK, Staton-Tindall M, et al. Organizational-level correlates of the provision of detoxification services and medication-based treatments for substance abuse in correctional institutions. Drug Alcohol Depend. 2009;1035:S73-S81.

Opioid Treatment Programs in the CTN are Quicker to Adopt Buprenorphine

This study was designed to assess the representativeness of opioid treatment programs (OTPs) participating in NIDA's Clinical Trials Network (CTN), and potential barriers to the effective diffusion of practices aimed at the treatment of opioid-dependent patients, specifically buprenorphine, to the general population of OTPs in the U.S. Interviews were conducted with clinical directors of the N=49 OTPs within the CTN and a sample (N=50) drawn from the population of U.S. OTPs outside the CTN. The two groups were compared on their organizational, clinical, and client characteristics, as well as their adoption of buprenorphine. The study documented significant differences between the CTN OTPs and the general population of OTPs on numerous variables, including nonprofit operations, number of employees (all staff, nurses, and Master's level counselors), annual caseflow, Medicaid coverage, client unemployment, and client criminal justice involvement - all of which were significantly higher in the CTN OTPs. As of 2006, OTPs in the CTN were more likely to have adopted buprenorphine than the general population of OTPs (42.8% vs. 24.0%, $p<.05$). However, involvement in the CTN's buprenorphine trials did not explain the differential uptake. In multivariate models, the CTN vs non-CTN difference in buprenorphine adoption persisted after controlling for the programs' structural characteristics (funding, staff, census), but not when controlling for clinical or client characteristics. These findings suggest that participation in the CTN, per se, did not convey a unique advantage to OTPs in preparing them to adopt buprenorphine, but rather that selection effects -specifically structural characteristics - were the key predictors of adoption. Consideration of site characteristics may be important in the development of dissemination materials and local constraints on the uptake of evidence-based practices. Ducharme LJ, Roman PM. Opioid treatment programs in the Clinical Trials Network: Representativeness and buprenorphine adoption. J Subst Abuse Treat. 2009;37:90-94.

Inadequate Documentation of Opioid Dependence and Methadone Maintenance Treatment (MMT) in the Medical Record

Opioid-dependent patients often have co-occurring chronic illnesses requiring medications that interact with methadone. Methadone maintenance treatment (MMT) is typically provided separately from medical care. Hence, coordination of medical care and substance use treatment is important to preserve patient safety. The authors reviewed medical records to identify potential safety risks among MMT patients engaged in medical care by evaluating the frequency that opioid dependence and MMT documentation are missing in medical records and characterizing potential medication-methadone interactions. Among patients from a methadone clinic who received primary care from an affiliated, but separate, medical center, electronic medical records were reviewed for documentation of methadone, opioid dependence, and potential drug-methadone interactions. The proportions of medical records without opioid dependence and methadone documentation were estimated and potential medication-methadone interactions were identified. Among the study subjects (n = 84), opioid dependence documentation was missing from the medical record in 30% (95% CI, 20%-41%) and MMT documentation was missing from either the last primary care note or the last hospital discharge summary in 11% (95% CI, 5%-19%). Sixty-nine percent of the study subjects had at least 1 medication that potentially interacted with methadone; 19% had 3 or more potentially interacting medications. This study shows that among patients receiving MMT and medical care at different sites, documentation of opioid dependence and MMT in the medical record occurs for the majority, but is missing in a substantial number of patients. This is despite the use of electronic medical records. Most of these patients are prescribed medications that potentially interact with methadone. This study highlights opportunities for

improved coordination between medical care and MMT. Walley A, Farrar D, Cheng D, Alford D, Samet J. Inadequate documentation of opioid dependence and methadone maintenance treatment (MMT) in the medical record. J Gen Intern Med. 2009;24(9):1007-1011.

Workplace Mandates Statistically Associated with Longer Stays in Addiction Treatment

A sample of 448 employed members of a private U.S. managed care plan were followed to determine whether those mandated to addiction treatment by their employers (n=75) had different outcomes from those who entered treatment without a mandate (n=373). Multivariate analyses, including control variables such as Addiction Severity Index intake scores, psychiatric diagnoses and services, and motivation were estimated to assess the statistical association between being mandated to treatment and length of stay, abstinence, psychiatric severity, and employment problem severity. Those with a workplace mandate stayed in treatment an average of 58 days longer in treatment ($p < 0.001$). Workplace mandates were not independently associated with other outcomes at 1 year in models that included length of stay. However, longer stays were associated with higher odds of abstinence (0R = 1.01 CI=1.01-1.01), and lower levels of employment problem severity ($\beta=-0.124$, $p = 0.009$). To the extent that workplace mandates actually caused the longer stays, they were associated with improved outcomes. Weisner C, Lu Y, Hinman A, et al. Substance use, symptom, and employment outcomes of persons with a workplace mandate for chemical dependency treatment. Psychiatr Serv. 2009;60(5):646-654.

TC Prison Programs Provide a Modest Cost-Offset

This study set out to examine whether there were any reductions in administrative costs from prison-based TC programs. The incremental economic costs of two therapeutic community (TC) yards in a California prison and their associated benefit in terms of saved administrative costs due to reduced disruptive prisoner behavior compared with the regular prison yard were estimated. A multivariate general linear model including race/ethnicity, prior incarceration, principal commitment offence, recidivism risk and a propensity score for TC assignment revealed that the TC yards were associated with an average reduction of $122,990 in administrative costs per yard, in 2005 dollars, over a two year period compared with the regular yard. This suggests that there is at least a small costs offset that can be applied to the approximately $2,000,000 average incremental cost of a TC yard. Zhang SX, Roberts RE. An economic analysis of the in-prison therapeutic community model on prison management costs. Journal of Criminal Justice 2009;37:388-395.

The Relationship Between Neighborhood Criminal Behavior and Oxford Houses

The present study investigated crime rates in areas surrounding 42 Oxford Houses and 42 control houses in a large city in the Northwestern United States. A city-run Global Information Systems' (GIS) website was used to gather crime data including assault, arson, burglary, larceny, robbery, sexual assault, homicide, and vehicle theft over a calendar year. Findings indicated that there were no significant differences between the crime rates around Oxford Houses and the control houses. These results suggest that well-managed and governed recovery homes pose minimal risks to neighbors in terms of criminal behavior. Deaner J, Jason LA, Aase DM, Mueller D. The Relationship between neighborhood criminal behavior and Oxford Houses. Therapeutic Communities 2009:3089-3093.

HIV-related Health Services in Adolescent Substance Abuse Treatment Programs

Given that alcohol and drug abuse heightens the risk of adolescents acquiring HIV, substance abuse treatment programs for youths may represent an important site of HIV prevention. In this research, the authorsn explored the adoption of three HIV-related health services: risk assessment during intake, HIV prevention programming, and HIV testing. Data were collection through telephone interviews with 149 managers of adolescent-only substance abuse treatment programs in the USA. About half of these programs had adopted HIV risk assessment and HIV prevention. On-site HIV testing was less widely adopted, with only one in four programs offering this service. At the bi-variate level, the availability of on-site primary medical care and the availability of an overnight level of care were positively associated with these three types of services. The association for the measure of an overnight level of care was no longer significant once medical services were controlled. However, in a separate analysis, it was found that programs offering an overnight level of care were much more likely to offer on-site medical care than outpatient-only facilities. There was also evidence that publicly funded treatment programs were more likely to offer HIV prevention and on-site HIV testing, after controlling for other organizational characteristics. Much more research about the adoption of HIV-related services in adolescent substance abuse treatment is needed, particularly to offer greater insight into why certain types of organizations are more likely to adopt these health services. Knudsen HK, Oser CB. Availability of HIV-related health services in adolescent substance abuse treatment programs. AIDS Care 2009;21(10):1238-1246.

Disparities in Access to Care Among Children in the Child Welfare System

This study examined health service access among children of different racial/ethnic groups in the child welfare system in an attempt to identify and explain disparities. Data were from the National Survey of Child and Adolescent Well-Being (n=2,505). Measures reflected child health services need, access, and enabling factors. Chi-square and t tests were used to compare across racial/ethnic groups. A logistic regression model further explored the greatest disparity identified, that between non-Latino/ Black and White children in caseworker-reported access to counseling. In general, caseworker reports of health care service receipt did not differ across racial/ethnic groups. However, Latino children had better reported access to vision services than non-Latino/ White children, and counseling access was lower for non-Latino/ Black children than non-Latino/ White children. Caseworkers' self-reported efforts to facilitate service access did not vary by race/ethnicity for any type of health care. In the multiple regression model, both private health insurance and a lack of insurance were negatively associated with counseling access, while a history of sexual abuse, adolescence, and greater caseworker effort to secure services were positively associated with access. Race was just barely non-significant after controlling for other factors expected to affect access. One possible reason why Black children are less likely to be identified as needing counseling is the fact that they are less likely than White children to have reports of sexual abuse, which strongly predicts counseling access. First, child welfare practice may be more equitable than many believe, with generally comparable health service access reported across children's racial/ethnic groups. Second, caseworkers may be under-identifying need for counseling services among Black children, although this might reflect less frequent reports of sexual abuse for Black children. Third, both privately insured and uninsured children were less likely to receive needed mental health counseling than those with public insurance. This suggests that policy makers should focus on increasing the numbers of children enrolled in public health insurance programs such as

Medicaid and the State Children's Health Insurance Program (SCHIP). Wells R, Hillemeier M, Bai Y, Belue R. Health Service Access across racial/ethnic groups of children in the child welfare system. Child Abuse Negl. 2009;33(5):282-292.

Adherence to Scheduled Sessions in a Randomized Field Trial of Case Management: The Criminal Justice Drug Abuse Treatment Studies Transitional Case Management Study

The Transitional Case Management (TCM) study, one of the projects of the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) cooperative, was a multi-site randomized test of whether a strengths-based case management intervention provided during an inmate's transition from incarceration to the community increases participation in community substance abuse treatment, enhances access to needed social services, and improves drug use and crime outcomes. As in many intervention studies, TCM experienced a relatively large percentage of treatment group participants who attended few or no scheduled sessions. The paper discusses issues with regard to participation in community case management sessions, examines patterns of session attendance among TCM participants (n=382), and analyzes client and case manager characteristics that are associated with number of sessions attended and with patterns of attendance. The average number of sessions (out of 12) attended was 5.7. Few client or case manager characteristics were found to be significantly related to session attendance. Prendergast M, Greenwell L, Cartier J, et al. Adherence to scheduled sessions in a randomized field trial of case management: The criminal justice drug abuse treatment studies transitional case management study. J Experimental Criminology. 2009:5273-5297.

The Drugs-Violence Nexus Among Rural Felony Probationers

Little research has focused on the drugs-violence nexus in rural areas. As such, the purpose of this study is to use Goldstein's tripartite conceptual framework to examine the relationship between drugs and violence among felony probationers in rural Appalachian Kentucky (n = 799). Data on demographics, substance use criminal history, and violence were collected between 2001 and 2004 using an interviewer-administered questionnaire. Rural probationers are partitioned into four groups based on lifetime violent victimization/perpetration experiences: (a) neither a perpetrator nor a victim, (b) perpetrator only, (c) victim only, and (d) both a perpetrator and a victim. Chi-square analyses indicate substance use, and criminal history varies across the four groups. Binary logistic regression analyses are used to explore the significant correlates of both perpetration and victimization. Multivariate analyses support both the psychopharmacological model and the economic compulsive models of perpetration and victimization. Oser CB, Mooney JL, Staton-Tindall M, Leukefeld CG. The drugs-violence nexus among rural felony probationers. J Interpers Violence 2009;24(8):1285-1303.

Clinical Supervision Provided to Therapists in Randomized Treatment Trials Can be Provided to Mental Health Professionals in the Workplace

This observational study used mixed-effects regression models to examine relations among supervisor adherence to a clinical supervision protocol, therapist adherence, and changes in the behavior and functioning of youths with serious antisocial behavior. The youths were treated with an empirically supported treatment, multi-systemic therapy. Participants were 1,979 youths and families treated by 429 clinicians across 45 provider organizations in North America. The mean age for youth was 14.0, and most were male (65.0%) and Caucasian (59.5%), with 19.3% of youth identified as African American, and 6.4% Asian or Pacific Islander. Four dimensions of clinical supervision were

examined. Mixed-effects regression model results showed that one dimension, supervisor focus on adherence to treatment principles, predicted greater therapist adherence. Two supervision dimensions, Adherence to the Structure and Process of Supervision and focus on Clinician Development, predicted changes in youth behavior. Conditions required to test hypothesized mediation by therapist adherence of supervisor adherence effects on youth outcomes were not met. However, direct effects of supervisor and therapist adherence were observed in models including both of these variables. The results reported here suggest that the training and clinical supervision provided to therapists in successful randomized treatment trials can be provided to mental health professionals in the workplace as part of a multi-component treatment transport strategy. To support the effective transport and implementation of empirically supported treatments in practice contexts, additional research is needed to evaluate the viability, implementation, and effects on client outcomes in usual care settings of the training and supervision protocols used in treatment trials. Schoenwald S, Sheidow A, Chapman J. Clinical supervision in treatment transport: Effects on adherence and outcomes. J Consult Clin Psychol. 2009;77(3):410-421.

Wraparound Services Among Substance Abuse Treatment Organizations Serving Criminal Offenders

Women's substance abuse treatment outcomes are improved when women-specific needs are addressed through wraparound services, such as the provision of child care, employment assistance, or mental health counseling. Despite a higher prevalence of pre-incarceration drug use, women in prison report receiving fewer services than their male counterparts, suggesting they likely have greater service needs upon release. It is unknown whether community-based treatment organizations with a women-specific program offer more wraparound services than programs without a focus on women. This study uses data from the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) research cooperative's National Criminal Justice Treatment Practices Survey (NCJTPS), a nationally representative sample of community-based treatment programs serving predominantly criminal offenders (n = 217). First, bivariate analyses identified differences between organizations with and without a women-specific program on the number of wraparound services adopted as well as organizational-level characteristics (i.e., organizational structure, personnel characteristics, culture, sources of information, and systems integration) related to their adoption. Second, Poisson regression was used to identify the organizational characteristics associated with the number of adopted wraparound services, with having a women-specific program being the primary covariate of interest. Results indicate larger organizations that utilized a greater number of treatment approaches and believed that treatment could reduce crime were more likely to offer a greater assortment of wraparound services. In an effort to improve behavioral treatment outcomes, it is imperative to examine organizational-level contextual factors that shape the availability of wraparound services for female offenders in community-based substance abuse treatment settings. Oser CB, Knudsen H, Staton-Tindall M, Leukefeld C. The adoption of wraparound services among substance abuse treatment organizations serving criminal offenders: The role of a women-specific program. Drug Alcohol Depend. 2009;1035:S82-S90.

The Black Box of Prescription Drug Diversion

A variety of surveys and studies are examined in an effort to better understand the scope of prescription drug diversion and to determine whether there are consistent patterns of diversion among various populations of prescription drug abusers. Data are drawn from the RADARS System, the National Survey of Drug Use and Health, the Delaware School Survey, and a series of quantitative and qualitative studies conducted in Miami, Florida. The data suggest that the

major sources of diversion include drug dealers, friends and relatives, smugglers, pain patients, and the elderly, but these vary by the population being targeted. In all of the studies examined, the use of the Internet as a source for prescription drugs is insignificant. Little is known about where drug dealers are obtaining their supplies, and as such, prescription drug diversion is a "black box" requiring concentrated, systematic study. Inciardi JA, Surratt HL, Cicero T, Kurtz SP, Martin SS, Parrino MW. The black box of prescription drug diversion. J Addict Dis. 2009; 28: 332-347.

Adoption of New Medications Takes Considerable Time as Clinics Adapt to Change

The National Drug Abuse Treatment Clinical Trials Network (CTN), a collaborative federal research initiative that brings together universities and community-based treatment programs (CTPs), conducted multiple clinical trials of buprenorphine for opioid dependence. Part of the CTN's mission is to promote the adoption of evidence-based treatment technologies. Drawing on a data collected during face-to-face interviews with administrators from a panel of 206 CTPs, this research examined the adoption of buprenorphine over a 2-year period. Results indicated that the adoption of buprenorphine doubled between the baseline and 24-month follow-up interviews. Involvement in a buprenorphine protocol continued to be a strong predictor of adoption at the 2-year follow-up. Adoption of buprenorphine tripled among those CTPs without buprenorphine-specific protocol experience. For-profit CTPs and those offering inpatient detoxification services were more likely to adopt buprenorphine over time. A small percentage of programs discontinued using buprenorphine. These findings point to the dynamic nature of service delivery in community-based addiction treatment and the continued need for longitudinal studies of organizational change. Knudsen HK, Abraham AJ, Johnson JA, Roman PM. Buprenorphine adoption in the National Drug Abuse Treatment Clinical Trials Network . J Subst Abuse Treat. 2009; 37:307-312.

Personal Versus Home Environmental Effects on Prenatal Care

Nearly one-fourth of African-American women receive no prenatal care during the first trimester of pregnancy. The aim of the current study is to identify factors that underlie inadequate prenatal care among African-American women. Maternal alcohol abuse has been examined as one risk factor for inadequate prenatal care, but findings have been inconsistent, perhaps because (a) alcohol use during pregnancy is substantially under-reported and (b) studies have not considered the wider social network in which maternal alcohol use takes place. The current study attempts to clarify relationships between personal alcohol use, alcohol use in the home environment, and prenatal care in a sample of post-partum women. Participants were 107 low-income, primarily African-American women. All participants completed a computer-based screening which assessed personal and environmental alcohol use, prenatal care and mental health. Environmental alcohol use was related to delayed prenatal care while personal alcohol use was not. More specifically, after controlling for demographic variables, the presence of more than three person-episodes of binge drinking in a woman's home environment increased the odds of seriously compromised prenatal care by a factor of seven. Findings suggest the need to further assess environmental alcohol use and to examine the reliability of personal alcohol use measures. Grekin ER, Ondersma SJ. The relationship between prenatal care, personal alcohol abuse and alcohol abuse in the home environment. Prenatal Care 2009;16(5):463-470.

Motivation Enhancement Therapy with Pregnant Substance-abusing Women

Some evidence suggests that motivational approaches are less efficacious - or even counter-productive - with persons who are relatively motivated at baseline. The present study was conducted to examine whether disordinal moderation by baseline motivation could partially explain negative findings in a previous study (Winhusen T, Kropp F, Babcock D, Hague D, Erickson SJ, Renz C, Rau L, Lewis D, Leimberger J, Somoza E. Motivational enhancement therapy to improve treatment utilization and outcome in pregnant substance users. J. Subst. Abuse Treat. 2008;35: 161-173). Analyses also focused on the relative utility of the University of Rhode Island Change Assessment (URICA) scale, vs. a single goal question as potential moderators of Motivation Enhancement Therapy (MET). Participants were 200 pregnant women presenting for substance abuse treatment at one of four sites. Women were randomly assigned to either a three-session MET condition or treatment as usual (TAU). Generalized Estimating Equations (GEE) revealed no significant moderation effects on drug use at post-treatment. At follow-up, contrary to expectations, participants who had not set a clear quit goal at baseline were less likely to be drug-free if randomized to MET (OR = 0.48); participants who did set a clear quit goalwere more likely to be drug-free if randomized to MET (OR = 2.53). No moderating effects were identified via the URICA. Disordinal moderation of MET efficacy by baseline motivation may have contributed somewhat to the negative results of the Winhusen, et al., 2008. study, but in the opposite direction expected. A simple question regarding intent to quit may be useful in identifying persons who may differentially respond to motivational interventions. However, moderation effects are unstable, may be best identified with alternate methodologies, and may operate differently among pregnant women. Ondersma SJ, Winhusen T, Erickson SJ, Stine S M, Wang Y. Motivation enhancement therapy with pregnant substance-abusing women: Does baseline motivation moderate efficacy? Drug Alcohol Depend. 2009;101:74-79.

Mortality Among Injection Drug Users in Chennai, India

Injection drug users (IDUs) have estimated mortality rates over 10 times higher than the general population; much of this excess mortality is HIV-associated. Few mortality estimates among IDUs from developing countries, including India, exist. IDUs (1158) were recruited in Chennai from April 2005 to May 2006; 293 were HIV positive. Information on deaths and causes was obtained through outreach workers and family/network members. Mortality rates and standardized mortality ratios were calculated; multivariate Poisson regression was used to identify predictors of mortality. We observed 85 deaths over 1998 person-years (p-y) of follow-up [mortality rate (MR) 4.25 per 100 p-y; 95% confidence interval (CI) = 3.41-5.23]. The overall standardized mortality ratio was 11.1; for HIV-positive IDUs, the standardized mortality ratio was 23.9. Mortality risk among HIV-positive IDUs (MR: 8.88 per 100 p-y) was nearly three times that of negative IDUs (MR: 3.03 per 100 p-y) and increased with declining immune status (CD4 cells>350: 5.44 per 100 p-y vs. CD4 cells200: 34.5 per 100 p-y). This association persisted after adjustment for confounders. The leading causes of mortality in both HIV negative and positive IDUs were overdose (n=22), AIDS (n=14), tuberculosis (n=8) and accident/trauma (n=9). Substantial mortality was observed in this cohort with the highest rates among HIV-positive IDUs with CD4 counts of less than 350 cells/ml. Although, in these 2 years, non-AIDS deaths outnumbered AIDS-related deaths, the relative contribution of AIDS-associated mortality is likely to increase with advancing HIV disease progression. These data reinforce the need for interventions to reduce the harms associated with drug use and increase HAART access among IDUs in Chennai. Solomon SS, Celentano DD, Srikrishnan A, et al. Mortality among injection drug users in Chennai, India (2005-2008). AIDS 2009;23:997-1004.

Availability and Capacity of Substance Abuse Programs in

Correctional Settings: A Classification and Regression Tree Analysis

The purpose of this study was to investigate the structural and organizational factors that contribute to the availability and increased capacity for substance abuse treatment programs in correctional settings. The authors used classification and regression tree statistical procedures to identify how multi-level data can explain the variability in availability and capacity of substance abuse treatment programs in jails and probation/parole offices. The data for this study combined the National Criminal Justice Treatment Practices (NCJTP) Survey and the 2000 Census. The NCJTP survey was a nationally representative sample of correctional administrators for jails and probation/parole agencies. The sample size included 295 substance abuse treatment programs that were classified according to the intensity of their services: high, medium, and low. The independent variables included jurisdictional-level structural variables, attributes of the correctional administrators, and program and service delivery characteristics of the correctional agency. The two most important variables in predicting the availability of all three types of services were stronger working relationships with other organizations and the adoption of a standardized substance abuse screening tool by correctional agencies. For high and medium intensive programs, the capacity increased when an organizational learning strategy was used by administrators and the organization used a substance abuse screening tool. This study presents the first phase of understanding capacity-related issues regarding treatment programs offered in correctional settings. Taxman FS, Kitsantas P. Availability and capacity of substance abuse programs in correctional settings: A classification and regression tree analysis. Drug Alcohol Depend. 2009;103S (S43-S53):1-11.

Associations Among State and Local Organizational Contexts: Use of Evidence-Based Practices in the Criminal Justice System

This study used hierarchical linear modeling (HLM) to examine the extent to which the organizational characteristics of state corrections agencies and local criminal justice facilities interacted in their associations with the extent to which local facilities are using evidence-based substance abuse treatment practices (EBPs). The study used data collected from two nationally representative surveys - one of state executives and the other of local prison wardens, justice administrators, and treatment directors - which were conducted as part of the National Criminal Justice Treatment Practices survey, as part of the Criminal Justice Drug Abuse Treatment Studies cooperative research program, and includes both adult criminal and juvenile justice samples. The sample consisted of correctional executives and criminal and juvenile justice (ns=100 and 70, respectively), criminal and juvenile justice administrators (ns = 289; 141), and treatment directors providing services for adult and juvenile offenders (ns = 142; 75). Results indicated that several state organizational characteristics were either associated with more EBP use or interacted with local organizational characteristics in associations with EBP use, including: (1) systems integration at the state level was associated with greater EBP use; (2) state staffing adequacy and stability accentuated the association between local training and resources for new programs and EBP use (i.e., in states with better staffing, the relationship between training/resources and EBP use in local facilities was stronger); and (3) state executives' attitudes regarding the missions and goals of corrections tended to diminish the extent to which corresponding local administrator attitudes were associated with EBP use. The study has implications for future research focused on EBP diffusion and implementation in correctional environments, particularly attempts to influence EBP use by working through state agencies. Henderson CE, Young DW, Farrell J, Taxman FS. Associations among state and local organizational contexts: Use of evidence-based practices in the criminal justice system. Drug

Alcohol Depend. 2009;103S:S23-S32.

More Counselor Training is Needed in Medication Assisted Treatment

Addiction treatment counselors play a central role in the dissemination of information about new treatment techniques to their patients, making them key players in the implementation of new treatment technologies. This study examines counselors' perceptions of the effectiveness and acceptability of pharmacotherapies for the treatment of alcohol dependence. Mail questionnaires were received from 1,140 counselors employed in a nationally representative sample of public-sector addiction treatment programs in 2006 (61% response rate). Counselors answered a series of questions about three FDA-approved medica-tions used in the treatment of alcohol dependence (disulfiram, tablet naltrexone, and acamprosate), indicating their extent of familiarity with each medication, its perceived effectiveness in the treatment of alcohol dependence, and its acceptability for use with alcohol-dependent patients. While most (71.8%) counselors were familiar with disulfiram, less than half (41.9%) were familiar with tablet naltrexone, and very few (23.9%) were familiar with acamprosate. Those who were familiar with each medication rated it at the midpoint of the provided scale for perceived effectiveness, and just above the midpoint of the provided scale for perceived acceptability for use in alcohol treatment. However, counselors reported having received little or no training about any of these medications. Moreover, with less than 20% of participating treatment facilities having adopted any of these medications, counselors have had little first-hand exposure to this treatment approach. Multivariate models showed that the receipt of medication specific training as well as indirect observation of the medication's use in the treatment program were significantly associated with diffusion counselors' awareness and perceptions of the effectiveness and acceptability of the medications for use in addiction treatment When exposed to information about medications to treat alcohol dependence, counseling staff appear quite receptive. More efforts are needed to disseminate information about medication-assisted treatment to front-line addiction treatment staff. Abraham AJ, Ducharme LJ, Roman PM. Counselor attitudes toward pharmacotherapies for alcohol dependence. J Stud Alcohol Drugs 2009;70:628-635.

Research on the Diffusion of Evidence-Based Treatments Within Substance Abuse Treatment: A Systematic Review

This article provides a comprehensive meta-analysis of research studies that have examined the diffusion of evidence-based treatments (EBTs) within the field of substance abuse treatment. Sixty-five research studies were identified and were grouped into one of three major classifications: attitudes toward EBTs, adoption of EBTs, and implementation of EBTs. Results suggests significant progress has been made with regard to the advancement of the fields' knowledge about attitudes toward and the extent to which specific EBTs have been adopted in practice, as well as with regard to the identification of organizational factors related to EBT adoption. In an effort to advance the substance abuse treatment field toward evidence-based diffusion practices, recommendations are made for greater use of scientifically rigorous experimental or quasi-experimental research designs, psychometrically sound instruments, and integration of quantitative and qualitative data collection when studying EBT implementation. Garner BR. Research on the diffusion of evidence-based treatments within substance abuse treatment: A systematic review. J Subst Abuse Treat. 2009;36:376-399.

Treatment Engagement is Influenced by Organizational Factors Regardless of Culture

Client functioning and treatment engagement were examined in relation to staff attributes and organizational climate across a diverse sample of drug treatment and outreach programs in England. Self-rating assessments were obtained from 1,539 clients and 439 counselors representing 44 programs, and results were interpreted using comparable data from studies of treatment programs in the United States. Client scores on treatment participation and counseling rapport in England were directly related to their higher levels of motivation and psychosocial functioning, as well as to staff ratings of professional attributes and program atmosphere. By linking records from English clients with their counselors in each program, findings also indicate these relationships are rooted in the personal interactions between clients and their counselor. Standardized assessments of treatment structure, process, and performance used across therapeutic settings and national boundaries show there is generalizability in the pattern of clinical dynamics, including the relationships between organizational functioning and quality of services. Simpson D, Rowan-Szal GA, Joe GW, Best D, Day E, Campbell A. Relating counselor attributes to client engagement in England. J Subst Abuse Treat. 2009;36; 313-320.

Cigarette Smoking Reduced Among Opioid-Dependent Clients in a Therapeutic Community

This study examines smoking behavior in a sample of 231 opioid-dependent clients entering therapeutic community treatment, and investigates the relationship between smoking behavior and drug treatment outcomes. Regression analyses for selected Addiction Severity Index composites (alcohol, drug, medical, psychiatric), including factors for smoking (number of cigarettes per day, expired-air carbon monoxide level, nicotine dependence), time (baseline, 6 and 12-month), and smoking-by-time interaction confirmed a high smoking prevalence (95%) among opioid users. Among participants interviewed at all time points (n =206), 13% shifted from smoking to non-smoking status at some time after admission. Participants who reported a greater number of cigarettes were more likely to report higher drug severity at any time point. Chun J, Haug NA, Guydish JR, et al. Cigarette smoking among opioid-dependent clients in a therapeutic community. Am J Addict. 2009;18:316-320.

Filling Service Gaps: Providing Intensive Treatment Services for Offenders

This study explores conditions and factors that may underlie the wide variation among states in the provision of intensive treatment for offenders in criminal justice settings, used multilevel modeling techniques with data from the National Criminal Justice Treatment Practices (NCJTP) survey, conducted as part of NIDA's Criminal Justice Drug Abuse Treatment Studies (CJDATS) cooperative research program. The NCJTP survey is a nationally representative multilevel survey designed to assess substance abuse service provision, and organizational factors associated with service provision, in adult and juvenile justice systems throughout the U.S. The samples consisted of state correctional executives in the adult criminal and juvenile justice systems, and a sample of administrators of adult criminal and juvenile justice administrators who run local facilities and justice agencies. The correctional facilities are nested at the local level within jurisdictions, which served as our sampling unit. The final sample employed in this analysis consisted of 426 correctional facility administrators and 97 executive administrators of state-level agencies from 41 states. The correctional facilities consisted of 287 adult facilities (66.7%) and 139 juvenile facilities (33.3%). Overall, these included 176 community corrections facilities or offices (41.3%), 147 adult prisons or juvenile institutions (34.5%), and 103 local jails or detention facilities (24.2%). Results

indicate that states' overall rates of substance abuse and dependence, funding resources, and the state governor's political party affiliation were significantly associated with intensive treatment provision. Numerous factors that have been implicated in recent studies of evidence-based practice adoption, including state agency executives' views regarding rehabilitation, agency culture and climate, and other state-level measures (e.g., household income, crime rates, and expenditures on treatment for the general population) were not associated with treatment provision. Future research should examine further variations in offenders' service needs, the role of legislators' political affiliations, and how other factors may interact with administrator characteristics in the adoption and expansion of intensive treatment services for offenders. Young DW, Farrell JL, Henderson CE, Taxman FS. Filling service gaps: Providing intensive treatment services for offenders. Drug Alcohol Depend. 2009;103S:S33-S42.

Director Leadership Quality Important in Addiction Counselor Job Satisfaction

Five-hundred and fifty counseling staff and directors from 94 outpatient "drug-free" programs in six states were interviewed to assess job satisfaction, burnout, and the quality of director leadership. Composite measures of each of these constructs were derived and assessed using confirmatory factor analysis and Rasch modeling. Separate multivariate hierarchical linear models were used to estimate the effect of a variety of organizational and counselor factors on each of these composite measures and only a few variables were significantly related to these measures. Counselor burnout overall was relatively low among these programs (24.07 on a 1 to 50 scale) and was associated only with director leadership quality. Counselors in programs with higher average director leadership ratings had slightly lower burnout ratings (-0.33, $p < 0.05$). Job satisfaction, with a mean score of 40.28 on a 1 to 50 scale, was lower for counselors with a caseload of more than 30 clients (-1.59, $p < 0.05$), and higher among those in programs with higher director leadership ratings (0.53, $p < 0.01$) and those in programs that provided more than one level of treatment (1.77, $p < 0.05$). Director leadership measures, with a mean rating of 37.92 on a one to 50 scale, were lower in programs that operated under a parent organization than stand-alone programs (-2.19, $p < 0.05$). Broome K, Knight D, Edwards J, Flynn P. Leadership, burnout, and job satisfaction in outpatient drug-free treatment programs. J Subst Abuse Treat. 2009;37(2):160-170.

Obstacles to Retention in Outpatient Treatment: Program- and Individual-Level Factors from the Clients' Perspective

Attrition from treatment for substance abuse disorders is a persistent challenge that severely limits the effectiveness of services. Although a large body of research has sought to identify predictors of retention, the perspective of clients of services is rarely examined. This exploratory qualitative study presents clients' stated reasons for leaving outpatient treatment ($n = 135$) and their views of what could have been done differently to keep them engaged in services. Participants were 57.2% male, with an average age of 39 years; most were from ethnic minority groups (62% African American, and 36.1% reported being Hispanic); 73.7% reported government assistance as their primary income source. Obstacles to retention fell into program- and individual-level factors. Program-level barriers include dissatisfaction with the program, especially counselors; unmet social services needs; and lack of flexibility in scheduling. Individual-level barriers to retention were low problem recognition and substance use. Study limitations are noted, including the small sample size and recruitment of research subjects from only two treatment programs in one city. The implications of findings for research and practice are discussed, emphasizing the need to understand and address clients' needs and

expectations to maximize treatment retention and the likelihood of positive outcomes. Substance use disorder clients in clinical settings present an opportunity for engagement in the change process including enhancing motivation for change. Laudet A, Stanick V, Sands B. What could the program have done differently? A qualitative examination of reasons for leaving outpatient treatment. J Subst Abuse Treat. 2009;37(2):182-190.

Adaptive Interventions May Optimize Outcomes in Drug Courts: A Pilot Study

Adaptive interventions apply a priori decision rules for adjusting treatment services in response to participants' clinical presentation or performance in treatment. This pilot study (n = 30) experimentally examined an adaptive intervention in a misdemeanor drug court. The participants were primarily charged with possession of marijuana (73%) or possession of drug paraphernalia (23%). Results revealed that participants in the adaptive condition had higher graduation rates and required significantly less time to graduate from the program and achieve a final resolution of the case. It took an average of nearly 4 fewer months for participants in the adaptive intervention to resolve their cases compared with those participating in drug court as usual. Participants in the adaptive condition also reported equivalent satisfaction with the program and therapeutic alliances with their counselors. These data suggest that adaptive interventions may enhance the efficiency and effectiveness of drug courts and justify examining adaptive interventions in large-scale drug court studies. Marlowe DB, Festinger DS, Arabia PL, et al. Adaptive interventions may optimize outcomes in drug courts: A pilot study. Curr Psychiatry Rep. 2009;11:370-376.

Organizational Relationships Among Child Welfare Agencies and Treatment Access for Vulnerable Children

Inter-organizational relationships (IORs) between child welfare agencies and mental health service providers may facilitate mental health treatment access for vulnerable children. This study investigates whether IORs are associated with greater use of mental health services and improvement in mental health status for children served by the child welfare system. This was a longitudinal analysis of data from a 36-month period in the National Survey of Child and Adolescent Well-Being (NSCAW). The sample consisted of 1,613 children within 75 child welfare agencies who were 2 years or older and had mental health problems at baseline. IOR intensity was measured as the number of coordination approaches between each child welfare agency and mental health service providers. Separate weighted multilevel logistic regression models tested associations between IORs and service use and outcomes, respectively. Agency-level factors accounted for 9% of the variance in the probability of service use and 12% of mental health improvement. Greater intensity of IORs was associated with higher likelihood of both service use and mental health improvement. Having greater numbers of ties with mental health providers may help child welfare agencies improve children's mental health service access and outcomes. Bai, Y., Wells, R., Hillemeier, M. Coordination between child welfare agencies and mental health service providers, children's service use, and outcomes. Child Abuse Negl. 2009;33(6) 372-381.

Examination of an Interventionist-Led HIV Intervention Among Criminal Justice-Involved Female Prisoners

The purpose of this study was to examine the implementation, adherence and protocol fidelity for the Reducing Risky Relationships for HIV (RRR-HIV) study. The RRR-HIV study is a phase III trial of a randomized intervention to reduce human immunodeficiency virus (HIV) risk behaviors among incarcerated

women in four US states: Connecticut, Delaware, Kentucky and Rhode Island. The intervention consists of five interventionist-led prison-based group sessions and a sixth individual community-based session. Data on adherence, implementation, acceptability and fidelity of the intervention were obtained from forms completed after the five prison-based sessions by both the interventionist and participant. Data from the sixth session were collected by the interventionist. Of the 363 women recruited to date, 173 (47.6%) have been randomly allocated to the experimental RRR intervention, of which implementation measures were available for 162 (93.6%). Almost three-quarters of women attended all five sessions, each of which lasted a median of 90 minutes, indicating successful implementation of the protocol across multiple study sites. Interventionists and participants alike reported that all of the topics for each session were discussed, suggesting adherence to the protocol. In addition, protocol interventionists indicated that more than 95% of the women were engaged/involved, interested, and understood the materials presented, indicating high levels of acceptability among the participants and fidelity to the intervention protocols. The majority of participants also answered all of the post-test questions correctly, which is another strong indicator of the fidelity to the intervention. Results suggest that the RRR-HIV study has been successfully implemented across multiple study sites. Havens JR, Leukefeld CG, Oser CB, et al. Examination of an interventionist-led HIV intervention among criminal justice-involved female prisoners. J Experimental Criminology 2009; 5:245-272.

Collaborative Behavioral Management: Integration and Intensification of Parole and Outpatient Addiction Treatment Services in the Step'n Out Study

Integration of community parole and addiction treatment holds promise for optimizing the participation of drug-involved parolees in re-entry services, but intensification of services might yield greater rates of technical violations. Collaborative behavioral management (CBM) integrates the roles of parole officers and treatment counselors to provide role induction counseling, contract for pro-social behavior, and to deliver contingent reinforcement of behaviors consistent with contracted objectives. Attendance at both parole and addiction treatment are specifically reinforced. The Step'n Out study of the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) randomly allocated 486 drug-involved parolees to either collaborative behavioral management or traditional parole with 3-month and 9-month follow-up. Bi-variate and multivariate regression models found that, in the first 3 months, the CBM group had more parole sessions, face-to-face parole sessions, days on which parole and treatment occurred on the same day, treatment utilization and individual counseling, without an increase in parole violations. The authors conclude that CBM integrated parole and treatment as planned and intensified parolees' utilization of these services, without increasing violations. Friedmann PD, Rhodes AG, Taxman FS. Collaborative behavioral management: Integration and intensification of parole and outpatient addiction treatment services in the Step'n Out study. J Exp Criminology 2009;2009(5):227-243.

When Goals Diverge: Staff Consensus and the Organizational Climate

A sample of correctional officers and prison substance abuse treatment staff collected by the National Criminal Justice Treatment Practices Survey is used to provide an exploratory study of an aspect of organizational culture consisting of consensus (agreement) among prison personnel regarding their beliefs about rehabilitation in the presence of conflicting organizational goals and aspects of the organizational climate important to change. Findings show that among those staff members responding to the survey (n=274), the belief in rehabilitation scale mean score was associated with higher levels of

organizational commitment, and interdepartmental coordination. However, an hierarchical linear modeling (HLM) analysis that used an index score derived from the standard deviation for staff consensus regarding these same beliefs about rehabilitation produced a different pattern of results, showing that high levels of consensus were associated with job frustration, cynicism towards the ability of the institution to change, and lower levels of organizational commitment. The authors conclude that, although the sample may not express the beliefs of corrections officers or prison-based treatment staff at large, within the sample, consensus appeared to play a unique role in evaluating the effect of divergent goals on organizational climate as it relates to change, and warrants consideration when considering the effects of organizational climate. Melnick G, Ulaszek WR, Lin H, Wexler H K. When goals diverge: Staff consensus and the organizational climate. Drug Alcohol Depend. 2009;103S:S17-S22.

Competing Values Among Criminal Justice Administrators: The Importance of Substance Abuse Treatment

This study applied latent class analysis (LCA) to examine heterogeneity in criminal justice administrators' attitudes toward the importance of substance abuse treatment relative to other programs and services commonly offered in criminal justice settings. The study used data collected from wardens, probation and/or parole administrators, and other justice administrators as part of the National Criminal Justice Treatment Practices survey (NCJTP), and includes both adult criminal justice (n=302) and juvenile justice (n=141) samples. Results of the LCA suggested that administrators fell into four different latent classes: (1) those who place a high importance on substance abuse treatment relative to other programs and services, (2) those who place equal importance on substance abuse treatment and other programs and services, (3) those who value other programs and services moderately more than substance abuse treatment, and (4) those who value other programs and services much more than substance abuse treatment. Latent class membership was in turn associated with the extent to which evidence-based substance abuse treatment practices were being used in the facilities, the region of the country in which the administrator worked, and attitudes toward rehabilitating drug-using offenders. The findings have implications for future research focused on the impact that administrators' attitudes have on service provision as well as the effectiveness of knowledge dissemination and diffusion models. Henderson CE, Taxman FS. Competing values among criminal justice administrators: The importance of substance abuse treatment. Drug Alcohol Depend. 2009;103S;7-16.

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

Research Findings - CTN-Related Research

Methods of Recruiting Adolescents With Psychiatric and Substance Use Disorders For A Clinical Trial

The present article reports on recruiting strategies in a 16-week, multi-site trial of osmotic-release methylphenidate combined with cognitive-behavioral therapy in adolescents with co-occurring attention deficit hyperactivity disorder and substance use disorder. A multifaceted recruiting strategy was employed that targeted multiple referral sources, used incentives, involved numerous staff members, emphasized the therapeutic alliance during prescreening, and utilized data to modify strategies based on results. Overall, 303 adolescents were randomized from 1,333 total referrals across 11 participating sites. Overall, existing treatment program sources, including treatment program staff, social services, the juvenile justice system, and mental health clinics provided a majority of referrals for pre-screening and randomization. These results support the feasibility of recruiting dually-diagnosed adolescents utilizing a multifaceted approach involving the entire study team. Jaffee WB, Bailey GL, Lohman M, Riggs P, McDonald L, Weiss RD. The American Journal of Drug and Alcohol Abuse. 2009 Sept; 35(5):381-384.

Predictors of Condom Use Among Men Enrolled In Drug Treatment Programs

This study identified predictors of condom use and developed a model of condom use in a sample of men (n = 324) enrolled in drug treatment. Utilizing a series of logistic regression analyses, reported condom use was predicted by possession of condoms, future intention to use condoms, future intention to increase condom use, having a high-risk partner, low Condom Barriers Scale scores, being unmarried and ethnic minority status. A probit path analysis revealed that taking condoms from clinic stocks was the best predictor of condom possession, which in turn was the best predictor of condom use. These study findings identify condom availability in treatment programs as an important risk reduction intervention. Treatment programs can apply these predictors of condom use to better identify individuals at risk for HIV and sexually transmitted infections to better target prevention interventions. Song YS, Calsyn DA, Doyle SR, Dierst-Davies R, Chen T, Sorensen JL. AIDS Educ Prev. 2009 Oct;21(5):460-473.

A Multisite Randomized Effectiveness Trial of Motivational Enhancement Therapy For Spanish-Speaking Substance Users

Hispanic individuals are underrepresented in clinical and research populations and are often excluded from clinical trials in the United States. Hence, there

Planned Meetings

Publications

Staff Highlights

Grantee Honors

are few data on the effectiveness of most empirically validated therapies for Hispanic substance users. This multisite randomized trial compared the effectiveness of 3 individual sessions of motivational enhancement therapy with that of 3 individual sessions of counseling as usual on treatment retention and frequency of substance use; all assessment and treatment sessions were conducted in Spanish among 405 individuals seeking treatment for any type of current substance use. Sixty-six percent of participants completed all 3 protocol sessions. Although both interventions resulted in reductions in substance use during the 4-week therapy phase, there were no significant Treatment Condition X Time interactions nor Site X Treatment Condition interactions. Results suggest that the individual treatments delivered in Spanish were both attractive to and effective with this heterogeneous group of Hispanic adults, but the differential effectiveness of motivational enhancement therapy may be limited to those whose primary substance use problem is alcohol and may be fairly modest in magnitude. (PsycINFO Database Record (c) 2009 APA, all rights reserved). Carroll KM, Martino S, Ball SA, et al. J Consult Clin Psychol. 2009 Oct;77(5):993-999.

Methodological Innovation To Increase the Utility and Efficiency of Psychotherapy Research For Patients With Co-Occurring Mental Health and Substance Use Disorders

Psychotherapy research with chronic and difficult-to-treat populations, such as those with co-occurring mental health and addictive disorders, can employ flexible research designs, which allow for a systematic yet nonlinear relationship between efficacy and effectiveness designs. Outcomes research can bypass the efficacy-effectiveness dichotomy through use of a hybrid model conducted in the context of community treatment settings. This approach was used as a means of advancing psychotherapy research and practice, while translating and disseminating empirically supported treatments with more efficiency. The study entitled "Women's Treatment for Trauma and Substance Use Disorder" was conducted within the National Institute on Drug Abuse's Clinical Trials Network as. Hien DA, Cohen LR, Campbell AN. Professional Psychology: Research and Practice. 2009 Oct:40(5):502-509.

External Pressure, Motivation, and Treatment Outcome Among Pregnant Substance-Using Women

The weight of evidence suggests that legal pressure to enter treatment facilitates retention. However, the extent to which such mandates (a) influence actual levels of substance use, or (b) also facilitate retention among pregnant women, is unclear. Associations between external pressure-defined as self-reported pressure to attend treatment under threat of incarceration, loss of child custody, and/or loss of subsidized housing-and the key outcomes of retention and substance use were therefore examined in a sample of 200 pregnant women receiving community-based substance abuse treatment. The role of external pressure was examined in a series of Cox and GEE regressions, which suggested that external pressure as measured at baseline was associated with decreased risk of dropout (Hazard Ratio=.47, p=.001) and fewer drug-positive urine tests throughout treatment and 12-week follow-up (OR=.48, p=.03). These differences did not appear to be the result of baseline differences between coerced and non-coerced participants in education, legal history, the presence or absence of a substance use disorder, employment, or motivation. The present findings extend the larger literature on external pressure by demonstrating effects on drug use as well as on retention, and among pregnant women. Ondersma SJ, Winhusen T, Lewis DF. Drug Alc Depend. 2009 Nov 16. [Epub ahead of print].

Do Treatment Improvements In PTSD Severity Affect Substance

Use Outcomes? A Secondary Analysis From A Randomized Clinical Trial In NIDA's Clinical Trials Network

The purpose of the analysis was to examine the temporal course of improvement in symptoms of posttraumatic stress disorder (PTSD) and substance use disorder among women in outpatient substance abuse treatment. Three hundred and fifty three women were randomly assigned to 12 sessions of either trauma-focused or health education group treatment. PTSD and substance use assessments were conducted during treatment and posttreatment at 1 week and after 3, 6, and 12 months. Trauma-focused treatment was significantly more effective than health education in achieving substance use improvement among those who were heavy substance users at baseline and had achieved significant PTSD reductions. PTSD severity reductions were more likely to be associated with substance use improvement, with minimal evidence of substance use symptom reduction improving PTSD symptoms. Results support the self-medication model of coping with PTSD symptoms and an empirical basis for integrated interventions for improved substance use outcomes in patients with severe symptoms. Hien DA, Jiang H, Campbell AN, et al. Am J Psychiatry. 2009 Nov 16. [Epub ahead of print].

Relationship Power and Sexual Risk Among Women In Community-Based Substance Abuse Treatment

Relationship power has been highlighted as a major factor influencing women's safer sex practices. Little research has specifically examined relationship power in drug-involved women, a population with increased risk for HIV transmission. Using baseline data from a NIDA Clinical Trials Network multisite trial of a women's HIV prevention intervention in community-based drug treatment programs, this paper examined the association between sexual relationship power and unprotected vaginal or anal sex. The Sexual Relationship Power Scale, a measure of relationship control and decision-making dominance, was used to assess the association between power and unprotected sex in relationships with primary male partners. It was hypothesized that increased relationship power would be associated with decreased unprotected sexual occasions, after controlling for relevant empirical and theoretical covariates. Findings show a more complex picture of the association between power and sexual risk in this population, with a main effect in the hypothesized direction for decision-making dominance but not for relationship control. Campbell AN, Tross S, Dworkin SL, Hu MC, Manuel J, Pavlicova M, Nunes EV. J Urban Health. 2009 Nov 18. [Epub ahead of print].

Predictors Of Buprenorphine-Naloxone Dosing In A 12-Week Treatment Trial For Opioid-Dependent Youth: Secondary Analyses From A NIDA Clinical Trials Network Study

The present investigation examines baseline patient characteristics to predict dosing of buprenorphine-naloxone, a promising treatment for opioid addiction in youths. This study of 69 opioid-dependent youths is a secondary analysis of data collected during a NIDA Clinical Trials Network study. Outpatients aged 15-21 were randomized to a 12-week buprenorphine-naloxone dosing condition (including 4 weeks of taper). Predictors of dosing included sociodemographic characteristics (gender, race, age, and education), substance use (alcohol, cannabis, cocaine, and nicotine use), and clinical characteristics (pain and withdrawal severity). Most (75.4%) reported having either "some" (n=40, 58.0%) or "extreme" (n=12, 17.4%) pain on enrollment. Maximum daily dose of buprenorphine-naloxone (19.7 mg) received by patients reporting "extreme" pain at baseline was significantly higher than the dose received by patients reporting "some" pain (15.0 mg) and those without pain (12.8 mg). In the adjusted analysis, only severity of pain and withdrawal significantly predicted

dose. During the dosing period, there were no significant differences in opioid use, as measured by urinalysis, by level of pain. These data suggest that the presence of pain predicts buprenorphine-naloxone dose levels in opioid-dependent youth, and that patients with pain have comparable opioid use outcomes to those without pain, but require higher buprenorphine-naloxone doses. Chakrabarti A, Woody GE, Griffin ML, Subramaniam G, Weiss RD. Drug Alcohol Depend. 2009 Nov 28. [Epub ahead of print].

Reducing Sex Under the Influence Of Drugs Or Alcohol For Patients In Substance Abuse Treatment

The effectiveness of the Real Men Are Safe (REMAS) intervention in reducing the number of unprotected sexual occasions among male drug abuse treatment patients was previously reported. A secondary aim of REMAS was to reduce the frequency with which men engage in sex under the influence (SUI) of drugs or alcohol. Men in methadone maintenance (n = 173) or out-patient psychosocial treatment (n = 104) completed assessments at baseline, 3 and 6 months post-intervention. The participants were assigned randomly to either REMAS (five sessions containing information, motivational exercises and skills training, including one session targeting reducing SUI) or HIV education (HIV-Ed; one session containing HIV prevention information). SUI during the most recent sexual event served as the primary outcome. Men assigned to REMAS reporting SUI at the most recent sexual event decreased from 36.8% at baseline to 25.7% at 3 months compared to an increase from 36.9% to 38.3% in the HIV-Ed condition (tintervention = -2.16, P = 0.032). No difference between the treatment groups was evident at 6-month follow-up. At each assessment time-point, sex with a casual partner versus a regular partner, and being in methadone maintenance versus psychosocial out-patient treatment, were associated with engaging in SUI. Overall, a motivational and skills training HIV prevention intervention designed for men was associated with greater reduction in SUI than standard HIV education at the 3-month follow-up. Calsyn DA, Crits-Christoph P, Hatch-Maillette MA, Doyle SR, Song YS, Coyer S, Pelta S. Addiction. 2010; 105(1):100-108.

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

Research Findings - International Research

INVEST Fellow: Anton Bespalov, Russia, 1994-1995
Marek GJ, Behl B, Bespalov AY, et al.
Glutamatergic (N-Methyl-D-Aspartate Receptor) Hypofrontality In Schizophrenia: Too Little Juice Or A Miswired Brain *Molecular Pharmacology.* 2009 Nov 23. [Epub ahead of print]

Dopamine D2 receptor blockade has been an obligate mechanism of action present in all medications which effectively treat positive symptoms of schizophrenia (e.g,, delusions and hallucinations) and have been approved by regulatory agencies since the 1950's. Blockade of 5-hydroxytrypatmine(2A) (5-HT(2A)) receptors plays a contributory role in the actions of the second generation of antipsychotic drugs, the so-called atypical antipsychotics. Nevertheless, substantial unmet medical needs remain for the treatment of negative symptoms and cognitive dysfunction. Recognition that dissociative anesthetics block the N-methyl-D-aspartate (NMDA) receptor channel has inspired a search for glutamatergic therapeutic mechanisms since ketamine and phencyclidine are known to induce psychotic-like symptoms in healthy volunteers and exacerabate the symptoms of schizophrenic patients. Current pathophysiological theories of schizophrenia emphasize that hypofunction of NMDA receptors in critical sites in local circuits modulate the function of a given brain region or control projections from one region to another (e.g., hippocampal-cortical or thalamocortical projections). The demonstration that a metabotropic glutamate2/3 (mGlu2/3) receptor agonist prodrug decreased both positive and negative symptoms of schizophrenia raised hopes that glutamatergic mechanisms may provide therapeutic advantages. In addition to discussing activation of mGlu2 receptors with mGlu2/3 receptor agonists or mGlu2 receptor positive allosteric modulators (PAMs), the authors also discuss other methods that may potentially modulate circuits with hypofunctional NMDA receptors such as glycine transporter (GlyT1) inhibitors and mGlu5 receptor PAMs. The hope is that by modulating glutamatergic neurotransmission, the dysfunctional circuitry of the schizophrenic brain (both local circuits and long-loop pathways) will be improved.

INVEST-CTN Fellow: Amit Chakrabarti, India, 2007-2008; HHH, 2002-2003
Mailankot M, Jayalekshmi H, Chakrabarti A, et al.
Effect of Alpha-Tocopherol Supplementation On Renal Oxidative Stress And Na+/K+ -Adenosine Triphosphatase In Ethanol Treated Wistar Rats *Indian Journal of Experimental Biology.* 2009 Jul;47(7):608-610.

Ethanol intoxication resulted in high extent of lipid peroxidation, and reduction in antioxidant defenses (decreased GSH, GSH/GSSG ratio, and catalase, SOD and GPx activities) and (Na+/K+)-ATPase activity in kidney. Alpha-tocopherol treatment effectively protected kidney from ethanol induced oxidative

challenge and improved renal (Na+/K+)-ATPase activity. Ethanol induced oxidative stress in the kidney and decreased (Na+/K+)-ATPase activity could be reversed by treatment with ascorbic acid.
PMID: 19761047 [PubMed - in process]

HHH Fellow: Artur de Andrade, Brazil, 1991-1992
Alexandrino-Silva C, Pereira ML, Bustamante C, et al.
Suicidal Ideation Among Students Enrolled In Healthcare Training Programs: A Cross-Sectional Study. *Revista Brasileira de Psiquiatria.* 2009 Oct 16. pii: [Epub ahead of print]

This study aimed to assess the presence of suicidal ideation, depressive symptoms and symptoms of hopelessness in three healthcare training programs. The study's population comprised all students enrolled at the Medical School of the Funda ‹o do ABC, Brazil, from 2006 to 2007 compared to students enrolled in nursing and pharmacy programs. We applied the Beck Scale for Suicidal Ideation, the Beck Depression Inventory and the Beck Hopeless Scale to assess psychiatric symptomatology. The general response rates of the medical, nursing, and pharmacy students were 56%, 56% and 61%, respectively. There was no difference regarding the presence of suicidal ideation among medical, nursing and pharmacy students. There was also no difference regarding the presence of either depression or hopelessness in medical students in comparison to nursing and pharmacy students. In comparison to nursing and pharmacy students, significantly higher severity rates in terms of hopelessness were observed only among medical students. Although the authors did not observe significant differences regarding suicidal ideation and depression among the three healthcare programs, these findings suggest that the presence of suicidal ideation is indeed a source of concern. Early identification of these symptoms is crucial in order to offer appropriate support and treatment and prevent deaths by suicide.
PMID: 19838592 [PubMed - as supplied by publisher]

HHH Fellow: Sergey Dvoryak, Ukraine, 1999-2000
Booth RE, Lehman WE, Dvoryak S, et al.
Interventions With Injection Drug Users In Ukraine. *Addiction*. 2009 Aug 4. [Epub ahead of print]

The aim of the study was to assess the effectiveness of a brief human immunodeficiency virus (HIV) testing and counseling intervention compared to a more time-consuming and expensive street-based intervention with injection drug users (IDUs). Design Cross-over experimental design in which 900 IDUs were recruited, followed by a 'wash-out' period with no recruitment, a reversal of intervention assignment areas and an additional recruitment of 900 IDUs with baseline and 6-month follow-up assessments. Setting Kiev, Odessa and Makeevka/Donesk Ukraine. Participants A total of 1798 IDUs. Measurements HIV testing and audio computer-assisted self-interview (ACASI) data on socio-demographics, drug use and injection and sex-related risk behaviors. Participants in both conditions reduced their injection and sex risks significantly; however, there was little difference in outcomes between conditions. IDUs who knew they were HIV-infected at baseline were significantly more likely to practice safe sex than those unaware or HIV-negative; those who first learned that they were infected at baseline changed their safe sex practices significantly more than those who already knew that they were infected at baseline and those who were HIV-negative. Younger IDUs and those injecting for a shorter period of time reported higher injection and sex risk behaviors following interventions. Conclusions Awareness of HIV infection by street-recruited drug injectors is associated with reduced sex risks. Additional interventions are required for younger IDUs and those injecting for shorter periods of time.

HHH Fellow: Alisher Latypov, Tajikistan, 2002-2003
Beyrer C, Patel Z, Stachowiak JA, et al.

Planned Meetings

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Characterization of the Emerging HIV Type 1 and HCV Epidemics among Injecting Drug Users in Dushanbe, Tajikistan. *AIDS Research and Human Retroviruses.* 2009 Aug 18. [Epub ahead of print]

Abstract: This study aimed to determine HIV, HCV, and syphilis prevalence and correlates, and to characterize the molecular epidemiology of HIV-1 among injecting drug users (IDUs) in Dushanbe, Tajikistan. A cross-sectional study assessing risk factors for HIV and HCV through an interview administered survey was conducted. A total of 491 active adult IDUs were recruited from May to November 2004 in Dushanbe, Tajikistan. HIV-1 antibody status was determined with rapid testing and confirmed with ELISA. HCV antibody testing was conducted using a BIOELISA HCV kit. HIV-1 subtyping was done on a subset with full-length sequencing. Correlates of HIV and HCV infection were assessed using logistic regression. Overall prevalence of HIV was 12.1%, HCV was 61.3%, and syphilis was 15.7%. In a multivariate logistic regression model controlling for gender and ethnicity, daily injection of narcotics [odds ratio (OR) OR 3.22] and Tajik nationality (OR 7.06) were significantly associated with HIV status. Tajik nationality (OR 1.91), history of arrest (OR 2.37), living/working outside Tajikistan in the past 10 years (OR 2.43), and daily injection of narcotics (OR 3.26) were significantly associated with HCV infection whereas being female (OR 0.53) and always using a sterile needle (OR 0.47) were inversely associated with HCV infection. Among 20 HIV-1-positive IDU with specimens available for typing, 10 were subtype A, 9 were CRF02_AG, and one was an A-CRF02_AG recombinant. Epidemics of HIV-1, HCV, and drug use are underway in Dushanbe. The molecular epidemiology is distinctive, with West African variants accounting for roughly 50% of prevalent infections. Targeted prevention programs offering both needle exchange programs and opiate substitution therapies are urgently called for to prevent the further spread of HIV and HCV in Tajikistan.

HHH Fellow: Isidore Obot, Nigeria, 1991-1992
Benegal V, Chand PK, Obot IS.
Packages of Care For Alcohol Use Disorders In Low- and Middle-Income Countries *PLoS Medicine.* 2009 Oct;6(10):e1000170. Epub 2009 Oct 27.

In the fourth in a series of six articles on packages of care for mental disorders in low- and middle-income countries, Vivek Benegal and colleagues discuss the treatment of alcohol use disorders. PMID: 19859536 [PubMed - in process]

HHH Fellow: Flavio Pechansky, Brazil, 1993-1994
von Diemen L, De Boni R, Kessler F, et al.
Risk Behaviors For HCV- and HIV-Seroprevalence Among Female Crack Users In Porto Alegre, Brazil. *Archives of Women's Mental Health.* 2009 Sep 16. [Epub ahead of print]

Several studies have shown a high prevalence of HIV-seropositive status among crack users, though most refer to North American populations. Few studies evaluate HCV prevalence among female crack users. In addition, there is a particular lack of data about risk behaviors and HIV/HCV prevalence in this population around the world. In order to ascertain the HIV/HCV serostatus and associated risk behaviors for infection of female crack users of Porto Alegre, Brazil. A cross-sectional study of a convenience sample of 73 current female crack users was conducted. Subjects answered NIDA's Risk Behavior Assessment and an AIDS Information Questionnaire. In addition, blood was collected from subjects for HIV/HCV tests. The overall prevalence of HIV was 37.0%; HCV seroprevalence was 27.7%; of 15.1% the sample was co-infected with HIV and HCV. Four years of schooling or fewer (OR 4.72-CI 95%; 1.49-14.99) and having three or more HIV tests in one's lifetime (OR 4.26-CI 95% (1.29-14.04)) were associated with HIV infection (after multivariate logistic regression). The single greatest risk factor for HCV infection was having 4 years of schooling or fewer (OR 4.51-CI 95%; 1.18-17.27). We found a very

high prevalence of HIV and HCV infection among female crack users, and low education was the most significant risk factor associated with both infections.
PMID: 19760050 [PubMed - as supplied by publisher]

HHH Fellow: Vladimir Stempliuk, Brazil, 2003-2004
Oliveira LG, Barroso LP, Wagner GA, et al.
Drug Consumption Among Medical Students In S‹o Paulo, Brazil: Influences Of Gender and Academic Year. *Revista Brasileira de Psiquiatria.* 2009 Sep;31(3):227-239.

The objective of the study was to analyze alcohol, tobacco and other drug use among medical students. Over a five-year period (1996-2001), the authors evaluated 457 students at the Universidade de S‹o Paulo School of Medicine, located in S‹o Paulo, Brazil. The students participated by filling out an anonymous questionnaire on drug use (lifetime, previous 12 months and previous 30 days). The influence that gender and academic year have on drug use was also analyzed. During the study period, there was an increase in the use of illicit drugs, especially inhalants and amphetamines, among the medical students evaluated. Drug use (except that of marijuana and inhalants) was comparable between the genders, and academic year was an important influencing factor. Increased inhalant use was observed among the medical students, especially among males and students in the early undergraduate years. This is suggestive of a specific behavioral pattern among medical students. These findings corroborate those of previous studies. The authors conclude that inhalant use is on the rise among medical students at the Universidade de S‹o Paulo School of Medicine. Because of the negative health effects of illicit drug use, further studies are needed in order to deepen the understanding of this phenomenon and to facilitate the development of preventive measures.
PMID: 19784490 [PubMed - in process]

HHH Fellow: Olga Toussova, Russia, 2001-2002
Kruse GR, Barbour R, Heimer R, et al.
Drug Choice, Spatial Distribution, HIV Risk, And HIV Prevalence Among Injection Drug Users In St. Petersburg, Russia *Harm Reduction Journal*. 2009 Jul 31;6:22.

The HIV epidemic in Russia has been driven by the unsafe injection of drugs, predominantly heroin and the ephedrine derived psychostimulants. Understanding differences in HIV risk behaviors among injectors associated with different substances has important implications for prevention programs. The authors examined behaviors associated with HIV risk among 900 IDUs who inject heroin, psychostimulants, or multiple substances in 2002. Study participants completed screening questionnaires that provided data on sociodemographics, drug use, place of residence and injection- and sex-related HIV risk behaviors. HIV testing was performed and prevalence was modeled using general estimating equation (GEE) analysis. Individuals were clustered by neighborhood and disaggregated into three drug use categories: Heroin Only Users, Stimulant Only Users, and Mixed Drug Users. Among Heroin Only Users, younger age, front/backloading of syringes, sharing cotton and cookers were all significant predictors of HIV infection. In contrast, sharing needles and rinse water were significant among the Stimulant Only Users. The Mixed Drug Use group was similar to the Heroin Only Users with age, front/back loading, and sharing cotton significantly associated with HIV infection. These differences became apparent only when neighborhood of residence was included in models run using GEE. The type of drug injected was associated with distinct behavioral risks. Risks specific to Stimulant Only Users appeared related to direct syringe sharing. The risks specific to the other two groups are common to the process of sharing drugs in preparation to injecting. Across the board, IDUs could profit from prevention education that emphasizes both access to clean syringes and preparing and apportioning drug with these clean syringes.

However, attention to neighborhood differences might improve the intervention impact for injectors who favor different drugs.

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

Kaymak SU, Demir B, SentŸrk S, et al.
Neurocognitive Functions In Patients With First-Episode Major Depressive Disorders. *European Archives of Psychiatry and Clinical Neuroscience.* 2009 Sep 12. [Epub ahead of print]

The aim of this study was to determine whether there was any relationship between hippocampal volume, and glucocorticoid regulation, and cognitive dysfunctions in drug-na•ve major depressive disorder (MDD) patients during their first episode. Twenty drug-free female MDD patients in their first episode and 15 healthy females as control subjects were included in the study. All subjects underwent 3.0 Tesla (T) magnetic resonance imaging (MRI), comprehensive neuropsychological testing and dexamethasone suppression tests (DST). The volumes of the right and left hippocampus of the patients were found to be significantly smaller than those of the controls. Patients were found to have significantly lower scores on measures of attention, working memory, psychomotor speed, executive functions, and visual and verbal memory fields. The performance of the patients only in the recollection memory and memory of reward-associated rules were positively correlated with hippocampal volumes. The volumes of the left and right hippocampus did not correlate with basal or post-dexamethasone cortisol levels. Our findings indicate that depressed patients have smaller hippocampi even in the earlier phase of their illness. Further research efforts are needed to explain the mechanisms that are responsible for the small hippocampus in depressed patients.
PMID: 19756819 [PubMed - as supplied by publisher]

Ertugrul A, Volkan-Salanci B, Basar K, et al.
The Effect Of Clozapine On Regional Cerebral Blood Flow And Brain Metabolite Ratios In Schizophrenia: Relationship With Treatment Response. *Psychiatry Research.* 2009 Nov 30;174(2):121-9. Epub 2009 Oct 17.

The purpose of this study was to investigate the effect of clozapine on regional cerebral blood flow (rCBF) and its relationship with response to treatment. In addition, the authors aimed to study the influence of clozapine on proton magnetic resonance spectroscopy ((1)H-MRS) findings in the dorsolateral prefrontal cortex (DLPFC) in a subgroup of patients. Psychopathology, neurocognitive functioning, and SPECT imaging of 22 patients were assessed at the baseline and 8 weeks after the initiation of clozapine treatment. In 10 of these patients intermediate-echo (TE: 135 ms) single-voxel (1)H-MRS was also performed at the baseline and after 8 weeks. Clozapine treatment increased the right frontal (superior and medial)/caudate perfusion ratio in the whole group, while it increased bilateral frontal (superior and medial)/caudate perfusion ratios in treatment responders. In addition, percentage changes in left and right frontal (superior and medial)/caudate perfusion ratios compared to the baseline were higher in treatment responders than in non-responders. The improvement in attention was related to the increase in percentage change in the right frontal (superior and medial)/caudate perfusion ratio, while the improvement in verbal fluency was related to the increase in percentage changes in both right and left frontal (superior and medial)/caudate perfusion ratios and to right frontal (superior and medial)/thalamus perfusion. Baseline frontal (superior and medial)/thalamus perfusion could explain 32% of the variability of percentage improvements in psychopathology. (1)H-MRS showed that the baseline PANSS general psychopathology score was inversely correlated with the baseline NAA/Cre ratio. An increased NAA/Cre ratio in DLPFC after 8 weeks of clozapine treatment was also revealed by (1)H-MRS. Our SPECT imaging results suggest the presence of an imbalance in fronto-

striato-thalamic circuitry that changes with clozapine, especially in the responders, while (1)H-MRS results indicate a supportive effect of clozapine on neuronal integrity.
PMID: 19837567 [PubMed - in process]

HHH Fellows:

- ***Tomas Zabransky, Czech Republic, 2003-2004***
- ***David Otiashvili, Georgia, 2003-2004***

Otiashvili D, Zabransky T, Kirtadze I, et al.
Why Do the Clients of Georgian Needle Exchange Programmes Inject Buprenorphine? *European Addiction Research.* 2009 Nov 2;16(1):1-8. [Epub ahead of print]

The aim of the study was to understand the prevalence and patterns of the non-medical injecting use of buprenorphine among drug injectors in Georgia. A self-administered questionnaire was distributed among injecting drug users enrolled in Georgian needle exchange programmes. The questions covered topics related to drug use career, patterns (frequency, history, dosage) and reasons for the use of buprenorphine. Pharmaceutical buprenorphine in the form of Subutex(R) was the most commonly injected drug in terms of lifetime (95.5%) and last-month (75%) prevalence of use. 48% of those study participants who had injected Subutex at some point reported having used it to cope with withdrawal or to give up other opioids. 90.5% of Subutex injectors used 1-2 mg as a single dose, and the mean frequency of its injection was 6 times per month. 75% of Subutex injectors had used 3 or more types of illegal drugs during the last 30 days. While widely misused by Georgian drug injectors, Subutex is neither the principal nor the favourite drug, and it is rather used as self-treatment. The authors consider the introduction of buprenorphine maintenance treatment to be a promising effective measure to decrease its non-medical and illegal use.

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Research Findings - Intramural Research

Biomedical Informatics Section, Administrative Management Branch

A Usability Study of Transactional Electronic Diary: Results From Expert Evaluation To Participants Use
This usability study suggests that the Transactional Electronic Diary can be efficiently used by polydrug abusing individuals to record their behaviors and moods in real time in their day-to-day environments. Lin JL, Vahabzadeh M, Mezghanni M, Epstein DH, Preston KL. A usability study of transactional electronic diary: results from expert evaluation to participants use. AMIA Annu Symp Proc. 2009: 937.

Clinical Pharmacology and Therapeutics

Cocaine Craving and Use During Daily Life
Craving is often assumed to cause ongoing drug use and relapse, but its relationship to drug use in daily life has not been documented in a rigorous, prospective manner. In a prospective, longitudinal, cohort design, 112 cocaine-abusing individuals on methadone maintenance rated their craving and mood at random times (two to five times daily prompted by electronic diaries) as they went about their everyday activities. They also initiated an electronic-diary entry each time they used cocaine. Cocaine use was further monitored by thrice-weekly urine testing. The authors found that during periods of urine-verified cocaine use, ratings of cocaine craving increased across the day and were higher than during periods of urine-verified abstinence. During the 5 hours prior to individual episodes of cocaine use, ratings of craving significantly increased. These patterns were not seen in ratings of heroin craving or mood. Thus, at both weekly and hourly time scales, cocaine craving is tightly coupled to cocaine use in users' normal environments. These findings provide previously unavailable support for a relationship that has been seriously questioned in some theoretical accounts. Preston KL, Vahabzadeh, M, Schmittner J, et al. Psychopharmacology 2009;207:291-301.

Office of the Scientific Director

Signal-Averaged Electrocardiogram In Physically Healthy, Recently Abstinent Chronic Cocaine Users
Cocaine use is associated with cardiac arrhythmias, but predicting who is at risk is difficult. Signal-averaged electrocardiography (SA-ECG), unlike standard ECG, can detect markers of ventricular late potentials (VLP), which may be a precursor to malignant ventricular arrhythmias. IRP scientists evaluated SA-ECG parameters in 60 medically screened, physically healthy, recently abstinent, chronic cocaine users and in 54 non-drug-using controls. SA-ECGs

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were done periodically for up to 12 weeks of monitored abstinence in 25 of the cocaine users. Cocaine users differed significantly from controls in only one of three SA-ECG parameters considered markers of VLPs. The proportion of subjects with abnormal SA-ECG parameters did not differ significantly between male cocaine users and male controls. There were no significant changes over time in either the mean values or proportion of subjects with abnormal values for any SA-ECG parameter. There were significant gender differences among controls, but not among cocaine users. These findings suggest that chronic cocaine use is not associated with a higher prevalence of abnormal SA-ECG parameters in physically healthy users. Kanneganti P, Copersino ML, Nelson RA, et al. Signal-averaged electrocardiogram in physically healthy, recently abstinent chronic cocaine users. Journal of Addiction Medicine. 2009;3(3):128-133.

Interest In Marijuana Treatment Programs Among Teenage Smokers and Nonsmokers

Many adolescents smoke marijuana, but little is known about adolescents' interest in marijuana treatment programs. IRP scientists evaluated this question by telephone interview in a convenience sample of 575 adolescents (13-17 years old) responding to advertisements for tobacco research studies at the NIDA IRP. 81% of respondents endorsed the need for marijuana treatment programs for adolescents. These adolescents were younger and less likely to smoke tobacco, smoke marijuana, or use alcohol than those not endorsing such a need. Among the 192 marijuana smokers, the 58.8% who endorsed the need for marijuana treatment programs took their first puff of marijuana at a younger age than those who did not endorse the need. Those who were willing to participate in a marijuana treatment program were more likely African-American and took their first marijuana puff at a younger age than those not interested in treatment. These findings suggest that a majority of adolescent marijuana smokers endorse the need for and are willing to attend marijuana treatment programs. Sheer AJ, Gorelick DA, Collins CC, et al. Interest in marijuana treatment programs among teenage smokers and nonsmokers. Journal of Substance Abuse Treatment. 2009; 37(4):421-425.

Behavioral Neuroscience Research Branch

A Ventral Tegmental CRF-Glutamate-Dopamine Interaction In Addiction

Stress-induced reinstatement of cocaine-seeking is blocked by antagonists for the stress-related neurohormone corticotropin-releasing factor (CRF). One site of this action is the ventral tegmental area (VTA), where mild footshock stress causes CRF release, glutamate release, and dopaminergic activation in cocaine-experienced but not cocaine-naive animals. Infusion of CRF into VTA has similar effects to footshock in cocaine-experienced animals but fails to cause significant VTA glutamate release or dopaminergic activation in cocaine-naive animals. The reinstatement, glutamate release, and dopamine release are prevented by VTA infusions of CRF-receptor 2 (CRF-R2) but not CRF-R1 antagonists. Reinstatement is triggered by some but not all CRF-R2 agonists and some but not all CRF-R1 agonists; the common denominator of the effective agonists is that they bind to the CRF-binding protein (CRF-BP), which appears to be essential for the behavioral and VTA effects of stress and CRF in cocaine-experienced animals. In situ hybridization reveals mRNA for CRF-R1 and CRF-BP but not CRF-R2 in a subset of VTA dopamine neurons. Electron microscopy reveals primarily asymmetric synapses between a subset of VTA terminals containing glutamate and CRF and a subset of VTA dopaminergic neurons and primarily symmetric synapses between a subset of CRF terminals that do not contain glutamate and a subset of GABAergic neurons in VTA. Thus, a complex and not yet fully understood interaction of CRF, glutamate, and the mesocorticolimbic dopamine system is established by experience with cocaine, and this alteration appears to contribute importantly to the transition from

casual to compulsive cocaine-seeking. Wise RA, Morales M. A ventral tegmental CRF-glutamate-dopamine interaction in addiction. Brain Res. 2009 [Epub ahead of print]

Roles For Nigrostriatal--Not Just Mesocorticolimbic--Dopamine In Reward and Addiction

Forebrain dopamine circuitry has traditionally been studied by two largely independent specialist groups: students of Parkinson's disease who study the nigrostriatal dopamine system that originates in the substantia nigra (SN), and students of motivation and addiction who study the role of the mesolimbic and mesocortical dopamine systems that originate in the ventral tegmental area (VTA). The anatomical evidence for independent nigrostriatal and mesolimbic dopamine systems has, however, long been obsolete. There is now compelling evidence that both nominal "systems" participate in reward function and addiction. Electrical stimulation of both SN and VTA is rewarding, blockade of glutamatergic or cholinergic input to either SN or VTA attenuates the habit-forming effects of intravenous cocaine, and dopamine in both nigrostriatal and mesocorticolimbic terminal fields participates in the defining property of rewarding events: the reinforcement of memory consolidation. Thus the similarities between nigrostriatal and mesolimbic dopamine systems can be as important as their differences. Wise RA. Roles for nigrostriatal--not just mesocorticolimbic--dopamine in reward and addiction. Trends Neurosci. 2009; 32(10):517-524.

Control of Within-Binge Cocaine-Seeking By Dopamine and Glutamate In the Core of Nucleus Accumbens

Dopamine and glutamate are thought to interact in the ventral striatum and to play important roles there in the cocaine-seeking of cocaine-experienced animals. IRP scientists sought to determine the relative roles of the two transmitters in the two major zones of the nucleus accumbens (NAS), the core and shell subregions. They assessed the effects of dopamine and glutamate receptor blockade in the core and shell on intravenous cocaine self-administration in rats. Trained animals were allowed to self-administer cocaine for an initial hour, and then D1-type or D2-type dopamine receptor blockers or NMDA-type or AMPA-type glutamate receptor blockers were infused by reverse microdialysis into one of the two regions for an additional 3 h of testing. The D1-type antagonist SCH23390 and the D2-type antagonist raclopride each increased cocaine intake whereas the AMPA-type antagonist CNQX decreased responding when infused into the core. SCH23390 increased cocaine intake less strongly when infused into the shell, while raclopride and CNQX were each ineffective when infused into the shell. The NMDA-antagonist CPP failed to affect cocaine self-administration when infused into either site. These findings implicate the core of NAS in the maintenance of established cocaine self-administration in trained animals, despite the fact that the reinforcement of responding in untrained animals appears to results from cocaine actions in the olfactory tubercle and medial shell and not the core of accumbens. Suto N, Ecke LE, Wise RA. Control of within-binge cocaine-seeking by dopamine and glutamate in the core of nucleus accumbens. Psychopharmacology (Berl). 2009;205(3):431-439.

Reinstatement Of Cocaine Seeking By Hypocretin (Orexin) in the Ventral Tegmental Area: Independence From the Local Corticotropin-Releasing Factor Network

Hypocretin (Hcrt), an arousal- and feeding-associated peptide, is expressed in lateral hypothalamic neurons that project to the rewardÑassociated dopaminergic neurons of the ventral tegmental area (VTA). Intra-VTA Hcrt reinstates morphine-conditioned place preferences, and intracerebroventricular and intra-VTA corticotropin-releasing factor (CRF) reinstate cocaine seeking. Each is presumed to act, at least in part, through actions local to the VTA. Here, IRP investigators examined the possibility that VTA perfusion of Hcrt reinstates cocaine seeking and, if so, whether it does so through the VTA

mechanism that is implicated in reinstatement by CRF. Rats were trained to lever-press for intravenous cocaine (2 weeks) and then underwent extinction training (saline substituted for cocaine: 3 weeks). Reinstatement behavior was tested and VTA dialysates were collected and assayed for glutamate or dopamine following footshock or perfusion of Hcrt or CRF, with or without Hcrt or CRF antagonists, into the VTA. Ventral tegmental area perfusion of Hcrt-1 or footshock stress reinstated cocaine seeking and caused release of VTA glutamate and dopamine. The effects of Hcrt-1 were blocked by a selective Hcrt-1 antagonist, but not a CRF antagonist, and were not mimicked by Hcrt-2. The Hcrt-1 antagonist did not block CRF-dependent footshock-induced reinstatement or glutamate or dopamine release. The behavioral and neurochemical effects of Hcrt-1 were attenuated but not blocked by kynurenic acid, an ionotropic glutamate antagonist that blocks footshock-induced reinstatement and glutamate release. While Hcrt and CRF are known to interact in some area of the brain, in the VTA proper they appear to have largely independent actions on the mesolimbic dopamine mechanisms of cocaine seeking. Wang B, You ZB, Wise RA. Reinstatement of cocaine seeking by hypocretin (orexin) in the ventral tegmental area: independence from the local corticotropin-releasing factor network. Biol Psychiatry. 2009 15;65(10):857-862.

Rapid EEG Desynchronization and EMG Activation Induced By Intravenous Cocaine In Freely Moving Rats: A Peripheral, Non-Dopamine Neural Triggering

Many important physiological, behavioral and psychoemotional effects of intravenous (iv) cocaine (COC) are too fast and transient when compared to pharmacokinetic predictions, suggesting a possible involvement of peripheral neural mechanisms in their triggering. In the present study, IRP researchers examined changes in cortical electroencephalogram (EEG) and neck electromyogram (EMG) induced in freely moving rats by iv COC administration at low, reinforcing doses (0.25-1.0 mg/kg) and compared them with those induced by an auditory stimulus and iv COC methiodide which cannot cross the blood-brain barrier. The authors found that COC induces rapid, strong, and prolonged EEG desynchronization, associated with decrease in alpha and increase in beta and gamma activities, and EMG activation that both begin within 2-6 s following the start of a 10-s injection; immediate components of this effect were dose-independent. The rapid COC-induced changes in EEG and EMG resembled those induced by an auditory stimulus; the latter effects had shorter onset latencies and durations and were fully blocked during urethane anesthesia. Although urethane anesthesia completely blocked COC-induced EMG activation and rapid components of EEG response, COC still induced EEG desynchronization that was much weaker, greatly delayed (~60 s), and associated with tonic decreases in delta and increases in alpha, beta and gamma activities. Peripherally acting COC methiodide fully mimicked rapid EEG and EMG effects of regular COC, but the effects at an equimolar dose were less prolonged than those with regular COC. These data suggest that in awake animals iv COC, like somato-sensory stimuli, induces cortical activation and a subsequent motor response via its action on peripheral neural elements and involving rapid neural transmission. By providing a rapid neural signal and triggering transient neural activation, such an action might play a crucial role in the sensory effects of COC, thus contributing to the learning and development of drug-taking behavior. Kiyatkin EA, Smirnov MS. Rapid EEG desynchronization and EMG activation induced by intravenous cocaine in freely moving rats: a peripheral, non-dopamine neural triggering. Am J Physiol Regul Integr Comp Physiol. 2009 [Epub ahead of print]

Phasic and Tonic Fluctuations In Brain, Muscle, and Skin Temperatures During Motivated Drinking Behavior In Rats: Physiological Correlates of Motivation and Reward

Since brain metabolism is accompanied by heat production, measurement of brain temperature offers a method for assessing global alterations in metabolic

neural activity. This approach, high-resolution (5-s bin) temperature recording from the nucleus accumbens (NAcc), temporal muscle, and facial skin, was used to study motivated drinking behavior in rats. Experienced animals were presented with a cup containing 5-ml of Coca-Cola(R) (Coke) beverage that resulted, within certain latencies, in initiation of a continuous chain of licking until all liquid was fully consumed. While cup presentation induced rapid, gradual NAcc temperature increase peaking at the start of drinking, temperatures slowly decreased during Coke consumption, but phasically increased again in the post-consumption period when rats were hyperactive, showing multiple interactions with an empty cup. Muscle temperatures followed a similar pattern, but the changes were weaker and delayed compared to those in the brain. Skin temperature rapidly dropped after cup presentation, steadily maintained at low levels during consumption, and slowly restored during the post-consumption period. Substitution of the expected Coke with either sugar-free Diet Coke(R) or water resulted in numerous drinking attempts but ultimately no consumption. During these tests, locomotor activation was much greater and more prolonged, brain and muscle temperatures increased monophasically, and their elevation was significantly greater than that with regular Coke tests. Food deprivation decreased drinking latencies, did not change the pattern of temperature fluctuations during Coke consumption, but temperature elevations were greater than in controls. These data suggest sustained neural activation triggered by appetitive stimuli and associated with activational (seeking) aspects of appetitive motivated behavior. This seeking-related activation is rapidly ceased following consumption, suggesting this change as a neural correlate of reward. In contrast, inability to obtain an expected reward maintains neural activation and seeking behavior, resulting in larger deviations in physiological parameters. Smirnov MS, Kiyatkin EA. Phasic and tonic fluctuations in brain, muscle, and skin temperatures during motivated drinking behavior in rats: Physiological correlates of motivation and reward. Brain Res. 2009 Nov 22. [Epub ahead of print]

Acute Methamphetamine Intoxication Brain Hyperthermia, Blood-Brain Barrier, Brain Edema, and Morphological Cell Abnormalities

Methamphetamine (METH) is a powerful and often abused stimulant with potent addictive and neurotoxic properties. While it is generally assumed that multiple chemical substances released in the brain following METH-induced metabolic activation (or oxidative stress) are primary factors underlying damage of neural cells, in this work IRP researchers present data suggesting a role of brain hyperthermia and associated leakage of the blood-brain barrier (BBB) in acute METH-induced toxicity. First, they show that METH induces a dose-dependent brain and body hyperthermia, which is strongly potentiated by associated physiological activation and in warm environments that prevent proper heat dissipation to the external environment. Second, they demonstrate that acute METH intoxication induces robust, widespread but structure-specific leakage of the BBB, acute glial activation, and increased water content (edema), which are related to drug-induced brain hyperthermia. Third, they document widespread morphological abnormalities of brain cells, including neurons, glia, epithelial, and endothelial cells developing rapidly during acute METH intoxication. These structural abnormalities are tightly related to the extent of brain hyperthermia, leakage of the BBB, and brain edema. While it is unclear whether these rapidly developed morphological abnormalities are reversible, this study demonstrates that METH induces multiple functional and structural perturbations in the brain, determining its acute toxicity and possibly contributing to neurotoxicity. Kiyatkin EA, Sharma HS. Acute methamphetamine intoxication brain hyperthermia, blood-brain barrier, brain edema, and morphological cell abnormalities. Int Rev Neurobiol. 2009;88:65-100.

Cocaine Action on Peripheral, Non-Monoamine Neural Substrates as a Trigger of Electroencephalographic Desynchronization and Electromyographic Activation Following I.V. Administration In Freely

Moving Rats

Many important physiological, behavioral and subjective effects of i.v. cocaine (COC) are exceptionally rapid and transient, suggesting a possible involvement of peripheral neural substrates in their triggering. In the present study, IRP scientists used high-speed electroencephalographic (EEG) and electromyographic (EMG) recordings (4-s resolution) in freely moving rats to characterize the central electrophysiological effects of i.v. COC at low doses within a self-administration range (0.25-1.0 mg/kg). They found that COC induces rapid, strong, and prolonged desynchronization of cortical EEG (decrease in alpha and increase in beta and gamma activity) and activation of the neck EMG that begin within 2-6 s following the start of a 10-s injection; immediate components of both effects were dose-independent. The rapid effects of COC were mimicked by i.v. COC methiodide (COC-MET), a derivative that cannot cross the blood-brain barrier. At equimolar doses (0.33-1.33 mg/kg), COC-MET had equally fast and strong effects on EEG and EMG total powers, decreasing alpha and increasing beta and gamma activities. Rapid EEG desynchronization and EMG activation was also induced by i.v. procaine, a structurally similar, short-acting local anesthetic with virtually no effects on monoamine uptake; at equipotential doses (1.25-5.0 mg/kg), these effects were weaker and shorter in duration than those of COC. Surprisingly, i.v. saline injection delivered during slow-wave sleep (but not during quiet wakefulness) also induced a transient EEG desynchronization but without changes in EMG and motor activity; these effects were significantly weaker and much shorter than those induced by all tested drugs. These data suggest that in awake animals, i.v. COC induces rapid cortical activation and a subsequent motor response via its action on peripheral non-monoamine neural elements, involving neural transmission via visceral sensory pathways. By providing a rapid neural signal and triggering neural activation, such an action might play a crucial role in the sensory effects of COC, thus contributing to the learning and development of drug-taking behavior. Smirnov MS, Kiyatkin EA. Cocaine action on peripheral, non-monoamine neural substrates as a trigger of electroencephalographic desynchronization and electromyographic activation following i.v. administration in freely moving rats. Neuroscience. 2009 Oct 25. [Epub ahead of print]

Permeability of the Blood-Brain Barrier Depends on Brain Temperature

Increased permeability of the blood-brain barrier (BBB) has been reported in different conditions accompanied by hyperthermia, but the role of brain temperature per se in modulating brain barrier functions has not been directly examined. To delineate the contribution of this factor, IRP researchers examined albumin immunoreactivity in several brain structures (cortex, hippocampus, thalamus and hypothalamus) of pentobarbital-anesthetized rats (50 mg/kg i.p.), which were passively warmed to different levels of brain temperature (32-42 degrees C). Similar brain structures were also examined for the expression of glial fibrillary acidic protein (GFAP), an index of astrocytic activation, water and ion content, and morphological cell abnormalities. Data were compared with those obtained from drug-free awake rats with normal brain temperatures (36-37 degrees C). The numbers of albumin- and GFAP-positive cells strongly correlate with brain temperature, gradually increasing from approximately 38.5 degrees C and plateauing at 41-42 degrees C. Brains maintained at hyperthermia also showed larger content of brain water and Na(+), K(+) and Cl(-) as well as structural abnormalities of brain cells, all suggesting acute brain edema. The latter alterations were seen at approximately 39 degrees C, gradually progressed with temperature increase, and peaked at maximum hyperthermia. Temperature-dependent changes in albumin immunoreactivity tightly correlated with GFAP immunoreactivity, brain water, and numbers of abnormal cells; they were found in each tested area, but showed some structural specificity. Notably, a mild BBB leakage, selective glial activation, and specific cellular abnormalities were also found in the hypothalamus and piriform cortex during extreme hypothermia (32-33 degrees C); in contrast to hyperthermia these changes were associated with decreased

levels of brain water, Na(+) and K(+), suggesting acute brain dehydration. Therefore, brain temperature per se is an important factor in regulating BBB permeability, alterations in brain water homeostasis, and subsequent structural abnormalities of brain cells. Kiyatkin EA, Sharma HS. Permeability of the blood-brain barrier depends on brain temperature. Neuroscience. 2009;161(3):926-939.

Neurobiology of Relapse Section

Role of Ventral Tegmental Area GDNF In Incubation of Cocaine Craving

Ventral tegmental area (VTA) brain-derived neurotrophic factor (BDNF) contributes to the time-dependent increases in cue-induced cocaine-seeking after withdrawal (incubation of cocaine craving). Here, IRP investigators studied the role in incubation of cocaine craving of glial cell-line-derived neurotrophic factor (GDNF) that, like BDNF, supports the survival and function of midbrain dopamine neurons. They first trained rats to self-administer intravenous cocaine for 10 d (6 h/d, cocaine injections were paired with a tone-light cue). They then manipulated VTA GDNF function and assessed cue-induced cocaine-seeking in extinction tests after withdrawal from cocaine. VTA injections of an adeno-associated virus (AAV) vector containing rat GDNF cDNA (5x108 viral genomes) on withdrawal day 1 increased cue-induced cocaine-seeking on withdrawal days 11 and 31; this effect was not observed after VTA injections of an AAV viral vector containing red fluorescent protein (RFP). Additionally, VTA, but not substantia nigra, GDNF injections (1.25 or 12.5 µg/side) immediately after the last cocaine self-administration session increased cue-induced drug-seeking on withdrawal days 3 and 10; this effect was reversed by VTA injections of U0126, which inhibits the activity of extracellular signal-regulated kinases (ERK). Finally, interfering with VTA GDNF function by chronic delivery of anti-GDNF monoclonal neutralizing antibodies via minipumps (600 ng/side/d) during withdrawal days 1-14 prevented the time-dependent increases in cue-induced cocaine-seeking on withdrawal days 11 and 31. Results indicate that during the first weeks of withdrawal from cocaine self-administration GDNF-dependent neuroadaptations in midbrain VTA neurons play an important role in the development of incubation of cocaine craving. Lu L, Wang X, Wu P, et al. Role of ventral tegmental area GDNF in incubation of cocaine craving. Biological Psychiatry 2009;66:137-145.

Preclinical Pharmacology Section

Regulation of Sigma-1 Receptors and Endoplasmic Reticulum Chaperones in the Brain of Methamphetamine Self-Administering Rats

Sigma-1 receptors are endoplasmic reticulum (ER) chaperones that are implicated in the neuroplasticity associated with psychostimulant abuse. IRP scientists immunocytochemically examined the distribution of sigma-1 receptors in the brain of drug naive rats, then examined the dynamics of sigma-1 receptors and other ER chaperones in specific brain subregions of rats that self-administered methamphetamine, received methamphetamine passively, or received only saline injections. Sigma-1 receptors were found to be expressed in moderate to high levels in the olfactory bulb, striatum, nucleus accumbens shell, olfactory tubercle, amygdala, hippocampus, red nucleus, ventral tegmental area, substantia nigra, and locus ceruleus. Methamphetamine, whether self-administered or passively received, significantly elevated ER chaperones including the sigma-1 receptor, BiP, and calreticulin in the ventral tegmental area and substantia nigra. In the olfactory bulb, however, only the sigma-1 receptor chaperone was increased, and this increase occurred only in rats that actively self-administered methamphetamine. Consistent with an increase in sigma-1 receptors, ERK was found to be activated and PKA attenuated in the olfactory bulb of methamphetamine self-administering rats. Sigma-1 receptors in the olfactory bulb were found to be co-localized with dopamine D1 receptors. These results

indicate that methamphet-amine induces ER stress in the ventral tegmental area and substantia nigra in rats whether the drug is received actively or passively. However, the changes seen only in rats that actively self-administered methamphetamine suggest that D1 and sigma-1 receptors in the olfactory bulb might play an important role in the motivational conditioning/learning aspects of methamphetamine self-administration in the rat. Hayashi T, Justinova Z, Hayashi E, et al. Journal of Pharmacology and Experimental Therapeutics, 2010;332:1-10.

Environmental Enrichment Reduces Cocaine Seeking and Reinstatement Induced By Cues and Stress But Not By Cocaine

Whereas earlier studies have focused on the preventive effects of enriched environments (EE) in drug addiction, in a recent study IRP researchers suggested that EE can also have 'curative' effects. In fact, they found that cocaine addiction-related behaviors can be eliminated by housing cocaine-treated mice in EE during periods of forced abstinence. However, those results were obtained with two simple models of addiction, conditioned place preference (CPP), and behavioral sensitization. In this study, the authors used intravenous drug self-administration procedures in rats to further investigate the beneficial effects of EE on cocaine addiction in a reinstatement model of relapse. Singly housed rats learned to self-administer cocaine during 10 consecutive daily sessions (0.6 mg/injection, 6 h/day). They were then housed three per cage in either standard environments (SE) or EE and were kept abstinent in the animal facility until testing for extinction and reinstatement. They found that 30 days of EE significantly and consistently reduced cocaine seeking during a 6-h extinction session. In addition, EE significantly reduced cue- and stress-induced reinstatement. Surprisingly, given our earlier results in mice with CPP, EE did not reduce cocaine-induced reinstatement regardless of the level of exposure to cocaine and the duration of the period of abstinence and exposure to EE. Altogether, these results support the hypothesis that EE can reduce cocaine-induced craving and highlight the importance of positive life conditions in facilitating abstinence and preventing relapse to cocaine addiction.Chauvet C, Lardeux V, Goldberg SR, Jaber M, Solinas M. Neuropsychopharma-cology. 2009, 34(13):2767-2778.

Fatty Acid Amide Hydrolase (FAAH) Inhibition Enhances Memory Acquisition Through Activation of PPAR-Alpha Nuclear Receptors

Inhibitors of fatty acid amide hydrolase (FAAH) increase endogenous levels of anandamide (a cannabinoid CB(1)-receptor ligand) and oleoylethanolamide and palmitoylethanolamide (OEA and PEA, ligands for alpha-type peroxisome proliferator-activated nuclear receptors, PPAR-alpha) when and where they are naturally released in the brain. Using a passive-avoidance task in rats, IRP scientists found that memory acquisition was enhanced by the FAAH inhibitor URB597 or by the PPAR-alpha agonist WY14643, and these enhancements were blocked by the PPAR-alpha antagonist MK886. These findings demonstrate novel mechanisms for memory enhancement by activation of PPAR-alpha, either directly by administering a PPAR-alpha agonist or indirectly by administering a FAAH inhibitor. Mazzola C, Medalie J, Scherma M, et al. Learning and Memory. 2009;16(5):332-337.

Effects of Nicotine In Experimental Animals and Humans: An Update on Addictive Properties

Tobacco use through cigarette smoking is the leading preventable cause of death in the developed world. Nicotine, a psychoactive component of tobacco, appears to play a major role in tobacco dependence, but the reinforcing effects of nicotine have often been difficult to demonstrate directly in controlled studies with laboratory animals or human subjects. Here IRP researchers review results obtained with drug self-administration, conditioned place preference, subjective reports of nicotine effects and nicotine discrimination indicate that nicotine can function as an effective reinforcer of drug-seeking and drug-taking behavior both in experimental animals and humans under

appropriate conditions. Interruption of chronic nicotine exposure produces ratings of drug withdrawal and withdrawal symptoms that may contribute to relapse. Difficulties encountered in demonstrating reinforcing effects of nicotine under some conditions, relative to other drugs of abuse, may be due to weaker primary reinforcing effects of nicotine, to aversive effects produced by nicotine, or to a more critical contribution of environmental stimuli to the maintenance of drug-seeking and drug-taking behavior with nicotine than with other drugs of abuse. Several recent reports suggest that other chemical substances inhaled along with nicotine in tobacco smoke may play a role in sustaining smoking behavior. However, conflicting results have been obtained with mice and rats and these findings have not yet been validated in nonhuman primates or human subjects. Taken together, these findings suggest that nicotine acts as a typical drug of abuse in experimental animals and humans in appropriate situations. Le Foll B, Goldberg SR. Handbook of Experimental Pharmacology. 2009;192:335-367.

Anandamide-Induced Behavioral Disruption Through A Vanilloid-Dependent Mechanism In Rats

Endocannabinoids are involved in a variety of behavioral and physiological processes that are just beginning to be understood. In the five-choice serial reaction-time task, exogenous cannabinoids have been found to alter attention, but endocannabinoids such as anandamide have not been studied. IRP scientists used this task to evaluate the effects of anandamide in rats. Since anandamide is a ligand for not only cannabinoid receptors but also transient receptor potential vanilloid 1 (TRPV1) receptors, and as recently suggested, peroxisome proliferator-activated nuclear receptor-alpha (PPARalpha), they also determined whether anandamide's effects in this task were mediated by each of these receptors. Whenever one of five holes was illuminated for 2 s, a food pellet was delivered if a response occurred in that hole during the light or within 2 s after the light. Anandamide increased omission errors and decreased responding during inter-trial intervals. These effects were blocked by the TRPV1 antagonist capsazepine, but not by the cannabinoid-receptor antagonist rimonabant or the PPARalpha antagonist MK886. Testing with open-field activity and food-consumption procedures in the same rats suggested that the disruption of operant responding observed in the attention task was not due to motor depression, anxiety, decreased appetite, or an inability to find and consume food pellets. The vanilloid-dependent behavioral disruption induced by anandamide was specific to the operant attention task. These effects of anandamide resemble effects of systemically administered dopamine antagonists and might reflect changes in vanilloid-mediated dopamine transmission. Panlilio LV, Mazzola C, Medalie J, et al. Psychopharmacology 2009;203(3):529-538.

Looking For the Role of Cannabinoid Receptor Heteromers In Striatal Function

The introduction of two concepts, "local module" and "receptor heteromer", facilitates the understanding of the role of interactions between different neurotransmitters in the brain. In artificial cell systems, cannabinoid CB(1) receptors form receptor heteromers with dopamine D2, adenosine A2A and mu opioid receptors. There is indirect but compelling evidence for the existence of the same CB1 receptor heteromers in striatal local modules centered in the dendritic spines of striatal GABAergic efferent neurons, particularly at a postsynaptic location. Their analysis provides new clues for the role of endocannabinoids in striatal function, which cannot only be considered as retrograde signals that inhibit neurotransmitter release. Recent studies using a new method to detect heteromerization of more than two proteins, which consists of sequential BRET-FRET (SRET) analysis, has demonstrated that CB1, D2 and A2A receptors can form heterotrimers in transfected cells. It is likely that functional CB1-A2A-D2 receptor heteromers can be found where they are highly co-expressed, in the dendritic spines of GABAergic enkephalinergic neurons. The functional properties of these multiple receptor heteromers and

their role in striatal function need to be determined. Ferré S, Goldberg SR, Lluis C, Franco R. Neuropharmacology 2009;56 Suppl 1:226-234.

Effect of Rate of Delivery of Intravenous Cocaine on Self-Administration In Rats

Many studies of drug self-administration in primates have shown that faster infusions of a drug are more reinforcing than slower infusions. Similar effects have not been shown in rats. IRP researchers assessed the influence of delivery rate by allowing rats to choose between the same doses of intravenous cocaine delivered over two different infusion speeds. Rats were trained in chambers containing two nose-poke response devices. In Experiment 1, responses in one nose-poke delivered 0.3 mg/kg/injection of cocaine over 10 s, and responses in the other delivered the same dose over 100 s. In Experiment 2, the same procedure was used, but with 1.0 mg/kg/injection dose delivered over 1.7 versus 100 s. During acquisition, most rats preferred the faster infusion. When the delivery rates associated with the nose pokes were reversed, rats trained with 0.3 mg/kg/injection failed to switch nose-poke preference, but half the rats trained with 1.0 mg/kg/injection did switch. In Experiment 3, the choice was between 1 mg/kg cocaine delivered over 1.7 s and no reinforcement. Here, rats quickly learned to respond in the nose-poke associated with cocaine and quickly switched their choice during reversal. In Experiment 4, two groups of rats were allowed to choose between food delivered with a delay of 1 versus 5 s or 1 versus 10 s, respectively. Rats preferred the shorter delay during initial training. In reversal, some rats in the 1 vs 5 s group failed to reverse, while all the rats in the 1 vs 10 s group reversed. These results show that faster infusions of cocaine are clearly more reinforcing during acquisition, but delivery rate may not be as important to the maintenance of self-administration once it has been established. The results with food suggest that these findings represent general principles of behavior and are not unique to drug self-administration. Schindler CW, Panlilio LV, Thorndike EB. Pharmacology Biochemistry and Behavior 2009;93(4):375-381.

Effects of Orbitofrontal Cortex Lesions on Cocaine Self-Administration

Previous research has implicated limbic and prefrontal cortical areas in the control of drug-seeking behavior. The present study examined the effects of orbitofrontal-cortex (OFC) lesions on acquisition, dose-dependence, within-session patterning, and reinstatement of cocaine self-administration. Rats received OFC or sham lesions before or after acquisition (0.3 mg/kg/injection, paired with a visual stimulus), then were tested with a range of doses (0, 0.03, 0.1, 0.3 and 1). Compared to controls, rats lesioned before acquisition acquired the behavior sooner, responded more at low doses, and responded more on the first day of extinction. Rats that were lesioned after acquisition showed an even larger increase in responding (approximately 250%) at the lowest dose, and they also showed increased timeout responding and drug "loading" at low doses. Pre-acquisition lesions were tested and found to have no effect on cocaine-induced reinstatement. In parallel experiments examining effects of pre-acquisition OFC lesions on food-reinforced responding, lesions did not alter acquisition, maintenance, or reinstatement, but accelerated the course of extinction. The increased cocaine self-administration seen in OFC-lesioned rats did not resemble the dysregulated drug intake observed in long-access models of addiction but might be due to impaired response inhibition or impaired tracking of the reward value of drug-related cues. Grakalic I, Panlilio LV, Quiroz C, Schindler CW. Neuroscience 2010 Jan 20;165(2):313-324.

Interactions Between Calmodulin, Adenosine A2A, and Dopamine D2 Receptors

The Ca(2+)-binding protein calmodulin (CaM) has been shown to bind directly to cytoplasmic domains of some G protein-coupled receptors, including the dopamine D(2) receptor. CaM binds to the N-terminal portion of the long third intracellular loop of the D(2) receptor, within an Arg-rich epitope that is also involved in the binding to G(i/o) proteins and to the adenosine A(2A) receptor,

with the formation of A(2A)-D(2) receptor heteromers. In the present work, by using proteomics and bioluminescence resonance energy transfer (BRET) techniques, IRP scientists provide evidence for the binding of CaM to the A(2A) receptor. By using BRET and sequential resonance energy transfer techniques, evidence was obtained for CaM-A(2A)-D(2) receptor oligomerization. BRET competition experiments indicated that, in the A(2A)-D(2) receptor heteromer, CaM binds preferentially to a proximal C terminus epitope of the A(2A) receptor. Furthermore, Ca(2+) was found to induce conformational changes in the CaM-A(2A)-D(2) receptor oligomer and to selectively modulate A(2A) and D(2) receptor-mediated MAPK signaling in the A(2A)-D(2) receptor heteromer. These results may have implications for basal ganglia disorders, since A(2A)-D(2) receptor heteromers are being considered as a target for anti-parkinsonian agents. Navarro G, Aymerich MS, Marcellino D, et al. J Biol Chem. 2009;284(41):28058-28068.

GPCR Homomers and Heteromers: A Better Choice As Targets For Drug Development Than GPCR Monomers?

G protein-coupled receptors (GPCR) are targeted by many therapeutic drugs marketed to fight against a variety of diseases. Selection of novel lead compounds are based on pharmacological parameters obtained assuming that GPCR are monomers. However, many GPCR are expressed as dimers/oligomers. Therefore, drug development may consider GPCR as homo- and hetero-oligomers. A two-state dimer receptor model is now available to understand GPCR operation and to interpret data obtained from drugs interacting with dimers, and even from mixtures of monomers and dimers. Heteromers are distinct entities and therefore a given drug is expected to have different affinities and different efficacies depending on the heteromer. All these concepts would lead to broaden the therapeutic potential of drugs targeting GPCRs, including receptor heteromer-selective drugs with a lower incidence of side effects, or to identify novel pharmacological profiles using cell models expressing receptor heteromers. Casad— V, Cortés A, Mallol J, et al. Pharmacol. Ther. 2009;124(2):248-257.

Key Modulatory Role of Presynaptic Adenosine A2A Receptors In Cortical Neurotransmission To the Striatal Direct Pathway

Basal ganglia processing results from a balanced activation of direct and indirect striatal efferent pathways, which are controlled by dopamine D1 and D2 receptors, respectively. Adenosine A2A receptors are considered novel antiparkinsonian targets, based on their selective postsynaptic localization in the indirect pathway, where they modulate D2 receptor function. The present study provides evidence for the existence of an additional, functionally significant, segregation of A2A receptors at the presynaptic level. Using integrated anatomical, electrophysiological, and biochemical approaches, IRP researchers demonstrate that presynaptic A2A receptors are preferentially localized in cortical glutamatergic terminals that contact striatal neurons of the direct pathway, where they exert a selective modulation of corticostriatal neurotransmission. Presynaptic striatal A2A receptors could provide a new target for the treatment of neuropsychiatric disorders. Quiroz C, Luj‡n R, Uchigashima M, et al. Scientific World Journal. 2009;9:1321-1344.

Calcium-Mediated Modulation of the Quaternary Structure and Function of Adenosine A(2A)-Dopamine D(2) Receptor Heteromers

The adenosine A(2A)-dopamine D(2) receptor heteromer is one of the most studied receptor heteromers. It has important implications for basal ganglia function and pathology. Recent studies using Bioluminescence and Sequential Resonance Energy Transfer techniques shed light on the role of Ca(2+) in the modulation of the quaternary structure of the A(2A)-D(2) receptor heteromer, which was found to depend on the binding of calmodulin (CaM) to the carboxy-terminus of the A(2A) receptor in the A(2A)-D(2) receptor heteromer. Importantly, the changes in quaternary structure correlate with changes in function. A Ca(2+)/CaM-dependent modulation of MAPK signaling upon agonist

treatment could be observed in cells expressing A(2A)-D(2) receptor heteromers. These studies provide a first example of a Ca(2+)-mediated modulation of the quaternary structure and function of a receptor heteromer. Ferré S, Woods AS, Navarro G, Aymerich M, Llu's C, Franco R. Curr. Opin. Pharmacol. 2009 Nov 5. [Epub ahead of print]

Chemical Biology Research Branch

Synthesis, Radiosynthesis and In Vivo Evaluation Of [123I]-4-(2-(Bis(4-Fluorophenyl) Methoxy) Ethyl)-1-(4-Iodobenzyl)Piperidine as a Selective Tracer For Imaging the Dopamine Transporter

Dopamine transporter (DAT) neuroimaging is a useful tool in Parkinson's disease diagnosis, staging and follow-up providing information on the integrity of the dopaminergic neurotransmitter system in vivo. 4-(2-(Bis(4-fluorophenyl)methoxy)ethyl)-1-(4-iodobenzyl)piperidine (7) has nanomolar affinity for DAT and better selectivity over the other monoamine transporters compared with the existing SPECT radioligands for DAT. The aim of this study was to synthesize and evaluate [123I]-7 as an in vivo tracer for DAT.The tributylstannyl precursor was synthesized with an overall yield of 25%. [123I]-7 was synthesized by electrophilic destannylation with a yield of 40±10%. Radiochemical purity appeared to be >98%, whereas specific activity was at least 667 GBq/µmol. Biodistribution studies in mice showed brain uptake of 0.96±0.53%ID/g at 30 s post injection (p.i.) and 0.26±0.02%ID/g at 3 h p.i. High blood activity was observed at all time points. Pretreatment with Cyclosporin A raised brain uptake indicating that [123I]-7 is transported by P-glycoprotein (P-gp) pumps. In rats, regional brain distribution of [123I]-7 was not in agreement with DAT distribution. These results indicate that [123I]-7 is not suitable for mapping DAT in vivo but could be a useful tracer for the P-gp transporter. De Bruyne S, Boos TL, Wyffels L, et al. J Labelled Comp Radiopharm. 2009;52(8):304-311.

[76Br]BMK-I-152, A Non-Peptide Analogue For PET Imaging of Corticotropin-Releasing Hormone Type 1 Receptor (CRHR1)

The study of corticotropin-releasing hormone is of significant interest in mental health. IRP investigators have developed a radiobromination procedure for the preparation of [76Br]BMK-I-152, a high-affinity corticotropin-releasing hormone type 1 receptor antagonist. The radiobromination procedure resulted in the formation of two radiobrominated products from the same trialkyltin precursor. Utilizing the results of several reaction conditions and the chromatographic and mass spectral data obtained from Waters Acquity and Q-TOF, the authors determined that both 3-bromo and 4-bromo isomers could be obtained. The authentic sample of the 3-bromo isomer was prepared to confirm the identity of a previously unknown radioactive side product; affinity assays revealed that the 4-bromo isomer had 70 times higher affinity than that of the 3-bromo compound. By manipulation of reaction conditions, the individual products could be selected. Under no-carrier-added conditions at room temperature in aqueous acetonitrile, the major radioactive product (>80%) was identified as the 3-[76Br]bromo-4-tributylstannyl analogue of BMK-I-152. The 4-[76Br]bromo isomer accounted for less than 1% of the total activity. The 3-[76Br]bromo BMK-I-152 could be obtained by treating this intermediate with trifluoroacetic acid to effect removal of the trialkyltin. If the radiobromination was conducted after first evaporating the water from the aqueous ammonium hydroxide solution of [76Br]bromide, the desired 4-[76Br]bromo isomer was obtained with a 58% radiochemical yield. Lang L, Ma Y, Kim BM, et al. J Labelled Comp Radiopharm. 2009;52(9):394-400.

Evidence That Opioids May Have Toll-Like Receptor 4 and MD-2 Effects

Opioid-induced proinflammatory glial activation modulates wide-ranging aspects of opioid pharmacology including: opposition of acute and chronic opioid analgesia, opioid analgesic tolerance, opioid-induced hyperalgesia, development of opioid dependence, opioid reward, and opioid respiratory

depression. However, the mechanism(s) contributing to opioid-(TLR4) was examined using in vitro, in vivo, and in silico techniques.Pharmacological blockade of TLR4 signaling in vivo potentiated acute intrathecal morphine analgesia, attenuated development of analgesic tolerance, hyperalgesia, and opioid withdrawal behaviors. TLR4 opposition to opioid actions was supported by morphine treatment of TLR4 knockout mice, which revealed a significant threefold leftward shift in the analgesia dose response function, versus wildtype mice. A range of structurally diverse Selectivity in the response was identified since morphine-3-glucuronide, a morphine metabolite with no opioid receptor activity, displayed significant TLR4 activity, whilst the opioid receptor active metabolite, morphine-6-glucuronide, was devoid of such properties. In silico docking simulations revealed ligands bound preferentially to the LPS binding pocket of MD-2 rather than TLR4. An in silico to in vitro prediction model was built and tested with substantial accuracy. These data provide evidence that select opioids may non-stereoselectively influence TLR4 signaling and have behavioral consequences resulting, in part, via TLR4 signaling. Hutchinson MR, Zhang Y, Shridhar M, et al. Brain Behav Immun. 2010;24(1): 83-85. Epub 2009 Aug 10.

Evidence For a Role of Heat Shock Protein-90 In Toll Like Receptor 4 Mediated Pain Enhancement In Rats

Spinal cord microglial toll-like receptor 4 (TLR4) has been implicated in enhancing neuropathic pain and opposing morphine analgesia. The present study was initiated to explore TLR4-mediated pain modulation by intrathecal lipopolysaccharide, a classic TLR4 agonist. However, IRP researchers'initial study revealed that intrathecal lipopolysaccharide failed to induce low-threshold mechanical allodynia in naive rats, suggestive that TLR4 agonism may be insufficient to enhance pain. These studies explore the possibility that a second signal is required; namely, heat shock protein-90 (HSP90). This candidate was chosen for study given its known importance as a regulator of TLR4 signaling. A combination of in vitro TLR4 cell signaling and in vivo behavioral studies of pain modulation suggest that TLR4-enhancement of neuropathic pain and TLR4-suppression of morphine analgesia each likely require HSP90 as a cofactor for the effects observed. In vitro studies revealed that dimethyl sulfoxide (DMSO) enhances HSP90 release, suggestive that this may be a means by which DMSO enhances TLR4 signaling. While 2 and 100 microg lipopolysaccharide intrathecally did not induce mechanical allodynia across the time course tested, co-administration of 1 microg lipopolysaccharide with a drug that enhances HSP90-mediated TLR4 signaling now induced robust allodynia. In support of this allodynia being mediated via a TLR4/HSP90 pathway, it was prevented or reversed by intrathecal co-administration of a HSP90 inhibitor, a TLR4 inhibitor, a microglia/monocyte activation inhibitor (as monocyte-derived cells are the predominant cell type expressing TLR4), and interleukin-1 receptor antagonist (as this proinflammatory cytokine is a downstream consequence of TLR4 activation). Together, these results suggest for the first time that TLR4 activation is necessary but not sufficient to induce spinally mediated pain enhancement. Rather, the data suggest that TLR4-dependent pain phenomena may require contributions by multiple components of the TLR4 receptor complex. Hutchinson MR, Ramos KM, Loram LC, et al. Neuroscience. 2009 Dec 29;164(4):1821-32. Epub 2009 Sep 27.

Stress Induced Potentiation Of Cocaine Reward Is Dependent On CRF1 Receptor and CREB

Both clinical and preclinical research have shown that stress can potentiate drug use; however, the underlying mechanisms of this interaction are unknown. Previously, IRP scientists have shown that a single exposure to forced swim (FS) reinstates extinguished conditioned place preference (CPP) to cocaine and that cAMP response element binding protein (CREB) is necessary for this response. CREB can be activated by corticotropin releasing factor (CRF) receptor type 1 (CRFR1) binding, which mediates neuroendocrine and behavioral responses to stress as well as to drugs of abuse. The present

experiments investigate whether changes in cocaine reward elicited by previous exposure to stress are mediated by CREB and/or CRFR1. Chronic exposure to FS in advance of conditioning enhances cocaine CPP in wild-type mice, but this is blocked in CREB-deficient mice. In addition, pretreatment with the CRFR1 antagonist, antalarmin, before FS exposure blocks this stress-induced enhancement of cocaine CPP. Furthermore, FS-induced increase in phosphorylated CREB (pCREB), specifically in the lateral septum (LS) and nucleus accumbens (NAc) is also blocked by antalarmin. Taken together, these studies suggest that both CREB and CRFR1 activation are necessary for stress-induced potentiation of drug reward. Kreibich AS, Cleck JN, Rice KC, et al. Neuropsychopharm. 2009;34(12):2609-2617.

Discriminative Stimulus (R)-(+)-{Alpha}-(2,3-Dimethoxyphenyl)-1-[2-(4-Fluorophenyl)Ethyl]-4-Pipidinemethanol (MDL100907) In Rats

Very little is known about constitutive activity in vivo. This study examined whether constitutive activity and inverse agonism contribute to discriminative stimulus effects of drugs acting at serotonin (5-HT)(2A) receptors. Rats were trained to discriminate between saline and either 0.56 mg/kg 5-HT(2) receptor agonist 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), 1.0 mg/kg 5-HT(2A) receptor antagonist ketanserin, or 0.1 mg/kg purported 5-HT(2A) receptor inverse agonist (R)-(+)-alpha-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-pipidinemethanol (MDL100907). Discriminative control was established with each drug after 33 to 35 sessions. MDL100907 and ketanserin did not occasion DOM lever responding but attenuated the discriminative stimulus effects of DOM. DOM did not occasion responding on the drug-associated lever in rats discriminating MDL100907 or ketanserin, but attenuated the discriminative stimulus effects of both drugs. Ketanserin and ritanserin occasioned MDL100907-lever responding, whereas rats discriminating ketanserin responded only partially on the drug-associated lever after receiving MDL100907, ritanserin, or the alpha(1)-adrenergic antagonist prazosin. Combining prazosin with MDL100907 or ritanserin resulted in near-complete ketanserin-lever responding, indicating that the ketanserin stimulus involves both 5-HT(2A) and alpha(1)-adrenergic receptors. Administration of p-chlorophenylalanine methyl ester, then fenfluramine, significantly decreased cortical 5-HT, enhanced sensitivity to the discriminative stimulus effects of DOM, and occasioned partial MDL100907-lever responding. Collectively, these results show that DOM and MDL100907 discriminative stimulus effects are mediated by 5-HT(2A) receptors and that ketanserin discriminative stimulus effects involve both 5-HT(2A) and alpha(1)-adrenergic receptors. Results in 5-HT-depleted rats further suggest that the discriminative stimulus effects of MDL100907 might involve antagonism of endogenous 5-HT and/or inverse agonism at 5-HT(2A) receptors. Li JX, Unzeitig A, Javors MA, Rice KC, Koek W, France CP. J Pharmacol Exp Ther. 2009 Nov;331(2):671-679. Epub 2009 Aug 17.

The "Toll" Of Opioid-Induced Glial Activation: Improving the Clinical Efficacy of Opioids By Targeting Glia

Glial activation participates in the mediation of pain including neuropathic pain, due to release of neuroexcitatory, proinflammatory products. Glial activation is now known to occur in response to opioids as well. Opioid-induced glial activation opposes opioid analgesia and enhances opioid tolerance, dependence, reward and respiratory depression. Such effects can occur, not via classical opioid receptors, but rather via non-stereoselective activation of toll-like receptor 4 (TLR4), a recently recognized key glial receptor participating in neuropathic pain as well. This discovery identifies a means for separating the beneficial actions of opioids (opioid receptor mediated) from the unwanted side-effects (TLR4/glial mediated) by pharmacologically targeting TLR4. Such a drug should be a stand-alone therapeutic for treating neuropathic pain as well. Excitingly, with newly-established clinical trials of two glial modulators for treating neuropathic pain and improving the utility of opioids, translation from rats-to-humans now begins with the promise of improved clinical pain

control.Watkins LR, Hutchinson MR, et al. Trends Pharmacol.Sci.2009;30(11):581-591.

CRF System Recruitment Mediates Dark Side of Compulsive Eating
Dieting to control body weight involves cycles of deprivation from palatable food that can promote compulsive eating. The present study shows that rats withdrawn from intermittent access to palatable food exhibit overeating of palatable food upon renewed access and an affective withdrawal-like state characterized by corticotropin-releasing factor-1 (CRF(1)) receptor antagonist-reversible behaviors, including hypophagia, motivational deficits to obtain less palatable food, and anxiogenic-like behavior. Withdrawal was accompanied by increased CRF expression and CRF(1) electrophysiological responsiveness in the central nucleus of the amygdala. IRP investigators propose that recruitment of anti-reward extrahypothalamic CRF-CRF(1) systems during withdrawal from palatable food, analogous to abstinence from abused drugs, may promote compulsive selection of palatable food, undereating of healthier alternatives, and a negative emotional state when intake of palatable food is prevented. Cottone P, Sabino V, Roberto M, et al. PNAS USA. 2009 Nov 24;106(47):20016-20020.

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 μ-opioid receptor affinity of the examined compounds (Ki = 0.35 μM). Iyer MR, Lee YS, Deschamps JR, et al. Bioorg. Med. Chem. Epub 2009 Nov 18.

Effects of Dose and Route of Administration on Pharmacokinetics of (±)-3,4-Methylenedioxy-methamphetamine (MDMA) in the Rat
Based on animal data, there is speculation that (±)-3,4-methylenedioxymethamphetamine (MDMA) is neurotoxic to humans. Extrapolation of MDMA findings from animals to humans requires assessment of pharmacokinetics in various species, and low-dose administration data from rats are lacking. Here IRP scientists examine MDMA pharmacokinetics in rats given low (2 mg/kg) and high (10 mg/kg) doses of racemic MDMA via i.p., s.c. and p.o. routes. Repeated blood specimens were collected from venous catheters, and plasma was assayed for MDMA and its metabolites, 4-hydroxy-3-methoxymethamphetamine (HMMA) and 3,4-methylenedioxyamphe-tamine (MDA), by gas chromatography mass spectrometry. After 2 mg/kg, maximum MDMA concentrations (Cmax) were ~200 ng/mL for i.p. and s.c. routes, but less for the p.o. route. MDMA plasma half-lives were < 1 h for low-dose groups, while HMMA and MDA half-lives were > 2 h. After 10 mg/kg, MDMA areas-under-the-curve (AUC) were 21-fold (i.p.), 10-fold (s.c.) and 36-fold (p.o.) greater than those at 2 mg/kg. By contrast, HMMA AUC values in high-dose groups were < 3-fold above those at 2 mg/kg. Several new findings emerge from this report of low-dose MDMA pharmacokinetics in rats. First, 2 mg/kg MDMA in rats can produce MDMA Cmax similar to those in humans, perhaps explaining why both species discriminate 1.5 mg/kg MDMA in laboratory paradigms. Second, these data provide additional support for non-linear kinetics of MDMA in rats, and analogous to humans, this phenomenon appears to involve impaired drug metabolism. Finally, given key similarities between MDMA pharmacokinetics in rats and humans, data from rats may be clinically-relevant when appropriate dosing conditions are employed. Baumann MH, Zolkowska D, Kim I, Scheidweiler KB, et al. Effects of dose and route of administration on pharmacokinetics of (±)-3,4-methylenedioxymethamphetamine (MDMA) in the rat. Drug Metab Dispos.

2009;37:2163-2170.

Identification of a Novel "Almost Neutral" Mu-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 scientists 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 muM (2S,4aR,6aR,7R,9S, 10aS,10bR)-9-(benzoyloxy)-2-(3-furanyl)dodecahydro-6a,10 b-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, et al. Identification of a novel "almost neutral" mu-opioid receptor antagonist in CHO cells expressing the cloned human mu-opioid receptor. 2009 Synapse 64:280-288.

Cellular Neurobiology Research Branch

Development and Plasticity Section, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Human Embryonic Stem Cells Which Express Hrgfp In the Undifferentiated State and During Dopaminergic Differentiation

Human embryonic stem cells (hESCs) which express a reporter gene consistently during all phases of differentiation would be valuable for basic research on cell transplantation. In this study, IRP investigators describe karyotypically-abnormal variant hESCs, BGO1V2-EFG, which express hrGFP driven by the EF1 promoter. BGO1V2-EFG cells were analyzed by using immunocytochemistry, single cell-based confocal image, and in vitro differentiation, including dopaminergic differentiation. Undifferentiated BGO1V2-EFG cells expressed pluripotent ESC markers and retained the ability to differentiate into cell types of all three germ layers. BGO1V2-EFG cells maintained stable and robust hrGFP expression in vitro in the undifferentiated state and during differentiation. The EF1 promoter retained activity during dopaminergic differentiation, as 76% of tyrosine hydroxlase (TH)-positive cells co-expressed hrGFP by confocal analysis. Treated with sodium butyrate (0.02 mM to 2.0 mM), an inhibitor of histone deacetylase (HDAC), during differentiation did not affect hrGFP expression, although TH expression was

reduced by higher concentrations of sodium butyrate. BGO1V2-EFG cells maintain stable and robust hrGFP expression in the undifferentiated state and during neural differentiation. Especially, the EF1 promoter was effective in driving hrGFP expression during dopaminergic differentiation. BGO1V2-EFG cells may be useful for transplantation studies in Parkinson disease animal models. Chen J, Tsai SY, Vazin T, Coggiano M, Freed WJ. Human embryonic stem cells which express hrGFP in the undifferentiated state and during dopaminergic differentiation. Restor Neurol Neurosci. 2009;27(4):359-370.

A Novel Combination of Factors, Termed SPIE, Which Promotes Dopaminergic Neuron Differentiation From Human Embryonic Stem Cells

Stromal-Derived Inducing Activity (SDIA) is one of the most efficient methods of generating dopaminergic (DA) neurons from embryonic stem cells (ESC). DA neuron induction can be achieved by co-culturing ESC with the mouse stromal cell lines PA6 or MS5. The molecular nature of this effect, which has been termed "SDIA" is so far unknown. Recently, IRP researchers found that factors secreted by PA6 cells provided lineage-specific instructions to induce DA differentiation of human ESC (hESC). In the present study, the authors compared PA6 cells to various cell lines lacking the SDIA effect, and employed genome expression analysis to identify differentially-expressed signaling molecules. Among the factors highly expressed by PA6 cells, and known to be associated with CNS development, were stromal cell-derived factor 1 (SDF-1/CXCL12), pleiotrophin (PTN), insulin-like growth factor 2 (IGF2), and ephrin B1 (EFNB1). When these four factors, the combination of which was termed SPIE, were applied to hESC, they induced differentiation to TH-positive neurons in vitro. RT-PCR and western blot analysis confirmed the expression of midbrain specific markers, including engrailed 1, Nurr1, Pitx3, and dopamine transporter (DAT) in cultures influenced by these four molecules. Electrophysiological recordings showed that treatment of hESC with SPIE induced differentiation of neurons that were capable of generating action potentials and forming functional synaptic connections. The combination of SDF-1, PTN, IGF2, and EFNB1 mimics the DA phenotype-inducing property of SDIA and was sufficient to promote differentiation of hESC to functional midbrain DA neurons. These findings provide a method for differentiating hESC to form DA neurons, without a requirement for the use of animal-derived cell lines or products. Vazin T, Becker KG, Chen J, et al. A novel combination of factors, termed SPIE, which promotes dopaminergic neuron differentiation from human embryonic stem cells. PLoS One. 2009 Aug 12;4(8):e6606.

Electrophysiology Research Section, Cellular Neurobiology Research Branch

Nogo Receptor 1 Regulates Formation Of Lasting Memories

Formation of lasting memories is believed to rely on structural alterations at the synaptic level. IRP scientists had found that increased neuronal activity down-regulates Nogo receptor-1 (NgR1) in brain regions linked to memory formation and storage, and postulated this to be required for formation of lasting memories. They now show that mice with inducible overexpression of NgR1 in forebrain neurons have normal long-term potentiation and normal 24-h memory, but severely impaired month-long memory in both passive avoidance and swim maze tests. Blocking transgene expression normalizes these memory impairments. Nogo, Lingo-1, Troy, endogenous NgR1, and BDNF mRNA expression levels were not altered by transgene expression, suggesting that the impaired ability to form lasting memories is directly coupled to inability to down-regulate NgR1. Regulation of NgR1 may therefore serve as a key regulator of memory consolidation. Understanding the molecular underpinnings of synaptic rearrangements that carry lasting memories may facilitate development of treatments for memory dysfunction. Karlén A, Karlsson TE, Mattsson A, et al. Nogo receptor 1 regulates formation of lasting memories.

Proc Natl Acad Sci USA. 2009 Nov 13. [Epub ahead of print].

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Expression Pattern of NuIP Gene In Adult Mouse Brain

IRP investigators previously reported the identification of the Nurr1 interacting protein (NuIP) that was demonstrated to modulate the transcriptional activity of Nurr1, the orphan nuclear receptor required for midbrain dopaminergic neuron differentiation. NuIP was also cloned by others and referred to as a small G protein signaling modulators. The open reading frame of NuIP predicts a protein with an N-terminal RUN domain (RPIP8, UNC-14, and NESCA) and a C-terminal TBC domain (Tre-2, Bub2, and Cdc16) both of which are found in proteins of the GTPase activating protein (GAP) family, involved in the GTPase signaling pathway. To characterize the NuIP gene product, the authors developed a polyclonal antibody. Since NuIP gene is expressed most abundantly in adult and the level of expression during development is below the detection limit of immunohistochemistry, we now report the expression pattern of NuIP in adult mouse brain compared with the expression pattern of Nurr1 protein. Many regions co-expressed Nurr1 and NuIP including cortex, hippocampus, substantia nigra, and the cerebellum. However, there are also regions that exclusively express NuIP such as striatum, septum, globus pallidus, and the reticular thalamic nucleus. The authors also find that NuIP protein expresses mainly in NeuN-positive (neuronal nuclei) neurons but can be detected in GFAP-positive (glial fibrillary acidic protein) glial cells in hippocampus. Interestingly, NuIP is expressed in high levels in midbrain dopaminergic neurons including ventral tegmental area (VTA) and substantia nigra (SN) dopaminergic neurons but is not expressed or expressed in low levels in other dopaminergic neurons such as olfactory bulb and hypothalamus. Overall, the expression pattern of NuIP in adult mouse brain suggests that it may be involved in motor activity control in basal ganglia as well as higher central nervous system (CNS) functions such as cognition and memory in cortex and hippocampus. Luo Y, Sarabi SA, Backman C, Shan L, Hoffer B, Federoff H. Expression pattern of NuIP gene in adult mouse brain. Brain Res. 2009;1302:42-53.

Selective Deletion Of PTEN In Dopamine Neurons Leads To Trophic Effects and Adaptation of Striatal Medium Spiny Projecting Neurons

The widespread distribution of the tumor suppressor PTEN in the nervous system suggests a role in a broad range of brain functions. PTEN negatively regulates the signaling pathways initiated by protein kinase B (Akt) thereby regulating signals for growth, proliferation and cell survival. PTEN deletion in the mouse brain has revealed its role in controlling cell size and number. In this study, we used Cre-loxP technology to specifically inactivate PTEN in dopamine (DA) neurons (PTEN KO mice). The resulting mutant mice showed neuronal hypertrophy, and an increased number of dopaminergic neurons and fibers in the ventral mesencephalon. Interestingly, quantitative microdialysis studies in PTEN KO mice revealed no alterations in basal DA extracellular levels or evoked DA release in the dorsal striatum, despite a significant increase in total DA tissue levels. Striatal dopamine receptor D1 (DRD1) and prodynorphin (PDyn) mRNA levels were significantly elevated in KO animals, suggesting an enhancement in neuronal activity associated with the striatonigral projection pathway, while dopamine receptor D2 (DRD2) and preproenkephalin (PPE) mRNA levels remained unchanged. In addition, PTEN inactivation protected DA neurons and significantly enhanced DA-dependent behavioral functions in KO mice after a progressive 6OHDA lesion. These results provide further evidence about the role of PTEN in the brain and suggest that manipulation of the PTEN/Akt signaling pathway during development may alter the basal state of dopaminergic neurotransmission and could provide a therapeutic strategy for the treatment of Parkinson's disease, and other neurodegenerative disorders.

Diaz-Ruiz O, Zapata A, Shan L, Zhang Y, Tomac AC, Malik N, de la Cruz F, BŠckman CM. Selective deletion of PTEN in dopamine neurons leads to trophic effects and adaptation of striatal medium spiny projecting neurons. PLoS One. 2009;4(9):e7027.

MAM: More Than Just A Housekeeper

The physical association between the endoplasmic reticulum (ER) and mitochondria, known as the mitochondria-associated ER membrane (MAM), plays important roles in various cellular functions including the highly efficient transmission of Ca2+ from the ER to mitochondria to stimulate the production of ATP from oxidative metabolism and, conversely, may enable the metabolically energized mitochondria to regulate the ER Ca2+ homeostasis. These two major functions affect each other. Recent studies have shed light on the molecular chaperones (e.g., calnexin, calreticulin, ERp44, ERp57, grp75, the sigma-1 receptor) at the interface that regulate the association between the two organelles. The MAM thus integrates signal transduction with energy metabolism to regulate the communication and functional interactions between the ER and mitochondrion. Hayashi T, Rizzuto R, Hajnoczky G, Su TP. Trends in Cell Biology. 2009;19:81-88.

When the Endogenous Hallucinogenic Trace Amine N,N-Dimethyltryptamine Meets the Sigma-1 Receptor

N,N-dimethyltryptamine (DMT) is a hallucinogen found endogenously in human brain that is commonly recognized to target the 5-hydroxytryptamine 2A receptor or the trace amine-associated receptor to exert its psychedelic effect. DMT has been recently shown to bind sigma-1 receptors, which are ligand-regulated molecular chaperones whose function includes inhibiting various voltage-sensitive ion channels. Thus, it is possible that the psychedelic action of DMT might be mediated in part through sigma-1 receptors. Here, IRP scientists present a hypothetical signaling scheme that might be triggered by the binding of DMT to sigma-1 receptors. Specifically, DMT might cause the translocation of sigma-1 receptors from the endoplasmic reticulum to the proximity directly apposing plasma membrane to chaperone the receptors or ion channels on the plasma membrane. Su TP, Hayashi T, Vaupel DB. Science-Signaling. 2009;2:12, online publication.

Delta Opioid Peptide DADLE Causes Cell Cycle Arrest and Differentiation In A CNS Neuronal Progenitor Cell Line

Opioids have been demonstrated to play an important role in CNS development by affecting proliferation and differentiation in various types of neural cells. This study examined the effect of a stable delta opioid peptide [D-Ala(2),D-Leu(5)]-enkephalin (DADLE) on proliferation and differentiation in an AF5 CNS neural progenitor cell line derived from rat mesencephalic cells. DADLE (1 pM, 0.1 nM, or 10 nM) caused a significant growth inhibition on AF5 cells. The opioid antagonist naltrexone at 0.1 nM also caused growth inhibition in the same cells. When DADLE and naltrexone were both added to the AF5 cells, the resultant growth inhibition was apparently additive. DADLE alone or DADLE in combination with naltrexone did not cause apoptosis as evidenced by negative TUNEL staining. The cell-cycle progression analysis indicated that both DADLE (0.1 nM) and naltrexone (0.1 nM) caused an arrest of AF5 cell cycle progression at the G1 checkpoint. Neuronal marker indicated that DADLE- or naltrexone-treated AF5 cells tend to differentiate more when compared to controls. Results demonstrate the non-opioid action of both DADLE and naltrexone on cell cycle arrest and differentiation in a CNS neural progenitor cell line. Results also suggest some potential utilization of DADLE and/or naltrexone in stem cell research. Tsai SY, Lee CT, Hayashi T, Freed WJ, Su TP. Synapse. 2010;64:267-273.

Hibernation-Like State Induced By An Opioid Peptide Protects Against Experimental Stroke

Delta opioid peptide [D-ala2,D-leU5]enkephalin (DADLE) induces hibernation in

summer ground squirrels and enhances preservation and survival of isolated or transplanted lungs and hearts. The present study investigated the protective effect of DADLE in the CNS by using a rat model of stroke. Adult Sprague-Dawley rats were pretreated with DADLE (4 mg/kg every 2 hr X 4 injections, i.p.) or saline prior to unilateral occlusion of the middle cerebral artery (MCA). Daily behavioral tests revealed that ischemic animals treated with DADLE did not show any significant behavioral dysfunctions compared to saline-treated ischemic animals. Opioid antagonists only transiently inhibited the protective effect of DADLE indicating the participation of non-opioid mechanisms in DADLE neuroprotection. Histological examination using triphenyltetrazolium chloride revealed that brains from ischemic animals treated with DADLE, either alone or with adjuvant opioid blockers, exhibited almost completely intact striata. In contrast, brains from ischemic animals that received saline showed significant infarction in the lateral striatum. Analyses of apoptotic cell death revealed a significant increase in the p-53 mRNA expression in the striatum of ischemic animals that received saline, while those that received DADLE exhibited near normal striatal p-53 expression. This protective effect was accompanied by significant increments in protein levels of glial cell line-derived neurotrophic factor in the striatum of DADLE-treated ischemic animals. These results indicate that DADLE protected against necrotic and apoptotic cell death processes associated with ischemia-reperfusion injury. The present study demonstrates that delta opioids are crucially involved in stroke suggesting that the opioid system is important in the study of brain injury and protection. Borlongan CV, Hayashi T, Oeltgen PR, Su TP, Wang Y. BMC Biology. 2009;7:31, online publication.

Sigma-1 Receptors Regulate Hippocampal Dendritic Spine Formation Via A Free Radical-Sensitive Mechanism Involving Rac.GTP Pathway
Sigma-1 receptors (Sig-1Rs) are endoplasmic reticulum (ER)-resident proteins known to be involved in learning and memory. Dendritic spines in hippocampal neurons play important roles in neuroplasticity and learning and memory. This study tested if Sig-1Rs might regulate denritic spine formation in hippocampal neurons and examined potential mechanisms therein. In rat hippocampal primary neurons the knockdown of Sig-1Rs by siRNAs causes a deficit in the formation of dendritic spines that is unrelated to ER Ca2+ signaling or apoptosis but correlates with the mitochondrial permeability transition and cytochrome c release, followed by caspase-3 activation, Tiam1 cleavage, and a reduction in Rac1áGTP. Sig-1R-knockdown neurons contain higher levels of free radicals when compared to control neurons. The activation of superoxide dismutase or the application of a hydroxyl free radical scavenger N-acetyl cysteine (NAC) to the Sig-1R-knockdown neurons rescues dendritic spines and mitochondria from deficits caused by the Sig-1R siRNA. Further, the caspase-3 resistant TIAM1 construct C1199DN, a stable guanine exchange factor able to constitutively activate Rac1 in the form of Rac1áGTP, also rescues the siRNA-caused dendritic spine deficits. These results implicate Sig-1Rs as endogenous regulators in hippopcampal dendritic spine formation and suggest a free radical-sensitive ER-mitochondrion-Rac1áGTP pathway in the regulation of dendritic spine formation in the hippocampus. The results also suggest the importance of free radicals in the learning and unlearning aspects of neurobiology and provide a potential mechanistic explanation on why an established mucolytic agent NAC might have a therapeutic potential as an antiamnesic agent. Tsai Y, Hayashi T, Harvey B, et al. PNAS USA. 2009; Dec 11; Epubmed ahead of print.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Theoretical Considerations on the Topological Organization of Receptor Mosaics
The concept of Receptor Mosaic (RM) is discussed; hence the integrative

functions of the assemblage of G-protein coupled receptors physically interacting in the plane of the plasma membrane. The main focus is on a hetero-trimer of G-protein coupled receptors, namely the A2A-D2-CB1 receptor trimer. A bioinformatics analysis was carried out on the amino acid sequence of these receptors to indicate domains possibly involved in the receptor-receptor interactions. Such a bioinformatic analysis was also carried out on the RM formed by mGLU R5, D2 and A2A. The importance of topology, i.e., of the reciprocal localization of the three interacting receptors in the plan of the membrane for the RM integrative functions is underlined. However, it is also pointed out that this fundamental aspect still awaits techniques capable of an appropriate investigation. Finally, it is discussed how RM topology can give hints for a structural definition of the concept of hub receptor. Thus, just as in any network, the receptor operating as a hub is the one that in the molecular network formed by the receptors has the highest number of inputs. Agnati LF, Fuxe K, Woods AS, Genedani S, Guidolin D. Theoretical considerations on the topological organization of receptor mosaics. Curr Protein Pept Sci. 2009 Sep 15. [Epub ahead of print].

Calcium-Mediated Modulation of the Quaternary Structure and Function of Adenosine A(2A)-Dopamine D(2) Receptor Heteromers

The adenosine A(2A)-dopamine D(2) receptor heteromer is one of the most studied receptor heteromers. It has important implications for basal ganglia function and pathology. Recent studies using bioluminescence and sequential resonance energy transfer techniques shed light on the role of Ca(2+) in the modulation of the quaternary structure of the A(2A)-D(2) receptor heteromer, which was found to depend on the binding of calmodulin (CaM) to the carboxy-terminus of the A(2A) receptor in the A(2A)-D(2) receptor heteromer. Importantly, the changes in quaternary structure correlate with changes in function. A Ca(2+)/CaM-dependent modulation of MAPK signaling upon agonist treatment could be observed in cells expressing A(2A)-D(2) receptor heteromers. These studies provide a first example of a Ca(2+)-mediated modulation of the quaternary structure and function of a receptor heteromer. Ferré S, Woods AS, Navarro G, Aymerich M, Llu's C, Franco R. Calcium-mediated modulation of the quaternary structure and function of adenosine A(2A)-dopamine D(2) receptor heteromers. Curr Opin Pharmacol. 2009 Nov 5. [Epub ahead of print]

Ammonium Sulfate and MALDI In-Source Decay: A Winning Combination For Sequencing Peptides

In previous papers, IRP investigators highlighted the role of ammonium sulfate in increasing peptide fragmentation by in-source decay (ISD). The current work systematically investigated effects of matrix assisted laser desorption ionization (MALDI) extraction delay, peptide amino acid composition, matrix, and ammonium sulfate concentration on peptide ISD fragmentation. The data confirmed that ammonium sulfate increased peptides signal-to-noise ratio as well as their in-source fragmentation, resulting in complete sequence coverage regardless of the amino acid composition. This method is easy, inexpensive, and generates the peptides sequence instantly. Delvolve A, Woods AS. Ammonium sulfate and MALDI in-source decay: A winning combination for sequencing peptides. Anal Chem. 2009 Oct 30. [Epub ahead of print]

Molecular Neurobiology Research Branch

Neural Protection and Regeneration Section

Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Reduces Ischemic Brain Injury and Promotes Behavioral Recovery In Rats

Mesencephalic astrocyte-derived neurotrophic factor (MANF), also known as Arginine-rich, Mutated in Early Stage of Tumors (ARMET), is a secreted protein which reduces endoplasmic reticulum (ER) stress. Previous studies have shown

that MANF mRNA expression and protein levels are increased in the cerebral cortex after brain ischemia, a condition which induces ER stress. The function of MANF during brain ischemia is still not known. The purpose of this study was to examine the protective effect of MANF after ischemic brain injury. Recombinant human MANF was administrated locally to the cerebral cortex before a 60-min middle cerebral artery occlusion (MCAo) in adult rats. Triphenyltetrazolium chloride (TTC) staining indicated that pretreatment with MANF significantly reduced the volume of infarction at two days after MCAo. MANF also attenuated TUNEL labeling, a marker of cell necrosis/apoptosis, in the ischemic cortex. Animals receiving MANF pretreatment demonstrated a decrease in body asymmetry and neurological score as well as an increase in locomotor activity after MCAo. Taken together, these data suggest that MANF has neuroprotective effects against cerebral ischemia, possibly through the inhibition of cell necrosis/apoptosis in cerebral cortex. Airavaara M, Shen H, Kuo CC, Peranen J, Saarma M, Hoffer BJ, Wang Y. Mesencephalic astrocyte-derived neurotrophic factor (MANF) reduces ischemic brain injury and promotes behavioral recovery in rats. J Comp Neurol 2009;515:116-124.

Diadenosine Tetraphosphate Reduces Toxicity Caused By High-Dose Methamphetamine Administration

Diadenosine tetraphosphate (AP4A), two adenosine moieties bridged by four phosphates, is an endogenous purinergic ligand found in brain. Previous studies have shown that AP4A reduced neurodegeneration caused by the dopaminergic neurotoxin 6-hydroxydopamine in rat striatum and substantia nigra. The purpose of this study was to determine whether AP4A is protective against methamphetamine (MA) -mediated toxicity. Primary neuronal cultures were prepared from rat embryonic (E14- E15) ventral mesencephalic tissue. Cultures treated with 2 mM MA exhibited decreased tyrosine hydroxylase (TH) immunoreactivity and increased cleaved caspase-3 immunoreactivity and TUNEL labeling. All these changes were lessened by pretreatment with AP4A. The protective effect of AP4A was also found in vivo. Adult Sprague-Dawley rats were injected with AP4A (25 µg/ 20 µl) or vehicle intracerebroventricularly followed by 4 doses of MA (5 or 10 mg/ kg), given subcutaneously every two hours. Administration of MA reduced locomotor activity one day after injection, which was significantly antagonized by the pretreatment with AP4A. Using immunohistochemical analysis, TH fiber density at the substantia nigra pars reticulata was found reduced while cleaved caspase-3 immunoreactivity in striatum was increased after MA treatment; these responses were also significantly antagonized by AP4A. Taken together, our data show that AP4A has protective effects against MA-mediated toxicity both in vitro and in vivo. The mechanism of action involves suppression of MA -induced apoptosis. Harvey BK, Chou J, Shen H, Hoffer BJ, Wang Y. Diadenosine tetraphosphate reduces toxicity caused by high-dose methamphetamine administration. Neurotoxicology 2009; 30:436-444.

GLP-1 Receptor Stimulation Preserve Primary Cortical and Dopaminergic Neurons In Cellular and Rodent Models Of Stroke and Parkinsonism

Glucagon-like peptide-1 (GLP-1) is an endogenous insulinotropic peptide secreted from the gastrointestinal tract in response to food intake. It enhances pancreatic islet beta-cell proliferation and glucose-dependent insulin secretion, and lowers blood glucose and food intake in patients with type 2 diabetes mellitus (T2DM). A long-acting GLP-1 receptor (GLP-1R) agonist, exendin-4 (Ex-4), is the first of this new class of antihypergly-cemia drugs approved to treat T2DM. GLP-1Rs are coupled to the cAMP second messenger pathway and, along with pancreatic cells, are expressed within the nervous system of rodents and humans, where receptor activation elicits neurotrophic actions. IRP scientists detected GLP-1R mRNA expression in both cultured embryonic primary cerebral cortical and ventral mesencephalic (dopaminergic) neurons. These cells are vulnerable to hypoxia- and 6-hydroxydopamine-induced cell death, respectively. They found that GLP-1 and Ex-4 conferred protection in

these cells, but not in cells from Glp1r knockout (-/-) mice. Administration of Ex-4 reduced brain damage and improved functional outcome in a transient middle cerebral artery occlusion stroke model. Ex-4 treatment also protected dopaminergic neurons against degeneration, preserved dopamine levels, and improved motor function in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease (PD). These findings demonstrate that Ex-4 can protect neurons against metabolic and oxidative insults, and they provide preclinical support for the therapeutic potential for Ex-4 in the treatment of stroke and PD. Li Y, Perry T, Kindy MS, et al. GLP-1 receptor stimulation preserve primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. PNAS USA 2009;106:1285-1290.

Delayed Treatment With A P53 Inhibitor Enhances Recovery In Stroke Brain

Cerebral ischemia can activate endogenous reparative processes, such as proliferation of endogenous neural progenitor cells (NPCs) in the subventricular zone (SVZ). Most of these new cells die shortly after injury. The purpose of this study was to examine a novel strategy for treatment of stroke at one week after injury by enhancing the survival of ischemia-induced endogenous NPCs in SVZ. Adult rats were subjected to a 90-min middle cerebral artery occlusion (MCAo). A p53 inhibitor pifithrin-alpha (PFT-a) was administered to stroke rats from days 6 to 9 after MCAo. Locomotor behavior was measured using an activity chamber. Proliferation, survival, migration, and differentiation of endogenous NPCs were examined using qRT-PCR, TUNEL, and immunohistochemistry. IRP researchers found that PFT-a enhanced functional recovery as assessed by a significant increase in multiple behavioral measurements. Delayed PFT-a treatment had no effect on the cell death processes in the lesioned cortical region. However, it enhanced the survival of SVZ progenitor cells and promoted their proliferation and migration. PFT-a inhibited the expression of a p53-dependent pro-apoptotic gene, termed PUMA (p53-upregulated modulator of apoptosis), within the SVZ of stroke animals. The enhancement of survival/proliferation of NPCs was further found in SVZ neurospheres in tissue culture. PFT-a dose-dependently increased the number and size of new neurosphere formation. In conclusion, our data suggest that delayed treatment with a p53 inhibitor PFT-a is able to modify stroke-induced endogenous neurogenesis and improve the functional recovery in stroke animals. Luo Y, Kuo CC, Shen H, Chou J, Greig NH, Hoffer BJ, Wang Y. Delayed treatment with a p53 inhibitor enhances recovery in stroke brain. Ann Neurol 2009;65:520-530.

9-Cis-Retinoic Acid Reduces Ischemic Brain Injury In Rodents Via Bone Morphogenetic Protein

Retinoic acid (RA), a biologically active derivative of vitamin A, has protective effects against damage caused by H2O2 or oxygen-glucose deprivation in mesangial and PC12 cells. In cultured human osteosarcoma cells, RA enhances the expression of bone morphogenetic protein -7 (BMP7), a trophic factor that reduces ischemia- or neurotoxin -mediated neurodegeneration in vivo. The purpose of this study is to examine whether RA reduces ischemic brain injury through a BMP7 mechanism. The authors found that intracerebroventricular administration of 9-cis-retinoic acid (9cRA) enhanced BMP7 mRNA expression, detected by RTPCR, in rat cerebral cortex at 24 hours after injection. Rats were also subjected to transient focal ischemia induced by ligation of the middle cerebral artery (MCA) at one day after 9cRA injection. Pretreatment with 9cRA increased locomotor activity and attenuated neurological deficits 2 days after MCA ligation. 9cRA also reduced cerebral infarction and TUNEL labeling. These protective responses were antagonized by BMP antagonist noggin given at one day after 9cRA injection. Taken together, these data suggest that 9cRA has protective effects against ischemia -induced injury and these effects involve BMPs. Shen H, Luo Y, Kuo CC, Deng X, et al. 9-Cis-Retinoic acid reduces ischemic brain injury in rodents via bone morphogenetic protein . J Neurosci Res 2009; 87:545-555.

Astaxanthin Reduces Ischemic Brain Injury In Adult Rats

Astaxanthin (ATX) is a dietary carotenoid of crustaceans and fish that contributes to their coloration. Dietary ATX is important for development and survival of salmonids and crustaceans and has been shown to reduce cardiac ischemic injury in rodents. The purpose of this study was to examine whether ATX can protect against ischemic injury in the mammalian brain. Adult rats were injected intracerebroventricularly with ATX or vehicle prior to a 60-min middle cerebral artery occlusion (MCAo). Treatment with ATX, compared to vehicle, increased locomotor activity in stroke rats and reduced cerebral infarction at 2 days after MCAo. To evaluate the protective mechanism(s) of ATX against stroke, brain tissues were assayed for free radical damage, apoptosis and excitoxicity. ATX antagonized ischemia -mediated loss of aconitase activity and reduced glutamate release, lipid peroxidation, translocation of cytochrome C and TUNEL labeling in the ischemic cortex. ATX did not alter physiological parameters, such as body temperature, brain temperature, cerebral blood flow, blood gases, blood pressure, and pH. Collectively, these data suggest that ATX can reduce ischemia-related injury in brain through the inhibition of oxidative stress, reduction of glutamate release, and anti-apoptosis. ATX may be clinically useful for patients vulnerable or prone to ischemic events. Shen H, Kuo CC, Chou J, et al. Astaxanthin reduces ischemic brain injury in adult rats. FASEB J 2009;23:1958-1968.

Severity of Controlled Cortical Impact Traumatic Brain Injury In Rats and Mice Dictates Degree Of Behavioral Deficits

The clinical presentation of traumatic brain injury (TBI) involves either mild, moderate, or severe injury to the head resulting in long-term and even permanent disability. The recapitulation of this clinical scenario in animal models should allow examination of the pathophysiology of the trauma and its treatment. To date, only a few studies have demonstrated TBI animal models encompassing the three levels of trauma severity. Thus, in the present study IRP scientists characterized in mice and rats both brain histopathologic and behavioral alterations across a range of injury magnitudes arising from mild, moderate, and severe TBI produced by controlled cortical impact injury technique. Here, they replicated the previously observed TBI severity-dependent brain damage as revealed by 2,3,5-triphenyltetrazolium chloride staining (severe > moderate > mild) in rats, but also extended this pattern of histopathologic changes in mice. Moreover, they showed severity-dependent abnormalities in locomotor and cognitive behaviors in TBI-exposed rats and mice. Taken together, these results support the use of rodent models of TBI as a sensitive platform for investigations of the injury-induced neurostructural and behavioral deficits, which should serve as key outcome parameters for testing experimental therapeutics. Yu S, Kaneko Y, Bae E, et al. Severity of controlled cortical impact traumatic brain injury in rats and mice dictates degree of behavioral deficits. Brain Res 2009;1287:157-163.

Psychobiology Section, Medications Discovery Research Branch

Reinforcing Effects Of ∑-Receptor Agonists In Rats Trained To Self-Administer Cocaine

Sigma receptor (σR) antagonists have been reported to block certain effects of psychostimulant drugs IRP researchers found that these same σR antagonists did not affect cocaine self-administration. Interestingly, these drugs block conditioned place preference induced by cocaine indicating that the two procedures used to assess abuse liability of drugs tap different aspects of the activity of drugs of abuse. In contrast to the inactivity of σR antagonists against cocaine self administration, σR agonists were effective reinforcers in subjects trained to self administer cocaine. In addition, σR agonists, like dopamine uptake inhibitors, potentiated the reinforcing effects of cocaine in the self-administration procedure. The σR antagonists antagonized the self administration of σR agonists, despite their inactivity against cocaine. Response

rates maintained by maximally effective doses of σR agonists were selectively decreased by σR antagonists (effective doses did not alter response rates maintained by food reinforcement). Although σR antagonists block some cocaine-induced effects, the lack of effect on cocaine self-administration suggests that the primary reinforcing effects of cocaine do not involve direct effects at σRs. However, the self-administration of σR agonists in cocaine-trained subjects, potentiation of cocaine self-administration by σR-agonists suggest enhanced abuse-related effects resulting from concomitant dopaminergically-mediated actions and σR-mediated actions of the drugs.
Hiranita T, Soto PL, Tanda G, Katz JL. Reinforcing effects of σ-receptor agonists in rats trained to self-administer cocaine. JPET Fast Forward. DOI:10.1124/jpet.109.159236.

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

Program Activities

New NIDA PAs and RFAs

On November 4, 2009, NIDA issued a PA entitled **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and/or Women and Sex/Gender Differences (R36) PAR-10-020**. This FOA will utilize the NIH Dissertation Award (R36) grant mechanism.

On November 5, 2009, NIDA issued **AIDS-Science Track Award for Research Transition (R03) PAR-10-021.** This FOA seeks to facilitate the entry of both newly independent and early career investigators to the area of drug abuse research on HIV/AIDS. This FOA, AIDS--Science Track Award for Research Transition (A-START), encourages Small Research Grant (R03) applications to support research projects on drug abuse and HIV/AIDS that can be carried out in a short period of time with limited resources. 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.

On January 4, 2010, NIDA issued **Mechanism for Time-Sensitive Drug Abuse Research (R01) PAR-10-072.** This is intended to support substance abuse prevention and treatment services research in rapidly evolving areas (e.g., changes in service systems, health care financing, policy, natural/man-made disasters, etc) where opportunities for empirical study are, by their very nature, only available through expedited review and award of support. There are three distinguishing features of an eligible study: 1) the study's scientific value and feasibility are clear, 2) rapid review and funding are required in order for the scientific question to be answered, and 3) the knowledge gained from the study is time-sensitive and seeking funding through the regular NIH cycle of review and award would result in a missed opportunity to conduct the research. It should be clear that the research question offers an uncommon and scientifically significant research opportunity that could only become available if the project is initiated with minimum delay. Opening Date: February 9, 2010 (Earliest date an application may be submitted to Grants.gov); Letters of Intent Receipt Date(s): 4 weeks prior to planned submission date: Application Submission/Receipt Date(s): March 9, 2010, June 9, 2010, September 10, 2010 December 9, 2010, March 9, 2011, June 9, 2011, September 9, 2011, December 9, 2011, March 9, 2012, June 8, 2012, September 10, 2012, December 10, 2012.

On September 3, 2009, NIDA issued RFAs entitled **Exploring Epigenomic Processes and Non-Coding RNAs in HIV/AIDS (R01) RFA-DA-10-010 and (R21) RFA-DA-10-011.** The purpose of these FOAs is to enhance our understanding of the role of epigenomics in HIV infection and pathogenesis in

Planned Meetings

Publications

Staff Highlights

Grantee Honors

combination with substance abuse. They invite applications proposing innovative research to stimulate new areas of research or develop new approaches to existing studies. Newly-formed collaborations to foster sharing of expertise between the fields of HIV/AIDS, drug abuse, and epigenomics research are encouraged. Letters of Intent Receipt Date(s) for this FOA: November 23, 2009; Application Due Date(s): December 23, 2009.

On September 17, 2009, NIDA issued an RFA entitled **Targeted Library Synthesis and Screening at Novel Targets for Potential Drug Addiction Treatments and Research Tools (R21/R33) RFA-DA-10-005.** This FOA solicits research applications from institutions/organizations that propose to promote the discovery of novel medications through the use of targeted library synthesis and screening for drug addiction treatment, as well as the discovery of CNS-active research tools for medication target validation in animal models of drug addiction. Letters of Intent Receipt Date(s): November 4, 2009; Application Due Date(s): December 4, 2009.

On September 24, 2009, NIDA issued an RFA entitled **Medications Development for Cannabis-Related Disorders (R01) RFA-DA-10-016.** The purpose of this FOA is to support research studies that focus on the identification, and preclinical and clinical evaluation, of medications that can be safe and effective for the treatment of cannabis-use and -induced disorders, as well as their medical and psychiatric consequences. The studies can be preclinical or FDA-defined Phase I, Phase II or Phase III clinical trials. Letters of Intent Receipt Date(s): March 30, 2010; Application Due Date(s): April 30, 2010.

On December 9, 2009, NIDA issued **Cognitive Remediation Approaches to Improve Drug Abuse Treatment Outcomes (R01) RFA-DA-10-006 and (R21) RFA-DA-10-007.** There is a significant public health need to improve the outcome of treatments of substance use disorders (SUDs). SUDs are often associated with cognitive changes that may negatively impact drug abuse treatment outcomes. The purpose of these FOAs is to solicit clinical research project applications that design and/or develop cognitive remediation strategies that enhance the outcome of SUD treatments. Letters of Intent Receipt Date(s): March 8, 2010; Application Due Date(s): April 7, 2010.

On December 18, 2009, NIDA issued the **2010 NIDA Avant-Garde Award Program for HIV/ AIDS Research (DP1) RFA-DA-10-012.** The NIDA Avant-Garde Award Program for HIV/AIDS Research is meant to complement NIDA's traditional investigator-initiated grant programs by supporting individual scientists of exceptional creativity who propose high-impact research that will open new avenues for prevention and treatment of HIV/AIDS among drug abusers. The term "avant-garde" is used to describe highly innovative approaches that have the potential to be transformativeÑopen new areas of research or lead to new avenues of treatment and prevention for HIV/AIDS among drug abusers. The proposed research should reflect ideas substantially different from those already being pursued by the investigator or others. The 2010 Avant-Garde Award competition will proceed in two phases. The first phase is a pre-application phase in response to PAR-10-068. Pre-applications will be evaluated by a group of external reviewers. Those investigators whose submissions are judged to be the most outstanding will be notified of the opportunity to submit full applications under this FOA (DP1). The 2010 Avant-Garde awardees will be selected from this group of applicants. Application Due Date(s): June 2, 2010.

PAs/RFAs Issued with Other NIH Components/Agencies

On October 14, 2009, NIDA, in collaboration with NIAAA, issued PAs entitled **Behavioral & Integrative Treatment Development Program (R03) PA-10-011 and (R34) PA-10-013.** The purpose of these FOAs is to encourage

early career investigators or investigators who are striving to make a shift in their research to propose discrete, well-defined projects that can be completed within two years with limited resources. Projects of interest fall within the research domain of behavioral, combined, sequential, or integrated (behavioral/pharmacological) (1) drug abuse treatment interventions, including interventions for patients with comorbidities, in diverse settings; (2) interventions to prevent the acquisition or transmission of HIV infection among individuals in drug abuse treatment; (3) interventions to promote adherence to drug abuse treatment, HIV and addiction medications; and (4) interventions to treat chronic pain. Specific examples include: 1) Stage I pilot or feasibility studies; 2) secondary analysis of existing data; 3) small, self-contained research projects; 4) development of research assessments or methodology; and 5) development of new research technology.

On October 14, 2009, NIDA, in collaboration with NIAAA and NINR, issued the PA entitled **Behavioral & Integrative Treatment Development Program (R01) PA-10-012.** The purpose of this FOA for R01 applications is to encourage Stage II or Stage III research to conduct clinical trials, examine mechanisms of behavior change, determine dose-response, optimize combinations, and/or ascertain best sequencing of behavioral, combined, sequential, or integrated behavioral and pharmacological (1) drug abuse treatment interventions, including interventions for patients with comorbidities, in diverse settings; (2) interventions to prevent the acquisition or transmission of HIV infection among individuals in drug abuse treatment; (3) interventions to promote adherence to drug abuse treatment, HIV and addiction medications; and (4) interventions to treat chronic pain.

On October 30, 2009, NIDA, in collaboration with NCI and OBSSR, issued the PA entitled **Accelerating the Pace of Drug Abuse Research Using Existing Epidemiology, Prevention, and Treatment Research Data (R01) PAR-10-018.** This FOA invites applications to support the innovative analysis of existing social science and behavioral data to study the etiology and epidemiology of drug using behaviors (defined as alcohol, tobacco, and other drug), HIV risk behaviors, related disorders, prevention and treatment of these behaviors, and health service utilization including quality, access, and costs. NIDA and NCI encourage coordinated analyses of substance abuse research data that are in public use or that are privately held by a principal investigator.

On November 16, 2009, NIDA, in collaboration with NCI and NHLBI, issued **Effectiveness Research on Smoking Cessation in Hospitalized Patients (U01) RFA-HL-10-020.** This FOA solicits Cooperative Agreement (U01) applications from institutions/organizations that propose to study the effectiveness of smoking cessation interventions for hospitalized patients. Hospitalization provides a unique opportunity for smoking cessation, and although the nature of cessation interventions during hospitalization varies widely, these interventions appear efficacious when continued cessation support is provided for at least one month post-discharge. Therefore, the purpose of this FOA is to encourage research to evaluate the translation of efficacious smoking cessation strategies initiated during hospitalization and continued post-discharge into effective programs that can be widely implemented in routine clinical practice and assess the cost-effectiveness of these interventions. Letters of Intent Receipt Date: December 18, 2009; Application Due Date: January 19, 2010.

On November 20, 2009, NIDA, in collaboration with NIMH, NIA, NIAAA and NIBIB, issued **Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders (R21) PA-10-023.** This FOA invites research grant applications from organizations/institutions that propose the development of novel radioligands for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging in human

brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies.

On November 20, 2009, NIDA, in collaboration with NIMH, NIA, and NIAAA, issued **Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders (Phased Innovation Award [R21/R33]) PAR-10-024.** This FOA invites research grant applications from organizations/ institutions that propose the development of novel radioligands for positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies.

On November 24, 2009, NIDA, in collaboration with NIMH and NIAID, issued **Seek, Test, and Treat: Addressing HIV in the Criminal Justice System (R01) RFA-DA-10-017.** This initiative solicits R01 applications to empirically test the seek, test, and treat paradigm in criminal justice populations. The seek, test, and treat model involves reaching out to high risk, hard to reach groups who have not been recently tested (seek), engaging them in HIV testing (test), and initiating, monitoring, and maintaining HAART for those testing positive (treat). Researchers are encouraged to develop, implement, and test strategies to increase HIV testing and the provision of HAART to HIV seropositive individuals involved with the criminal justice system, with particular focus on continuity of HAART during and after community re-entry following incarceration. Key outcome measures include linkage to care (e.g., seen at care center post-release) and viral suppression (e.g., proportion with undetectable viral load 6 months or more after initiation of ART). Applications responsive to this FOA may propose intervention research at the individual, organizational, or system level that leads to effective approaches for expanding access to HIV testing and HAART treatment in the criminal justice system and in community organizations working with criminal justice systems and populations. Letters of Intent Receipt Date(s): March 2, 2010; Application Due Date(s): April 1, 2010.

On December 4, 2009, NIDA and NIAAA issued **Support Opportunity for Addiction Research (SOAR) for New Investigators (R03) RFA-DA-10-015.** This FOA solicits applications to supplement new investigators who have, or have a commitment of support to conduct research in basic or clinical alcohol or drug abuse research from funding sources other than NIH (e.g. private foundation). In addition, those applicants currently supported to conduct research on psychiatric disorders that are often found to be co-morbid with substance abuse, are also eligible to apply to SOAR for the purpose of adding a substance or alcohol abuse research component to their on-going research. It is hoped that the SOAR program will facilitate ongoing supported substance abuse and co-morbidity research among entry-level new investigators. This FOA is intended to support new investigators' on-going basic or clinical alcohol, drug abuse and/or related co-morbidity research. The primary goal of this Support Opportunity for Addiction Research (SOAR) is for new investigators to leverage existing research programs in order to strengthen, possibly expand, and/or further develop alcohol, drug abuse, and co-morbidity research.Letters of Intent Receipt Date(s): March 16, 2010; Application Due Date(s): April 16, 2010.

On January 29, 2010 NIDA, in collaboration with NIMH and NICHD, issued **Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) [U01] RFA-HD-10-015.** The purpose of this FOA is to invite applications from investigators willing to participate with NICHD, NIDA, and NIMH under a cooperative agreement to support the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN). The primary mission of the ATN will be to conduct research, both independently and in collaboration with existing research networks and individual investigators, in HIV-infected and HIV-at-risk

pre-adolescents, adolescents, and young adults up to age 25 years. This network will have the capacity for developing and conducting selected behavioral, community-based translational, prophylactic, therapeutic, microbicide and vaccine trials. Letters of Intent Receipt Date(s): March 14, 2010; Application Receipt Dates(s):April 14, 2010.

Additional PAs/RFAs Issued with Numerous Other NIH/HHS Components

Limited Competition for the Pediatric HIV/AIDS Cohort Study (U01) RFA-HD-09-006. Application Receipt Date: October 28, 2009

Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) (R01) RFA-GM-10-009. Application Due Date(s): November 24, 2009

Recovery Act Limited Competition: Building Sustainable Community-Linked Infrastructure to Enable Health Science Research (RC4) RFA-OD-09-010. Letters of Intent Receipt Date(s): November 12, 2009; Application Due Date(s): December 11, 2009

NIH Blueprint for Neuroscience Research Competitive Revisions for Studies Focused on Neuropathic Pain or Neural Plasticity to Promote Collaborative Pain Research (R01) PAR-09-264. Application Due Date(s): November 23, 2009

Bioengineering Nanotechnology Initiative (STTR [R41/R42]) PA-09-266

Bioengineering Nanotechnology Initiative (SBIR [R43/R44]) PA-09-267

Drug Discovery for Nervous System Disorders (R01) PAR-10-001

Drug Discovery for Nervous System Disorders (R21) PAR-10-002

Mechanisms, Models, Measurement, & Management in Pain Research (R01) PA-10-006

Mechanisms, Models, Measurement, & Management in Pain Research (R21) PA-10-007

Mechanisms, Models, Measurement, & Management in Pain Research (R03) PA-10-008

Bioengineering Research Grants (BRG) (R01) PA-10-009

Exploratory/Developmental Bioengineering Research Grants (EBRG) [R21] PA-10-010

Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32) PA-10-036

Ruth L. Kirschstein National Research Service Award Short-Term Institutional Research Training Grants (T35) PA-10-037

Blueprint Program for Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (R25) RFA-MH-10-070. Letters of Intent Receipt Date(s): February 24, 2010; Application Submission/Receipt Date(s): March 24, 2010

Dissemination and Implementation Research in Health (R01) PAR-10-038

Dissemination and Implementation Research in Health (R03) PAR-10-039

Dissemination and Implementation Research in Health (R21) PAR-10-040

Mentored Research Scientist Development Award (Parent K01) PA-10-056

Independent Scientist Award (Parent K02) PA-10-057

Mentored Clinical Scientist Research Career Development Award (Parent K08) PA-10-059

Mentored Patient-Oriented Research Career Development Award (Parent K23) PA-10-060

Midcareer Investigator Award in Patient-Oriented Research (Parent K24) PA-10-061

Mentored Quantitative Research Development Award (Parent K25) PA-10-062

NIH Pathway to Independence Award (Parent K99/R00) PA-10-063

NIH Small Research Grant Program (Parent R03) PA-10-064

Research Project Grant (Parent R01) PA-10-067

NIH Exploratory Developmental Research Grant Program (Parent R21) PA-10-069

Academic Research Enhancement Award (Parent R15) PA-10-070

ARRAOS: Recovery Act Limited Competition: Behavioral Economics for Nudging the Implementation of Comparative Effectiveness Research: Clinical Trials (RC4) RFA-OD-10-001

ARRAOS: Recovery Act Limited Competition: Behavioral Economics for Nudging the Implementation of Comparative Effectiveness Research: Pilot Research (RC4) RFA-OD-10-002

Recovery Act Limited Competition: NIH Director's Opportunity for Research in Five Thematic Areas (RC4) RFA-OD-10-005

Recovery Act Limited Competition: NIH Basic Behavioral and Social Science Opportunity Network (OppNet) Short-term Mentored Career Development Awards in the Basic Behavioral and Social Sciences for Mid-career and Senior Investigators (K18) RFA-OD-10-003

NIH Support for Conferences and Scientific Meetings (Parent R13/U13) PA-10-071

Recovery Act Limited Competition: Institutional Comparative Effectiveness Research Mentored Career Development Award (KM1) RFA-OD-10-011. Opening Date: February 25, 2010; Application Due Date: March 25, 2010

PHS 2010-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]) PA-10-050

PHS 2010-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42]) PA-10-051

Other Program Activities

Clinical Trials Network (CTN) Update

Protocols: A total of 43 protocols have been initiated since 2001, including multi-site clinical trials (29), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 18 ancillary studies have been supported by CTN and non-CTN funds. Over 11,000 participants have 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 0018**, Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment
- **Protocol CTN 0019**, Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment
- **Protocol CTN 0021**, Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse. This is the first Spanish-only protocol in the CTN.

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

In addition, the following protocols have submitted primary paper:

- **Protocol CTN 0017**, HIV and HCV Intervention in Drug Treatment Settings
- **Protocol CTN 0030A2**, Effects of Chronic Opioids in Subjects with a History of Opioid Use

The following protocols have locked the data:

- **Protocol CTN 0014**, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)
- **Protocol CTN 0028**, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD).
- **Protocol CTN 0030**, Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Pre-screening began in May 2006. The study, carried out in 9 sites, has randomized 653 participants into phase 1 and 360 participants into phase 2 and is currently in the close-out phase.
- **Protocol CTN 0030A1**, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR and it is in the data analysis phase.

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 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.
- **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 who completed the data collection and blood draw procedures.
- **Protocol CTN 0031A2**, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study. In collaboration with DESPR. The baseline data obtained in this research formed the foundation for an R01 grant awarded 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 seeks to evaluate the most effective strategy to ensure that persons in drug treatment programs are tested for HIV and receive their HIV test results. The protocol has completed enrollment and is currently collecting the 6-month follow-up data. Twelve hundred and eighty one patients in 12 CTN community drug abuse centers were enrolled in 5 months.
- **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.

The following protocols are in the development phase:

- **Protocol CTN 0037**, Exercise as a Treatment for Substance Use Disorders. This clinical trial will test the effectiveness of the addition of exercise in improving drug abuse treatment outcomes.
- **Protocol CTN-0038-Ot**, Barriers to Substance Abuse Treatment among Asian Americans and Pacific Islanders. The objective of this study is to gain a better understanding of the factors that may influence the under-utilization of substance abuse treatment services by Asian Americans and Pacific Islanders (AAPIs) and the readiness of substance abuse treatment programs serving AAPIs to participate in clinical trials and adopt evidence based practices. This study is a collaboration with NIH NCMHD.
- **Protocol CTN 0044**, Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders. The purpose of this study is to evaluate the effectiveness of adding an interactive, web-based version of the Community Reinforcement Approach (CRA) intervention plus abstinence incentives as an adjunct to community-based, outpatient substance abuse treatment.
- **Protocol CTN 0045-Ot**,Rates of HIV Testing and Barriers to Testing in

African Americans Receiving Substance Abuse Treatment. This is an observational study seeking to: (1) Compare the proportion of African American and non-African Americans receiving treatment at substance abuse treatment clinics that have been tested for HIV within the past 12 months; (2) Observe relationships between rates of African Americans who have not been tested and a) the types of testing offered at substance abuse treatment clinics and b) the types of outreach strategies used to engage persons in HIV testing; and (3) assess African American clients' self-reported barriers to accessing HIV testing, in relation to other ethnicities.

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

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

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

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

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

Abood, Mary E. -- Temple University
Pamoic Acid Analogues as Potent GPR35 Agonists Inducing Antinociception

Ananthan, Subramaniam -- Southern Research Institute

Development of Dopamine D3 Ligands as Medications for Psychostimulant Addiction

Andersen, Susan L. -- McLean Hospital (Belmont, MA)
Early Drug Exposure and Drug Reward Mechanisms

Andrews, Judy A. -- Oregon Research Institute
Salivary Biomarkers (DNA, RNA and Cortisol), Life Stress and Nicotine Dependence

Anokhin, Andrey P. -- Washington University
Neurocognitive Effects of Nicotine Deprivation and Dopamine Genes

Anokhin, Andrey P. -- Washington University
Neurocognitive Predictors of Smoking Cessation

Arria, Amelia M. -- Treatment Research Institute, Inc. (TRI)
Internet as Supplier: Preventing Adolescent Use of Non-Medical Addictive Rx

Ball, Kevin -- Bloomsburg University of Pennsylvania
Neural Mechanisms Underlying Individual Differences in 3,4-Methylenedioxymethamphetamine

Barry, Colleen L. -- Yale University
Expanding Treatment of Opioid Dependence among the Privately Insured

Barth, Alison L. -- Carnegie-Mellon University
Development of a Fos-Channel Rhodopsin Transgenic Mouse

Beech, Robert David -- Yale University
Progesterone-Induced Gene Expression Changes and Risk of Relapse to Cocaine Use

Biglan, Anthony -- Oregon Research Institute
Creating the Scientific Infrastructure for the Promise Neighborhood Initiative

Blakely, Randy D. -- Vanderbilt University
Forward Genetics and the Presynaptic Dopamine Transporter

Blankenship, Kim M. -- Duke University
Drug Policy, Incarceration, Community Re-entry, and Race Disparities in HIV/AIDS

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

Bohn, Laura M. -- Scripps Research Institute
Physiological Implications of Serotonin Receptor Regulation

Bolton, Philip H. -- Wesleyan University
Finding Small Molecules that Modulate Gene Expression

Boyer, Edward W. -- University of Massachusetts Medical School, Worcester
A Mobile Enabling Technology to Promote Adherence to Behavioral Therapy

Bradberry, Charles W. -- University of Pittsburgh at Pittsburgh
Cognitive Dysfunction and Impaired Inhibitory Control in Cocaine Dependence

Breiter, Hans C. -- Massachusetts General Hospital
Imaging of DLPFC and Amygdala Impact on Relative Preference in Cocaine Addiction

Brooks, Adam C. -- Treatment Research Institute, Inc. (TRI)
Evaluation of Web-based Recovery Monitoring with Clinical Alerts

Buch, Shilpa J. -- University of Nebraska Medical Center
Cocaine & HIV: Role of PDGF/PDGF-Receptor Axis in Blood Brain Barrier Disruption

Buckner, Jane Hoyt -- Benaroya Research Institute at Virginia Mason
Linking Genetic Variation in the PTPN2 Gene to Autoimmune Disease Susceptibility

Bush, Terry -- Free and Clear, Inc.
Developing Behavioral Treatment Approaches for Obese Tobacco Quit Line Users

Carelli, Regina M. -- University of North Carolina Chapel Hill
Combined Voltammetry/Electrophysiology in Behaving Rats

Chen, Benjamin K. -- Mount Sinai School of Medicine of NYU
Imaging Virological Synapses During Parenteral HIV Transmission

Chen, Chi -- University of Minnesota Twin Cities
Metabolomic Investigation of Biosignatures of Chronic Cocaine Exposure

Chen, Xiangning -- Virginia Commonwealth University
Variants in Nicotine Receptors and Pharmacogenetics

Chen, Xiangning -- Virginia Commonwealth University
Variants in CHRNA5/CHRNA3/CHRNB4 and Nicotine Dependence

Cherner, Mariana -- University of California, San Diego
Genetics of Monooxygenase Activity & Methamphetamine-Related Brain Injury in HIV

Clarke, William P. -- University of Texas Health Sciences Center, San Antonio
Regulation of Opioid Receptor Function in Trigeminal Ganglion

Coatsworth, J. Douglas -- Pennsylvania State University-University Park
Efficacy Trial of a Mindfulness-Enhanced Strengthening Families Program

Collins, R. Lorraine -- State University of New York at Buffalo
Applying Behavioral Economics and EMA to Physical Activity and Marijuana Use

Colon, Vivian -- University of Puerto Rico Medical Sciences
HPV Infection among High-Risk Young Men in Puerto Rico

Compton, Margaret Ann -- University of California Los Angeles
Pain, Opioids and Pro-Inflammatory Immune Responses

Cottler, Linda B. -- Washington University
Transformative Approach to Reduce Research Disparities towards Drug Users

Cravatt, Benjamin F. -- Scripps Research Institute
A Quantitative Proteomics Platform to Characterize the Nicotine-Dependent Brain

Crystal, Ronald G. -- Weill Medical College of Cornell University
Adenovirus-based Anti-Cocaine Vaccine

Davis, Thomas Paul -- University of Arizona
Blood-to-CNS Drug Uptake in Pain

Dawson-Rose, Carol S. -- University of California, San Francisco
Impact of a Computer-Assisted SBIRT Program in an HIV Care Setting

De Felice, Louis J. -- Virginia Commonwealth University
Amphetamine Acts as a Molecular Stent in the Dopamine Transporter

De La Garza, Richard -- Baylor College of Medicine
RTI-336 as a Treatment for Methamphetamine Dependence

De La Garza, Richard -- Baylor College of Medicine
Modafinil and Escitalopram for Cocaine Addiction

De Wit, Harriet -- University of Chicago
Is Ecstasy an Empathogen? Effects of MDMA on Social and Emotional Processing

Deadwyler, Samuel A. -- Wake Forest University Health Sciences
Neuroimaging Correlates of Cocaine Reinforcement for Cognitive Performance

Delgado, Mauricio R. -- Rutgers The State University of New Jersey, Newark
Neural Mechanisms of Avoidance Learning and Active Coping via Emotion Regulation

Donny, Eric Christian -- University of Pittsburgh at Pittsburgh
Polymorphisms Related to Dopamine Receptor Function and Smoking

Dugosh, Karen Leggett -- Treatment Research Institute, Inc. (TRI)
Improving Ethics in Research Development of the Coercion Assessment Scale (CAS)

Dukic, Vanja -- University of Chicago
Translational Approaches to Multilevel Models of Prenatal Exposure to Cigarettes

Dunlap, Eloise -- National Development & Research Institutes
Video Games' Role in Developing Substance Use

Duran, Bonnie M. -- Northwest Indian College
CBPR with Tribal Colleges-Universities: Alcohol Problems-Solutions

Edberg, Jeffrey C. -- University of Alabama at Birmingham
Functional Evaluation of ITGAM SNPs

Edelen, Maria Orlando -- Rand Corporation
Development and Evaluation of a Smoking Module for Promis

Ehringer, Marissa A. -- University of Colorado at Boulder
Nicotinic Receptor Genes & Substance Abuse: Functional Studies of Associated SNPs

Ellinor, Patrick Thomas -- Massachusetts General Hospital
Functional Assessment of the Locus for Atrial Fibrillation on Chromosome 4q25

Evans-Campbell, Teresa A. -- Northwest Indian College
Caring for our Generations: Supporting Native Mothers and their Families

Feingold, Alan J. -- Oregon Social Learning Center, Inc.
Woman Substance Use and Intimate Partner Violence

Fishbein, Diana H. -- Research Triangle Institute
Effects of Yoga on Physiological and Behavioral Precursors of Drug Abuse

Flynn, Patrick M. -- Texas Christian University
Extending Drug Abuse Treatment & Assessment Resources (DATAR5)

Gabuzda, Dana H. -- Dana-Farber Cancer Institute
Systems Biology of Immune Reconstitution in HIV/AIDS

Gahring, Lorise C. -- University of Utah
Mechanisms of TNFa Enhancement of Nicotinic Receptor Upregulation

Gelernter, Joel -- Yale University
Genomewide Association Study of Cocaine Dependence in two Populations

Gelovani, Juri G. -- University of Texas MD Anderson Cancer Center
HDAC Class IIa specific PET radiotracers for PET imaging of CNS

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

Gintzler, Alan R. -- SUNY Downstate Medical Center
Sex-Dependent Tolerance and Withdrawal Mechanisms

Grant, Jon E. -- University of Minnesota Twin Cities
N-Acetyl Cysteine plus Behavioral Therapy for Nicotine Dependent Pathological Gam

Greene, Kathryn L. -- Rutgers the State University of New Jersey, New Brunswick
Active Involvement in Creating High School Substance Use Prevention Messages

Guo, Guang -- University of North Carolina, Chapel Hill
Genetic/Epigenetic Markers, Social Contexts, Lifecourse and Risky Health Behavior

Hall, Sharon M. -- University of California, San Francisco
Maintaining Nonsmoking

Hauser, Kurt Francis -- Virginia Commonwealth University
Fractalkine as a Therapeutic for Opioid Accelerated Neurotoxicity In HIV

Hawrylycz, Michael -- Allen Institute for Brain Science
Co-expression Networks of Addiction-Related Genes in the Mouse and Human Brain

Heintz, Nathaniel -- Rockefeller University
Translational and Epigenetic Profiling of Cell Types Associated with Addiction

Hemby, Scott Edwards -- Wake Forest University Health Sciences
Proteomic Biosignatures of Withdrawal from Cocaine in Rhesus Monkeys

Henry, Loren Keith -- University of North Dakota
Computational and Biochemical Docking of Dopamine Transporter Antagonists

Hoffer, Lee David -- Case Western Reserve University
Researching the Social Dynamics of a Local Methamphetamine Market

Hoffman, Kim -- Oregon Health and Science University
Agency Process Improvement and Client Outcomes

Hohmann, Andrea Grace -- University of Georgia
An Animal Model of Therapeutic Self-Medication for Neuropathic Pain

Holtz, R. Barry -- Intervexion Therapeutics, LLC
Chimeric anti-Methamphetamine Monoclonal Antibody for Treating Stimulant Toxicity

Hooper, Scott L. -- Ohio University Athens
Using Perturbation to Characterize, and Build Models of, Individual Neurons

Hunt, Geoffrey P. -- Scientific Analysis Corporation
Asian American MSM, Club Drugs and Nightlife

Husbands, Stephen M. -- University of Bath
Discovery of New Treatments for Drug Abuse

Hutchison, Kent E. -- The Mind Research Network
Effectiveness of Varenicline: Testing Individual Differences

Jernigan, Terry L. -- University of California, San Diego
Creating a Pediatric Imaging-Genomics Data Resource

Johnson, Eric O. -- Research Triangle Institute
Genome-Wide Association Study of Heroin Abuse: A Multiethnic Study

Kaminski, Norbert E. -- Michigan State University
THC Impairment of CD4/CD8 T Cell-Mediated Host Resistance to HIV and Influenza

Karn, Jonathan -- Case Western Reserve University
Manipulating Epigenetic Control Mechanisms to Control HIV Transcription

Kessler, Paul D. -- Nabi Biopharmaceuticals
Phase III Study of a Nicotine Vaccine for Smoking Cessation

Kiehl, Kent A. -- The Mind Research Network
Socio-Moral Processing in Psychopathy and Substance Abuse

Killen, Joel D. -- Stanford University
Extended Treatment for Smoking Cessation

Knowles, James A. -- University of Southern California
Transcriptional Atlas of Human Brain Development

Kollins, Scott H. -- Duke University
Genetic Basis of Smoking Abstinence, Smoking Reinforcement, and Inhibitory Control

Koob, George F. -- Scripps Research Institute
Neuronal Substrates of Cocaine Reward

Latimer, William W. -- Johns Hopkins University
Adapt US Version of IFCBT-HIVPI to Prevent HIV among Drug Users in South Africa

Latkin, Carl A. -- Johns Hopkins University
Feasibility of Pharmacy-Based HIV Interventions among IDUs: India

Lee, Tong H. -- Duke University
Novel Ondansetron Formulation for Combination Treatment of Psychostimulant Abuse

Lerman, Caryn -- University of Pennsylvania
Nicotine Abstinence-Induced Cognitive Alterations by COMT Genotype

Lerman, Caryn -- University of Pennsylvania
Functional Characterization of OPRM1 A118G in Nicotine Dependence

Lesage, Mark G. -- Minneapolis Medical Research Foundation, Inc.
Determinants of Nicotine Reinforcement Thresholds and Demand Elasticity in Rats

Lester, Henry A. -- California Institute of Technology
Mice with Functional Fluorescent Nicotinic Receptor Subunits

Lever, John Riley -- University of Missouri-Columbia
Development of Anti-Cocaine Medications

Linares, Lourdes O. -- Mount Sinai School of Medicine of NYU
Early Prevention of Substance Use Initiation in Foster Care

Loftis, Jennifer M. -- Oregon Health and Science University
Pre-Clinical Testing of a Novel Immunotherapy [Recombinant T Cell Receptor Ligand]

Maidment, Nigel T. -- University of California, Los Angeles
Peptide Biomarkers of Drug Exposure: From Brain Microdialysate to Plasma

Malison, Robert T. -- Yale University
DBH, D2High and Cocaine Paranoia/Aversion: A [11C]PHNO PET Study

Marcondes, Maria Cecilia Garibaldi -- Scripps Research Institute
Free Radicals and Methamphetamine Abuse

Martinez, Diana M. -- Columbia University Health Sciences
Imaging the Neurochemistry of Negative Reinforcement in Cocaine Abuse

Martinez, Diana M. -- New York State Psychiatric Institute
PET Imaging of the mGluR5 in Cocaine Abuse

Mash, Deborah C. -- University of Miami School of Medicine
CNS Mechanisms in Cocaine-Related Sudden Death

Mayfield, Roy D. -- University of Texas, Austin
Blood and Brain Gene Profiling in Stimulant Self-Administration

Mbilinyi, Lyungai Filela -- University of Washington
Motivating Substance Abusing Batterers To Seek Treatment

McCaul, Mary E. -- Johns Hopkins University
Imaging Varenicline Effects on Nicotine & Dopamine: Gene Modulation

McDonald, Douglas Corry -- Abt Associates, Inc.
Conduct a Nationwide Epidemiological Study of Rx Drug Diversion for Non-Medical Use

McKay, Dennis Brian -- Ohio State University
Novel Lead Molecule Optimization Targeting Nicotinic Receptor Subtypes

Mclean, John Alan -- Vanderbilt University
Elucidation of Leukocyte and Macrophage Biomarker Signatures from Drugs of Abuse

McMahon, Robert J. -- University of Washington
Emergence of Adolescent Substance Use Problems from the Externalizing Spectrum

Medina, Krista Lisdahl -- University of Cincinnati
Effects of SLC6A4, BDNF and Ecstasy Use on Brain Structure in Young Adults

Mello, Nancy K. -- Mc Lean Hospital (Belmont, MA)
Preclinical Evaluation of Medications to Treat Polydrug Addiction

Metrik, Jane -- Brown University
Genetic Variation and Marijuana's Pharmacologic and Cue-Elicted Effects

Milan, David J. -- Massachusetts General Hospital
The Genetic Basis of Novel Loci Influencing Myocardial Repolarization

Mitchell, Suzanne H. -- Oregon Health and Science University
Exercise-Induced Changes in Impulsivity and Cocaine Self-Administration

Mizel, Steven B. -- Wake Forest University Health Sciences
Development of a Flagellin-Cocaine Conjugate Vaccine

Mohlke, Karen L. -- University of North Carolina, Chapel Hill

Identifying Disease-Related Functional Regulatory Variants in Open Chromatin

Morgan, Michael M. -- Washington State University
Psychostimulants Induce Long-Term Changes in Nociception

Morgenstern, Jon -- Morgenstern National Center on Addiction/Substance Abuse
Treating Addiction as a Chronic Illness

Moult, John -- University of Maryland Biotechnology Institute
Mechanisms of Action of SNPs Associated with Common Disease

Mueller, Devin -- University of Wisconsin Milwaukee
Glutamate and Prefrontal Regulation of Cocaine Seeking After Extinction

Mukhin, Alexey G. -- Duke University
Improving the Efficacy of Anti-Nicotine Immunotherapy

Narendran, Rajesh -- University of Pittsburgh at Pittsburgh
PET Imaging of Cortical Dopamine Transmission in Cocaine Addiction

Neubert, John K. -- University of Florida
Placebos as Insights into Intersections of Pain and Reward in a Preclinical Model

Nikulina, Ella M. -- University of Arizona
Social Stress and Psychostimulant Cross-Sensitization

Nyamathi, Adeline M. -- University of California, Los Angeles
Health Promotion Coaching/Vaccine for Homeless Parolees

Obasi, Ezemenari M. -- University of Georgia
Stress and Drug Use Vulnerability in Rural African Americans

O'Brien, Richard M. -- Vanderbilt University
Characterization of Effects of G6PC2 Gene Variants on Transcription and Splicing

Ogawa, Masaaki -- University of Maryland, Baltimore
Neural Mechanisms of Associative Learning from Negative Reward Prediction Errors

Ophoff, Roel A. -- University of California, Los Angeles
Epigenetics and Disease: The Role of DNA Methylation in Schizophrenia Susceptibility

Palmer, Abraham A. -- University of Chicago
Weighted Genome-Wide Association Study of Amphetamine Sensitivity in Humans

Pan, Zhizhong Z. -- University of Texas MD Anderson Cancer Center
Synaptic Mechanisms for Interactions of Chronic Pain and Opioid Addiction

Paulson, Pamela Elizabeth -- University of Michigan at Ann Arbor
Neuroimaging of CNS Interactions in Addiction, Chronic Pain and Analgesia

Pavlopoulos, Spiro -- University of Connecticut, Storrs
Methods for the Development of Arrestin2 Inhibitors

Pereira Arboleya, Mariana -- Rutgers The State University of New Jersey, Newark
Cocaine Disruption of Maternal Motivation: Preference for Pups Vs. Cocaine

Perkins, Kenneth Alan -- University of Pittsburgh at Pittsburgh
Behavioral Genetics of Mood-Induced Smoking

Perron, Brian E. -- University of Michigan at Ann Arbor
Symptoms and Structure of Inhalant Use Disorders

Petry, Nancy M. -- University of Connecticut School of Medicine/Dentistry
Reinforcing Exercise in Cocaine Abusers

Phillips, Paul E. M. -- University of Washington
Spatiotemporal Dynamics of Striatal Dopamine Release in Reinforcement Learning

Piomelli, Daniele -- University of California, Irvine
Lipid Biosignatures of Drug Addiction

Pisano, M. Michele -- University of Louisville
Developmental Cigarette Smoke Exposure: Biomarkers of Neurotoxicity

Rangel, Antonio -- California Institute of Technology
A Neuroimaging Test of the Reenforcement Learning Dysregulation Model of Addiction

Rawls, Scott M. -- Temple University
Beta-Lactam Chemical Probes for GLT-1 Transporter-Related Pathologies

Rawson, Richard A. -- University of California, Los Angeles
Aerobic Exercise to Improve Outcomes of Treatment for Methamphetamine Dependence

Rodriguez Zas, Sandra L. -- University of Illinois, Urbana-Champaign
Integration of Resources and Studies to Elucidate Neuropeptide Signaling

Sacks, Stanley -- National Development & Research Institutes
Computerized Psychosocial Treatment for Offenders with Substance Use Disorders

Schnitzler, Gavin R. -- Tufts Medical Center
Does The Extreme Variability Of Methadone Metabolism Have An Epigenetic Cause?

Schulman, Howard -- PPD, Inc.
Proteomic Biosignatures of Chronic Drug Exposure

Schwartz, Robert P. -- Friends Research Institute, Inc.
SBIRT in New Mexico

Schweizer, Felix E. -- University of California Los Angeles
Indicators of Early Neurodegeneration: Gene-Toxin Interactions at the Syanpse

Sekaly, Rafick-Pierre -- Oregon Health and Science University
Novel Concepts for the Eradication of HIV

Shaboltas, Alla V. -- Biomedical Center
International Feasibility Study of Pharmacy-Based HIV Prevention: St. Petersburg

Sharp, Burt M. -- University of Tennessee Health Sciences Center
Neuron-Specific Candidate Gene Expression and Adolescent Vulnerability to Smoking

Sigmon, Stacey C. -- University of Vermont & State Agricultural College
Individual Differences in Stimulant Reinforcement as a Function Of DRD2 Allele

Smith, Emilie P. -- Pennsylvania State University-University Park
Prevention and Promotion with Youth in Community-Based Afterschool Programs

Smith, Mark A. -- Davidson College
Physical Activity and Substance Abuse

Smits, Jasper -- Southern Methodist University
Exercise Intervention for Smoking

Sofuoglu, Mehmet -- Yale University
Sensitivity to Intravenous Nicotine: Genetic Moderators

Sombers, Leslie A. -- North Carolina State University, Raleigh
Characterization of Cholinergic Modulation of Dopamine Neurotransmission

Soreca, Isabella -- University of Pittsburgh at Pittsburgh
The Effect of Exercise on Acute Nicotine Withdrawal: Human Study

Spoth, Richard L. -- Iowa State University
Rural Youth and Family Competencies Building Projects

Spoth, Richard L. -- Iowa State University
Toward a PROSPER State Partnership Network: Building Infrastructure and Capacity

Stacy, Alan W. -- Claremont Graduate University
Teenage Stimulant Use: Neurally Plausible Spontaneous and Protective Processes

Stella, Nephi -- University of Washington
Role of ABHD6 in 2-AG Signaling

Stinchcomb, Audra L. -- Alltranz, Inc.
Transdermal Cannabinoid Prodrug Treatment for Cannabis Withdrawal and Dependence

Stitzel, Jerry A. -- University of Colorado at Boulder
Function of the CHRNA5 D398N SNP: Implications for Addiction and Lung Cancer Risk

Stormshak, Elizabeth A. -- University of Oregon
An Internet Infrastructure for Quality Implementation of the Family Check-Up

Sumikawa, Katumi -- University of California, Irvine
Maternal Nicotine Exposure and Development of Hippocampal Circuits

Swerdlow, Neal R. -- University of California, San Diego
Genetics of Individual Differences in Amphetamine Effects on Startle Gating

Szapocznik, Jose -- University of Miami School of Medicine
Brief Strategic Family Therapy versus Treatment as Usual: Extended Follow-up

Thomas, David L. -- Johns Hopkins University
Hepatitis C Pathogenesis and the Human Genome

Thomas, Lisa R. -- Northwest Indian College
Native Pathways to Sobriety: Pacific Northwest Oral Life Histories

Toborek, Michal J. -- University of Kentucky
Exercise as a Novel Strategy to Target Methamphetamine-Induced Cerebrovascular

Umbricht, Annie -- Johns Hopkins University
Effect of Zonisamide on Cocaine Reinforcement, Craving and Relapse

Wager, Tor Dessart -- Columbia University New York, Morningside
Learning to Avoid Pain: Computational Mechanisms and Application to Methamphetamine

Warner, Tamara Duckworth -- East Carolina University
Brain Development, Behavior and Cognition in Pre- and Postnatal Cocaine Exposure

Waterhouse, Barry Dale -- Drexel University
Locus Coeruleus Function and Methylphenidate Action

Watson, Dennis Paul -- Loyola University of Chicago
Housing First Model Fidelity and Implications for Substance Abuse Treatment

Weinshenker, David -- Emory University
Effects of Voluntary Exercise on Reinstatement of Cocaine Seeking

Wessling-Resnick, Marianne -- Harvard University (School of Public Health)
HFE: A Genetic Determinant of Olfactory Mn Absorption and Toxicity

Whitesell, Nancy Rumbaugh -- University of Colorado Denver/Health Sciences Center, Denver
Factors Related to Substance Use Development in Young American Indian Adolescents

Wickstrom, Eric -- Thomas Jefferson University
Neuronal mRNA PET Imaging

Williams, Mark L. -- University of Texas Health Sciences Center, Houston
Tanzanian Drug Treatment as AIDS Prevention - Reliability and Validity Study

Winger, Gail D. -- University of Michigan at Ann Arbor
Impulsivity and Demand for Drug in Rhesus Monkeys

Wolgemuth, Debra J. -- Columbia University Health Sciences
Role of Intronic Variants Affecting Splicing in Juvenile Myoclonic Epilepsy

Woods, James H. -- University of Michigan at Ann Arbor
Dopamine D2/D3 Receptors in Compulsive Disorders

Woody, George E. -- University of Pennsylvania
Adherence to HIV Therapy in Heroin Addicts: Oral vs Extended Release Naltrexone

Wu, Nancy S. -- University of California, Los Angeles
Real-time Assessment for Adolescents' Substance Use Behaviors

Xiao, Guanghua -- University of Texas SouthWest Medical Center/Dallas
Secondary Data Analyses for Substance Abuse Research

Xiao, Xinshu Grace -- University of California, Los Angeles
Functions of Genetic Variants in Alternative Splicing and Biological Networks

Yadid, Gal -- Bar-Ilan University
Possible Treatment of Cocaine Craving and Relapse by Memory Erasure

Yin, Hang -- University of Colorado at Boulder
Probing Opioid-Induced Glial Activation with Peptide Antagonists

Youngentob, Steven L. -- Upstate Medical University
Fetal Nicotine Exposure and Chemosensory Plasticity

Zaveri, Nurulain T. -- Astraea Therapeutics, LLC
Discovery of Bifunctional NOP/Opioid Receptor Ligands for Drug Abuse Therapy

Zubieta, Jon-Kar -- University of Michigan at Ann Arbor
Interaction of Smoking and Chronic Pain at Neurochemical and Phenotypic Levels

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1,205 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 819 applications.

OEA arranged and managed 14 grant review meetings in which 183 applications were evaluated. OEA's reviews included applications in chartered, standing review committees and Special Emphasis Panels (SEPs). In addition, OEA's Contracts Review Branch (CRB) arranged and managed 15 contract proposal review meetings.

NIDA's chartered committees consist of NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). Applications that formerly were assigned to NIDA E (Treatment Review Committee) are now reviewed in CSR. This review cycle also marked the last meetings of NIDA-F and NIDA-L; starting with applications being reviewed for the May 2010 Council, CSR will review applications in the scientific areas that had been assigned to these two committees.

In addition to meetings of the chartered committees, OEA staff held 11 Special Emphasis Panels to review grant applications for a variety of reasons:

- Conflicts with the chartered committees
- Cutting-Edge Basic Research Awards (CEBRA)
- Behavioral Science Track Award for Rapid Transition (B/START)
- Imaging Science Track Award for Research Transition (I/START)
- Conference Grants (R13)
- Requests for Applications (RFAs)

OEA managed the following RFA reviews:

- DA10-003 - Integrating Translational Neuroscience and Adolescent Drug Abuse Treatment (R21)
- DA10-004 - Economic Studies of Health Insurance Coverage on Drug Abuse Treatment Availability, Access, Costs, and Quality (R01)

Completed contract-related review activity from the Contracts Review Branch since the last Council includes:

R&D and non-R&D Contract Reviews

- NO1DA10-9913 - Out Patient Drug Treatment Research Clinic

Planned Meetings

Publications

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- N01DA-10-7773 - Production, Analysis, and Distribution of Cannabis, Marijuana Cigarettes, and related Materials

Phase I SBIR Contract Reviews

- N43 DA10-2218 - New Technologies: Integrating Data from Prescription Monitoring Program(s) to Current Clinical Practice
- N43 DA10-2219 - Development of Innovative Techniques/Tools for the Screening, Recruitment and Follow-up of Clinical Trial Participants
- N43 DA10-2220 - Innovative Diagnostic Drug Screening Tests for Drugs of Abuse
- N43 DA10-4412 - Web Based Cognitive/Neuropsychological testing for Substance Abuse
- N43 DA10-5558 - Development of State-of-the-Art Mechanisms for Epidemiological Records
- N43 DA10-5559 - Using Handheld Devices to Support Recovery
- N43 DA10-5560 - Tools to Promote Security and Appropriate Prescribing of Scheduled Prescription Drugs
- N43 DA10-5561 - Marketing Evidence-Based Prevention Interventions for Substance Abuse Prevention
- N43 DA10-7774 - Rapid and Sensitive Method for the Determination of Nicotine & its Major Cotinine and trans-3'-hydroxycotinine, in Biological Fluids: A Personalized Medicine Approach for Smoking Cessation
- N43 DA10-7775 - Tool Development for New or Improved Capture Reagents
- N43 DA10-7776 - Development of Alternate Drug Delivery Dosage Forms for Drug Studies
- N43 DA10-8892 - Design and Synthesis of Treatment Agents for Drug Abuse
- N43 DA10-8893 - Pharmaceutical Approaches for Development of Pharmacotherapies for Drug Addiction

Certificates of Confidentiality

Between August 11, 2009 and January 4, 2010, OEA processed 149 Certificate of Confidentiality applications, including 27 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: The NIH Public-Private Partnership Program and the Foundation of the National Institutes of Health (Barbara Mittleton, MD, Director PPPP; Ann Ashby, Deputy Director Foundation for NIH, Andrea Baruchin, Associate Director Foundation for NIH); NIH/NSF Collaborations (Josh Rosenthal, FIC); NIH Staff training on implementing the Enhancing Peer Review changes; All Things SBIR (Jerry McLaughlin, OEA; Catherine Sasek, OSPC; Craig Sager, CMB; Diana Haikalis, GMB); and NIH Scientific Publication Information Retrieval and Evaluation System (SPIRES; Paul Jordan, eRA).

CTN-Related Review Activities

The Protocol Review Board met on September 14, 2009 to review the study proposal CTN 0047, Screening, Motivational Assessment, Referral and Treatment in Emergency Departments (SMART-ED).

The Data and Safety Monitoring Board(s) met:

- October 6, 2009 to discuss the final study report for study CTN 0028, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD)
- October 19, 2009, to discuss study protocols CTN 0027, Starting Treatment with Agonist Replacement Therapies (START) and CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12).

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Congressional Affairs (Prepared January 20, 2010)

Appropriations

On December 16, 2009, the President signed into law P.L. 111-117, the Consolidated Appropriations Act. This Act includes appropriations for NIH of $31.009 billion, and within that total $1.06 billion for NIDA. This represents a 2.6% increase over the pre-ARRA FY 2009 total for NIDA. The bill as passed does NOT defund any NIH grants, as per original House language. The bill also changes federal law regarding potential funding for syringe exchange programs. Federal funds may now be used to fund these programs, in the context of preventing the spread of blood borne pathogens, as long as local law enforcement and public health officials agree on the locations of such programs.

Legislation of Particular Interest

Health Reform - This topic continues to trump most others in the current Congress. The House and Senate passed separate bills, and intense negotiations toward a single bill and final vote in both bodies continues. Future Reports to Council will include more detail specific to issues of particular relevance to NIH and the substance abuse and addiction field, once the language is final.

Resolutions in Support of Drug Facts Chat Day - Resolutions were introduced in both the House and Senate supporting the goals of NIDA's annual Drug Facts Chat Day. H.Res. 728 was introduced 9/9/09 by Representatives Patrick Kennedy (D-RI), Mary Bono Mack (R-CA) and Rick Larsen (D-WA)) and S.Res. 256 was introduced 9/9/09 by Senator Carl Levin (D-MI). Neither bill was brought up for a vote.

SBIR/STTR - H.R. 2965, the Enhancing Small Business Research and Innovation Act of 2009, as passed by the House, would loosen the requirements for venture capital-backed small businesses to receive funding from the SBIR and STTR programs without set-aside increases, as does the Senate reauthorization bill, S. 1233.

H.R. 2965 would also: provide special consideration for small business projects that include energy-related research, rare disease-related research, transportation and infrastructure research and research related to nanotechnology; reauthorize the SBIR/STTR programs only through fiscal 2011; and increase small business award levels (raise to $250,000 from $100,000 for participation in the Phase I level; and raise to $2 million from $750,000 for participation in Phase II)

S. 1233 also includes some change in the venture capital provisions. It would

also increase the SBIR set-aside from 2.5 percent to 3.5 percent over the period of FY 2011-2020, and double the STTR from 0.3 percent to 0.6 percent from FY 2011 to FY 2015. Award levels would also rise, from $100,000 to $150,000 for Phase I awards and $750,000 to $1 million for Phase II awards - and the language also would limit awards from exceeding 50 percent above the recommended award levels.

The current, short-term extension of the program's authorization expires on January 31, 2010. We continue to await Congressional action to extend the date further pass a longer term reauthorization bill.

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. 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.

S. 1789 - On October 15, 2009, Senator Richard Durbin (D-IL) introduced the Fair Sentencing Act of 2009, to restore fairness to Federal cocaine sentencing. The bill was referred to the Senate Judiciary Committee. See H.R. 265

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International Activities

International Honors

NIDA Director Honored by French Government for Addiction Research
NIDA Director Dr. Nora D. Volkow was awarded the International Prize from the French Institute of Health and Medical Research (Inserm) for her pioneering work in brain imaging and addiction science. Dr. Volkow received the award at a December 17, 2009, ceremony at the College of France learning center in Paris. Inserm, a government-supported biomedical research organization, is the French equivalent of the U.S. National Institutes of Health. Each year, it honors researchers for their contributions to basic and clinical research that enhance public health. Of the seven 2009 Inserm award winners, only Dr. Volkow was not from France. Dr. Volkow's selection acknowledges her innovative imaging research, which shows that drug addiction is a disease of the brain that usurps the reward circuitry and leads to compulsive behaviors. A research psychiatrist and scientist, Dr. Volkow is considered one of the world's leading specialists in the mechanisms underlying drug abuse and addiction. As NIDA's director since 2003, she leads an organization that supports most of the world's research on drug abuse and its associated health consequences.

Funding Initiatives

New NIH, International AIDS Society Grants Encourage Innovation in HIV Research
The U.S. National Institutes of Health Centers for AIDS Research Program (CFAR) and the International AIDS Society (IAS) have created a new research grant program for early career investigators with no prior experience in HIV research. The awards will provide up to $150,000 per year, for up to 2 years, depending on the proposal. IAS also will provide funding for awardees to attend IAS meetings during the period of research. Both domestic and international early stage investigators who are new to the HIV field are encouraged to apply. Applicants should have completed a terminal degree (M.D., Ph.D., or equivalent) within the last 10 years. Awards will be announced at the 2010 International AIDS Conference in Vienna.

Binational Agreement

NIDA, Dutch Addiction Programme Mark 10th Anniversary of Binational Collaboration
Celebrating a decade of progress through a uniquely successful binational agreement, officials from NIDA and the Dutch Addiction Programme (DAP) heard from jointly funded research teams at the U.S.-Netherlands Workshop on Binational Research Collaboration on Drug Abuse and Addiction, which was held October 22 and 23, 2009, in Washington, DC. Workshop participants met with

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White House Office of National Drug Control Policy (ONDCP) Deputy Director Dr. A. Thomas McLellan, who described the Obama Administration's priorities for drug control strategies, suggested ways that research can inform policy development, and congratulated NIDA and DAP for their "long and fruitful collaboration." NIDA and DAP representatives reviewed the factors contributing to what NIDA Deputy Director Dr. Timothy P. Condon called the Institute's "most successful international collaboration" and identified priority areas for future collaboration. NIDA IP Director Dr. Steven W. Gust and DAP Chair Dr. Sineke ten Horn chaired the workshop. Dutch Ministry of Health, Welfare, and Sport Senior Policy Officer Wil M. de Zwart emphasized the unique and successful collaboration and discussed the drug policy review currently underway in The Netherlands.

NIDA, Dutch Addiction Program Funds Three New Binational Research Teams

Continuing the binational funding agreement between NIDA and DAP, three new research teams have received funding to explore ways of addressing the use of and dependence on cocaine. NIDA funds the U.S. researchers; DAP supports the Dutch scientists. The newly funded teams are:

- Dr. George Koob, Scripps Research Institute, and Dr. Judith R. Homberg, University of Nijmegen, will investigate whether an inherited serotonin transporter (5-HTT) genetic variation confers vulnerability to cocaine dependence by enhancing cocaine-induced neuroadaptations in the central corticotropin-releasing factor (CRF) stress system and associated negative emotionality.
- Dr. Christopher Pierce, University of Pennsylvania, and Dr. Louk Vanderschnuren, Utrecht University, will study striatal circuits involved in drug taking and drug seeking and further explore the efficacy of deep brain stimulation in attenuating drug-related behaviors.
- Dr. Raymond Booth, University of Florida, and Dr. Wim van den Brink, University of Amsterdam, will continue efforts to find an efficacious medication for stimulant addiction by scaling up synthesis of potential compounds (5HT2A inverse agonist/5HT2C agonist) to conduct in vivo functional evaluation assays, which include cocaine-induced down-regulation of D2 receptor expression using single photon emission computed tomography (SPECT) imaging techniques and the attenuation of cocaine consumption in rat self-administration models.

Polish Ministry of Science and Higher Education Promotes NIDA International Program Activities

The Polish Ministry of Science and Higher Education (MSHE) will consider collaboratively funding research grant applications submitted in response to the NIDA International Program Announcements (PAs), International Research Collaboration on Drug Abuse and Addiction (R01: PA-09-020, R21: PA-09-021, and R03: PA-09-022). Mr. Wojciech Dziedzic, Director, MSHE Department for European and International Cooperation, said that the Ministry has established an administrative coordinator to promote applications in response to the PAs. MSHE also is encouraging Polish scientists to consider applying for relevant NIDA IP drug abuse research fellowships and participating in the NIDA International Forum.

Online Initiatives

Updated NIVC Offers Multiple Working Groups and Interdisciplinary Research Options

The NIDA International Virtual Collaboratory (NIVC) has been updated to permit users to join multiple discussion or work groups within NIVC and to join two other Virtual Collaboratories that foster cooperation on interdisciplinary projects. NIVC users now will be able to work virtually with researchers who

belong to the NIDA/National Institute of Mental Health (NIMH)/National Institute on Alcohol Abuse and Alcoholism Virtual Collaboratory for Integrative Behavioral Health Services Research Network or the NIMH Virtual Collaboratory for Suicide Studies.

NIDA IP encourages interested researchers to join the existing NIVC working groups or consider creating their own public or private group. Public groups accepting new members include:

- **Inhalants Broad Interest Group (IWG-Broad)**, chaired by NIDA consultant Dr. M. Patricia Needle, compiles resources on inhalant abuse research and conducts a discussion forum for posing questions and answers.
- **International Research Ethics**, chaired by Dr. Linda Cottler, Washington University in St. Louis, focuses on drug abuse research ethical dilemmas that cross cultures and geographic borders, such as confidentiality, informed consent, conflicts with DSM and ICD efforts, and cooperation with pharmaceutical companies.
- **International Women's and Children's Health and Gender Group (InWomen)**, chaired by Dr. Wendee Wechsberg, RTI International, is a multidisciplinary forum that addresses all aspects of the consequences of substance use among these vulnerable populations.
- **Volatile Substance Abuse (VSA)**, chaired by Dr. Colleen Anne Dell, University of Saskatchewan, is comparing VSA use patterns, prevention interventions, and treatment protocols across Canada, the United States, Mexico, and Australia.

In addition to the public groups, several invitation-only groups exchange information or plan future activities, including groups for former Humphrey, INVEST, INVEST-CTN, and DISCA/USDISCA fellows and for researchers focusing on child neurodevelopment and prevention interventions.

Fellowships

NIDA and International AIDS Society Expand Fellowships in HIV and Drug Use Research

NIDA and the IAS have expanded their fellowship program that focuses on HIV research related to drug abuse. In 2010, four IAS/NIDA Research Fellowships in HIV and Drug Use will be awarded, doubling the number of awards made in 2009. The goal of the program is to contribute to advances in the scientific understanding of drug abuse and HIV, while fostering multinational research on the topic. Two awards of $75,000 each will be made to junior HIV and drug abuse scientists for 18-month postdoctoral training at a leading research institute in the field. Two more awards of $75,000 each will be made to well-established HIV scientists, not currently active in the drug abuse field, for 8-month professional development training on HIV and drug abuse. While applications from across the globe are welcome, scientists from Eastern Europe and Central Asia are strongly encouraged to apply. The fellowships will be announced in conjunction with the XVIII International AIDS Conference (AIDS 2010) in Vienna, Austria, July 18-23, 2010.

INVEST-CTN Fellows Present at Clinical Trials Network (CTN) Meeting

In October presentations to the NIDA CTN Steering Committee, fellows Hanhui Chen, M.D., China, and Mario Zapata, M.D., M.Sc., Colombia, reviewed the drug abuse situation in their respective countries, summarized their research during the INVEST-CTN Fellowship year, and discussed their future plans. NIDA IP and CTN support the 12-month postdoctoral training program for scientists who work with a mentor affiliated with 1 of the 16 CTN Regional Research and Training Centers.

- Dr. Chen estimated that China has 5 million to 10 million drug users, with

opiates accounting for 70 percent of problem drug use and amphetamine type stimulants accounting for 30 percent of drug use. He reported that methadone maintenance treatment has expanded rapidly since its introduction but is underutilized and that professional training and clinical research into drug treatment and prevention need to be expanded. His fellowship focused on best practices in clinical research and treatment, data analysis, and scientific writing.

- Dr. Zapata focused on developing and implementing clinical trial protocols, learned to deliver Brief Strategic Family Therapy, and designed a pilot project to test treatment effectiveness in Colombia. Citing the dramatic increase in coca cultivation since 2005, Dr. Zapata noted that the United Nations attributes more than 50 percent of South American cocaine production to Colombia. He reported that the primary drugs of abuse among adolescents are marijuana, nitrate "poppers", cocaine, and inhalants.

NIDA Welcomes Humphrey Fellows at JHU, VCU, and Emory

Ms. Dale Weiss, NIDA IP program analyst, and Fellowships Administrator Ms. Lisa Jordre met with Hubert H. Humphrey Fellows to introduce NIDA opportunities available during the fellowships. The pair met with NIDA Humphrey Fellows in Drug Abuse and Public Health at Johns Hopkins University (JHU) on September 3, 2009; NIDA Humphrey Fellows in Substance Abuse Education, Treatment, and Prevention at Virginia Commonwealth University (VCU) on September 10, 2009; and NIDA Humphrey Fellows at the Rollins School of Public Health, Emory University, on November 17 and 18, 2009. Ms. Weiss introduced NIDA resources, including the NIVC, a password-protected tool to support geographically distant partners in collaborative research, discussion, and education. Ms. Weiss also met individually with the fellows to discuss their research affiliations and plans for their Humphrey fellowships.

The NIDA Humphrey Fellows at JHU include:

Dr. Wali Omer, Iraq, focuses on family health and initiated a pilot project for a family health center. He is interested in technological tools to assist in development of improved service delivery for families.

Ms. Esther Arye, Ghana, a biomedical scientist working to identify sexually transmitted and other infectious diseases, will use her fellowship to learn more about epidemiology and establishing HIV/AIDS counseling programs.

Ms. Hamida Ebadi, Afghanistan, focuses on public policy development to reduce infant mortality and improve maternal health at the Afghan Ministry of Health. She will use her fellowship to focus on evidence-based policy development to reduce infant mortality and improve maternal health for women.

Mr. Kyaw Aung, Burma, is involved with a UNICEF primary care project identifying unserved and underserved health care populations. He will spend his fellowship focusing on policy development to improve maternal and child health to reduce mortality and morbidity.

Ms. Andrea Domanico, Brazil, is an ethnographer working with crack cocaine users, human rights issues related to drug addiction and incarceration, and stigma for women drug users. She will spend her fellowship learning how prevention and risk-reduction policies are developed and about research into human rights.

Dr. Sergey Koren, Russia, focuses on psychoactive substance users and drug treatment initiatives and will spend his fellowship learning about HIV prevention programs for high-risk populations and distance-learning activities.

Ms. Aysha Ghafoori, Afghanistan, is a child protection worker who works with addicted women and their children. She will spend her fellowship focusing on

establishing treatment programs and developing policies to improve women's and children's health, minimize gender discrimination, and improve civil rights.

The NIDA Humphrey Fellows at VCU include:

Dr. Murilo Battisti, Brazil, investigates ecstasy and club drug use in Brazil and will use his fellowship to learn about substance abuse research to develop evidence-based practices and policies to address substance abuse among Brazilian youth.

Ms. Gabriela (Gabby) Olivera, Uruguay, focuses on violence and other gender issues that influence women's abuse of prescription drugs and alcohol. During her fellowship, she will concentrate on designing evidence-based substance abuse policies and programs.

Ms. Chinyere Celestina (Chi Chi) Okonkwo, Nigeria, has worked in psychiatric hospitals with patients relapsing to drug abuse and will use her fellowship to improve her knowledge of the behavioral aspects of drug abuse and addiction, psychological management of substance abuse, and ways to conduct research that will inform the development of better services for patients.

Mr. Mohd Muzafar Shah bin Mohd Razali, Malaysia, currently is working with VCU faculty members to design a culturally valid instrument to identify at-risk youth in Malaysia. He will use his fellowship to further refine the tool.

Mr. Valeriy Ryabukha, Ukraine, has trained with the Medford, Massachusetts, Police Department and the Massachusetts State Police and has created a pilot drug abuse prevention project in his home country. During his fellowship, he would like to identify effective prevention models that could be implemented in Ukraine and learn how to improve and obtain funding for his pilot program.

Mrs. Rawnak Aqraw, Iraq, has worked on initial assessments of drug use and psychiatrists' perceptions of substance use disorders among Iraqi patients. She will spend her fellowship learning how to design and implement evidence-based treatment programs.

Dr. Thanda Khin, Burma, focuses on drug-related HIV/AIDS in her country and will use her fellowship to learn more about epidemiology and developing and evaluating treatment and prevention programs.

The Humphrey Fellows at Emory include:

Ms. Tetiana Khristoforivna Kiriazova, Ukraine, works in health education and HIV/AIDS prevention in Odessa. During her fellowship, she will focus on HIV/AIDS policy and prevention and on skills in policy-making, strategic planning, preventive education, and monitoring and evaluation.

Dr. Myo Lwin, Burma, is responsible for organizing and promoting civil, religious, and government response to the HIV/AIDS epidemic. He plans to use his fellowship to learn about sustainable public health and HIV policies for resource limited countries.

Dr. Mya Win, Burma, leads projects on the management of sexually transmitted diseases (STDs) and reproductive health. He plans to concentrate on HIV/AIDS public health policy, management, and leadership and community home based care during his fellowship.

Mr. Cletus Adohinzin, Benin, is responsible for assessing, evaluating, and providing advocacy for HIV/AIDS prevention and control programs. He intends to focus his fellowship on increasing his knowledge and skills in HIV/AIDS policy and prevention.

Dr. Lama Hamish Ahmad, Syria, is the Chief of the Non-Communicable

Diseases Section of the Ministry of Health in Damascus. She plans to use her fellowship to learn more about public health policy, management, prevention, and international health regulation.

Dr. Rania Elsayed Hassanein, Egypt, is the Head of the Blood Issuing Department for the National Blood Transfusion Service in Egypt. During her fellowship, she will focus on public health policy and management and on blood donor practices.

Dr. Komenan Kassi, C™te D'Ivoire, is a dermatologist and skin surgeon concerned with the impact of Buruli ulcers on vulnerable populations. During his fellowship he plans to learn more about Buruli ulcer control and care and acquire new skills in public health policy and management.

Mr. Adjane Kossivi Koura, Togo, works to increase the safety and quality of blood transfusions throughout his country. During his fellowship, he hopes to learn more about public health policy and management, social marketing, and quality management in relation to blood transfusion services.

Ms. Sarmila Shrestha Shrestha, Nepal, received the 2006 "Woman of the Year" award from Soroptimist International for her dedication to the poor and marginalized. She will focus her fellowship on developing skills in behavioral change communication and the development, management, and implementation of HIV/AIDS and STD prevention and care programs.

Dr. Hoang Huy Vu, Vietnam, is a current masters degree student at Emory who has helped build capacity for managing HIV/AIDS in the workplace. During his fellowship, Dr. Vu will study HIV/AIDS policy and prevention, the social health and economic impacts, and health policy and management.

NIDA Selects Two New INVEST Fellows

NIDA has selected scientists from China and Russia as 2010 INVEST Fellows: **Huaihui Zhang, M.D., Ph.D.,** a psychiatrist at the Shanghai Yangpu District Mental Health Center, initiated psychosocial research in local methadone maintenance treatment clinics and is especially interested in amphetamine type stimulant abuse among this population. She has served as co-Principal Investigator with Prof. Yih-ing Hser, University of California, Los Angeles (UCLA), on a NIDA R21 grant, Improving Methadone Maintenance Treatment Compliance and Outcomes in China. Dr. Zhang has attended training programs at UCLA, University of Miami, the German-Chinese Academy for Psychotherapy, and Hong Kong University. Working with her INVEST mentor, Richard S. Schottenfeld, M.D., Yale University, she will evaluate the prevalence, clinical correlates, and impact on treatment response of co-occurring abuse of other illicit substances among heroin-dependent patients receiving opioid agonist maintenance treatment, with the goal of informing practice guidelines and policies.

Mikhail Torban, M.D., is a research fellow at St. Petersburg Psychoneurological Scientific Institute, Russia, where he investigates injection drug use, HIV and hepatitis risk behaviors, and drug treatment. Dr. Torban is a former trainee in the International Clinical, Operational and Health Services Research Training Award for AIDS and TB program directed by his INVEST mentor, Robert Heimer, Ph.D., Yale University. Drs. Torban and Heimer have worked together since 2005, publishing two peer-reviewed articles, preparing grant applications, and conducting a research project to study the attitudes and knowledge of Russian substance abuse treatment professionals. Dr. Torban attended Johns Hopkins University Graduate Summer Institute of Epidemiology and Biostatistics, and wants to improve his skills in qualitative data collection and analysis. During his INVEST Fellowship, he will use Rapid Assessment and Response protocols to explore the differences among Connecticut migrant communities to develop culturally appropriate substance abuse and HIV interventions for Bosnian, Russian, and Salvadorian injection drug users and to

identify the individual, community, and structural facilitators of and barriers to care.

Travel Support

NIDA Supports 13 International Scientists at NHSN Conference
The National Hispanic Science Network (NHSN) International Conference, which was held October 29-31, 2009 in Miami, Florida, focused on interdisciplinary research on the epidemiology and prevention of cigarette, alcohol, and drug use/abuse in adolescence; interventions for the treatment of tobacco and substance abuse disorders; genetic and environmental factors that influence addiction; and mentoring and training activities to promote career development from graduate students to senior scientists. NIDA supported 13 scientists from Chile, Mexico, and Spain who presented their research at the International Poster Session. The supported scientists included:

- **Chile:** Luis Caris, Universidad de Chile, and Carmen Gloria Hidalgo, Universidad Católica de Chile.
- **Mexico:** Octavio Campollo, University of Guadalajara; Marycarmen Bustos Gamino, Ma. De Lourdez Gutierrez, Michelle Breton Cirett, Midiam Moreno, and Jorge Ameth Villatoro, Instituto Nacional de Psiquiatria Ramon de la Fuente Muñiz.
- **Spain:** Anna Robert, Benito Menni CASM; Francisco Jose Montero-Bancalero, Fundation Forja XXI; Francisco Javier Romero, Universidad CEU Cardenal Herrera; Claudia Cristina Morales-Manrique, Universidad de Valencia; and Francisco Bueno, Plan Municipal Drogodependencias.

VII Congreso Programa Cambio
NIDA IP and the National Hispanic Science Network on Drug Abuse jointly supported the participation of Antonio Cepeda-Benito, Ph.D., Texas A&M University, as an invited speaker at the Seventh International Congress on Addiction Treatment and Prevention (VII *Congreso Programa Cambio*), which is sponsored by Programa Cambio. The conference was held in Cordoba, Argentina, from October 8 - 10, 2009.

Meeting on Pain and Palliative Care
At the request of the NIDA ARP, the NIDA IP supported the travel of Willem Scholten, PharmD., M.P.A., World Health Organization, to the meeting on Consultation on Pain and Palliative Care in Resource-Limited Settings, which was held on November 16 and 17, 2009, in Bethesda, Maryland. NIDA and NIH sponsored the meeting in cooperation with the William J. Clinton Foundation Clinton HIV/AIDS Initiative.

Scientist from Hungary Visits NIDA Intramural Research Program (IRP)
NIDA IP provided partial support to doctoral student Mano Aliczki from the Institute of Experimental Medicine, Hungarian National Academy of Sciences, Budapest, Hungary, who worked with Dr. Steve Goldberg at NIDA IRP from October 29, 2009, through February 16, 2010. Mr. Aliczki trained in techniques for intravenous drug self administration in rats in order to run a series of collaborative self administration experiments that will be part of an ongoing collaboration between Dr. Goldberg and Dr. Jozsef Haller, Institute of Experimental Medicine, Hungarian National Academy of Sciences. The already fruitful collaboration should become more productive with the added capability of experiments in Budapest.

Society for Neuroscience (SfN) Annual Meeting
NIDA IP supported the participation of 16 international scientists from 13 different countries at the NIDA mini-convention, "Frontiers in Addiction Research" on Friday, October 16, 2009, in Chicago, Illinois, as part of the Society for Neuroscience (SfN) annual meeting. The following individuals

traveled to the meeting and presented a poster at the Early Career Investigators Poster Session:

- Alexis Bailey, United Kingdom
- Alvaro Berzal, Spain
- Veronica Bisagno, Argentina
- Elias Blanco, Chile
- Alicia Brusco, Argentina
- Eric J. Downer, Ireland
- Alexander Friedman, Israel
- Ruth van Holst, The Netherlands
- Tiffany T.Y. Lee, Canada
- Liang Liu, Australia
- Gustavo Moraga, Chile
- Olasunmbo Owolabi, Nigeria
- Neta Rimmerman, Israel
- Chi Xu, China
- Jasesuk Yun, Japan
- Vanna Zachariou, Greece

The International Association of Forensic Toxicologist (TIAFT) Annual Meeting

The NIDA IP supported the attendance of J. Michael Walsh, Ph.D., The Walsh Group, at the TIAFT Annual Meeting in Geneva, Switzerland, on August 23-27, 2009. Dr. Walsh attended the meeting at the invitation of the European Commission (EC) and chaired a workshop session. He also met with organizers for the European Union (EU) DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) project to discuss the possibilities of conducting a joint NIDA/EU conference in 2010 or 2011 to develop a 5-year plan of international collaborative research. NIDA and EC each provided partial travel support for Dr. Walsh.

International Visitors

On November 4, 2009 Mr. Mark Gilman the Regional Manager of the National Treatment Agency (NTA) for Substance Misuse in Manchester England visited NIDA. Mr. Gilman described the work done by the Agency. Mr. Gilman also described the work done by US Distinguished International Scientist Award receipient Dr. Dwayne Simpson and how valuble it was to the NTA. Meeting with Mr. Gilman from NIDA were Dr. Dionne Jones, DESPR and Dr. Steve Gust and Ms. Dale Weiss, IP.

Dr. Gustavo Turecki, Director, FRSQ Suicide Research Axis visited NIDA on November 5, 2009. The Fonds de la recherche en santé du Québec (FRSQ) Quebec Suicide Research Network (QSRN) is a multidisciplinary group of researchers from all Quebec Universities that conduct suicide research. The purpose of the visit was to learn more about how NIDA is organized and about the various fellowships and exchanges offered by the NIDA International Program. Ms. Dale Weiss, IP met with Dr. Turecki.

Other International Activities

At the annual meeting of the International Society of Addiction Medicine (ISAM), Dr. Ivan Montoya, DPMCDA, chaired the International Fellowship Session. It included the following presentations: Women's Interactive Screening to establish HIV risks: Results from effectiveness evaluation by

Susanne Nemes (USA); Cross-generational transmission of violence within families of alcoholic women by Ana Pedriali (Brazil); HCV knowledge level and HCV infection among drug users in MMT clinic by Jiang Du (China); Cultural adaptations of the Therapeutic Community in a Muslim country Mahmoud Nazar (Malaysia); Epidemiology of cannabis consumption in 12-18 year old adolescents in Valencia, Spain and neighboring towns Jose Martinez-Raga (Spain). Dr. Montoya also chaired a symposium entitled "Vaccines and other large molecules for treatment of substance related disorders". It included the following presentations: Monoclonal antibodies for treating methamphetamine overdose and addiction by Mike Owens (USA); Immunotherapy for Nicotine Addiction by Paul Pentel (USA); Vaccines for the treatment of cocaine dependence Thomas Kosten (USA). Dr. Montoya also gave an oral presentation on pharmacotherapies for nicotine dependence.

Dr. Jonathan D. Pollock, DBNBR, participated in the International Neuroinformatics Coordinating facility topical workshop entitled, "Roles of Neuroinformatics in the Process of Building, Evaluating and Using Genetic Animal Models for Brain Diseases. Karolinska Institute, Stockholm, Sweden, December 13-15, 2009.

Dr. Joseph Frascella, Director, DCNBR, participated in and chaired a session on neurocognitive factors in drug abuse at the U.S. - Netherlands Workshop on Bi-National Research Collaboration on Drug Abuse and Addiction held in Washington, DC, October 22-23, 2009.

Dr. Wilson M. Compton, Director, DESPR, presented on Screening and Brief Intervention or Referral to Treatment at the Experts Meeting of CIDAD, Mexico City, Mexico September 29 to October 1, 2009.

Dr. Wilson M. Compton presented on Mainstreaming Addictions in Medicine at the International Council on Alcohol and Addictions, Estoril, Portugal, October 13-15, 2009.

Dr. Wilson M. Compton presented on Understanding Addiction as a Brain Disease to the SANCA-INL Conference, Cape Town, South Africa, October 18-20, 2009.

Drs. Wilson M. Compton, Elizabeth Robertson and Eve Reider participated in an experts panel on drug abuse prevention with the Mentor International Foundation at the Residence of the Swedish Ambassador, October 22, 2009. The purpose of the meeting was for Her Majesty Queen Silvia of Sweden and Mentor to meet with and learn about the work and role of key organizations working in the drug field within the United States and explore the development of Mentor's work in the USA in order to promote positive collaboration and cooperation between organizations. Participants included members of the Mentor Foundation, Office of National Drug Control Policy, NIDA, and SAMHSA.

Dr. Wilson M. Compton presented on Addiction as a Neuropsychiatric Medical Condition to the Ministry of Health, Rome, Italy, November 4-5, 2009.

Moira O'Brien, DESPR, gave a presentation on "Public Health Drug Abuse Surveillance in the United States" at the World Health Organization (WHO) meeting, "Monitoring Systems for Alcohol, Drugs and other Psychoactive Substance Use: Review of Current Practices," held in Valencia, Spain, October 22-23, 2009.

Dr. Tom Hilton, DESPR, represented NIDA at the 2009 Work Stress & Health Conference held in Puerto Rico November 5 through 9, 2009. He also served on the conference organizing committee and chaired a symposium.

Dr. Jag Khalsa, DPMCDA, chaired two symposia: "Clinical Implications of Research on Genetics of Drug Addiction", and "Medical Co-morbidity in Children Prenatally Exposed to Drugs of Abuse" at the annual meeting of the

International Society of Addiction Medicine (ISAM), in Calgary, Canada, September 24-27, 2009. He also co-chaired two other symposia: one with Dr. Greg Bunt entitled: "Drug Addiction Research in the International Settings" and another with Dr. Ahmed Elkashef from DPMCDA entitled "Advances in the Pharmacotherapies of Drug Abuse". In addition, Dr. Khalsa replaced Dr. Mark Willenbring (NIAAA) in the role of chair of the symposium entitled "Alcohol Research in Developing Countries."

Dr. Amy Newman, IRP, was invited to give a lecture at the University of Bath, Department of Medicinal Chemistry, Bath, U.K., in September 2009.

Dr. Yun Wang, IRP, presented "Bone Morphogenetic Protein-7 Reduces Methamphetamine-mediated Neurotoxicity" at the 2nd International Drug Abuse Research Society/International Society for Neurochemistry Satellite Meeting, Seoul, Korea, August 17-21, 2009.

Dr. Jonathan Katz, IRP, initiated collaborations with Dr. Juan J. Canales, Biopsychology and Comparative Neuroscience Group, Cavanilles Institute (ICBiBE), University of Valencia - FGUV.

Dr. Marilyn Huestis, IRP, traveled to Montreal, Canada to finalize the new 2010 Prohibited Drug List for the World Anti-doping Agency's (WADA) Prohibited List Committee.

Dr. Marilyn Huestis gave a plenary address at the International Association of Therapeutic Drug Monitoring and Clinical Toxicology meeting in Montreal, Canada in October 2009. Dr. Marta Concheiro received an international fellowship to attend the meeting and present her research on in utero drug exposure to buprenorphine and illicit drugs.

Dr. Marilyn Huestis was a plenary speaker at the XVI Brazilian Congress of Toxicology held in Belo Horizonte, Brazil. Dr. Huestis discussed the global problem of Driving Under the Influence of Drugs (DUID) and the usefulness of Alternative Matrices for Biological Monitoring of drug exposure. She also taught a five-day graduate course in toxicology at the University of Sao Paolo, Ribeiro Preto, Brazil for post-doctoral and doctoral students at the School of Medicine.

Dr. Marilyn Huestis was the guest of the Barcelona Biomedical Research Park, IMIM-Hospital del Mar in Barcelona, Spain in December 2009. She gave lectures on CDM's recent research in the field of in utero drug exposure and on disposition of drugs in alternative matrices. She also met with investigators and students in the Pediatrics Department and the Neuropsychopharmacology Program.

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Meetings/Conferences

NIDA's Neuroscience Consortium once again organized the **Frontiers in Addiction Research Mini-convention at the 2009 Society for Neuroscience** meeting, October 16, 2009. This year's mini-convention included sessions on Non-cannabinoid receptor-mediated actions of endo-cannabinoids; Delayed neurobiological plasticity in drug abuse and chronic pain; Epigentics, central nervous system function and disease; and Neurotrophic factors and drug addiction. The mini-convention was organized by Drs. Roger Sorenson, Susan Volman, David Thomas, John Satterlee, Jonathan Pollock, David Shurtleff, Mary Kautz and Cathrine Sasek.

Dr. David Shurtleff chaired a symposium **Neurotrophic Factors and Drug Addiction** as part of NIDA's mini-convention "Frontiers in Addiction Research" held in Chicago on November 16, 2009. Speakers included Drs. Mart Saarma (University of Helsinki); Yavin Shaham (NIDA IRP) David W. Self (UT Southwestern Medical Center); Jacqueline F. McGinty (Medical University of South Carolina) and Eric Nestler (Mount Sinai School of Medicine)

Dr. Roger Sorensen, DBNBR, organized and chaired a symposium titled: **Non-Cannabinoid Receptor-Mediated Actions of Endo-Cannabinoids**, that was held on October 19, 2009 as part of the 2009 NIDA/SfN "Frontiers in Addiction Research" mini-convention in Chicago, IL.

Drs. Susan Volman and David Thomas, DBNBR, co-chaired a symposium on **Delayed Neurobiological Plasticity in Drug Abuse and Chronic Pain at the NIDA Mini-convention SFN satellite meeting** in Chicago, IL, October, 2009. The symposium featured presentations by Drs. Julie Blendy, Bruce Hope, David Borsook, and Michel Barrot.

Dr. Susan Volman organized the **Early Career Investigators Poster Session** at the NIDA Miniconvention SFN satellite meeting in Chicago, IL, October, 2009. Eighty posters were presented, including 17 by international investigators co-sponsored by six international organizations (CPDD, IBRO, ICRS, IDARS, INRC, and IUPHAR).

Drs. Mary Kautz and Cathrine Sasek chaired the 7th annual **Society for Neuroscience Jacob P. Waletsky Memorial Award lecture at the annual Frontiers in Addiction Research Mini-convention** at the annual Society for Neuroscience meeting. This year's winner was Dr. Geoffrey Schoenbaum. The Jacob P. Waletsky Memorial Award was established in 2003 to recognize the research contributions made by outstanding junior scientists in the area of drug addiction or alcoholism, and the nervous system.

Dr. Roger Sorensen coordinated and chaired **The 3rd Annual Julius Axelrod Lecture**, held on October 18, 2009 in conjunction with the 2009 Annual Meeting of the Society for Neuroscience (SfN) in Chicago, IL. This year's

winner, Dr. Michael Greenberg, spoke on "Signaling Networks that Regulate Synapse Development and Cognitive Function". NIDA served as the lead Institute for this year's event, which was also co-hosted by NIMH and NINDS.

NIDA hosted a **Research Training Directors' Meeting** on November 2, 2009 at the Pooks Hill Bethesda Marriott Hotel. Research training directors or representatives from over 35 training programs attended. The meeting comprised presentations, updates, and open discussion on best practices, state of the programs, grants management and review concerns, recruitment, evaluation, and other training issues. Drs. Mimi Ghim, Ericka Boone, Belinda Sims, and Eliane Lazar-Wesley, as well as Beth Babecki, Debra Grossman, Usha Charya, and Anna Staton organized the meeting on behalf of the Research Training Committee.

The Blending Hand-Off Meeting for computerized motivational incentives was convened on December 8, 2009 in Chevy Chase, Washington DC and chaired by Dr. Timothy P. Condon, Deputy Director, and co-chaired by Dr. Cindy Miner, Deputy Director, OSPC. The objective of the meeting was to present and discuss research results regarding computerized contingency management interventions and to determine whether a new Blending Team product should be developed. This Blending Team will be coordinated by Dr. Denise Pintello and participants include ATTC directors, NIDA researchers, NIDA and SAMHSA staff and CTP members.

On November 23-24 2009, NIDA's Director, Dr. Nora Volkow convened the first meeting of the **NIDA Science of Genetics Council Review Work Group** in Bethesda, Maryland. The focus of this meeting was to assist NIDA in identifying new scientific directions and opportunities that will serve to maximize the Institute's scientific investment in the genetics research portfolio. This meeting was chaired by Dr. Eric Nestler and organized and coordinated by Dr. Denise Pintello, Special Assistant to the NIDA Deputy Director.

NIDA's Special Populations Office (SPO) held a joint meeting of the **NIDA Researchers and Scholars Workgroups** October 14-15, 2009 in Bethesda, Maryland. The meeting convened members of the African American, American Indian/Alaska Native and Asian American/Pacific Islander Researchers and Scholars Workgroups, representatives of the National Hispanic Science Network and NIDA staff. Workgroup members provided updates on current activities and new initiatives centered on mentoring, training, and career development of early career investigators. Staff from the Special Populations Office, including Flair Lindsey, Program Analyst and Pamela Goodlow, Public Health Analyst, provided updates on office activities and programs. Drs. Nora Volkow and Timothy Condon provided an overview of current NIDA research and participated in a discussion of workgroup members' recommendations respectively.

Drs. Wilson Compton, Eve Reider, Elizabeth Robertson and Belinda Sims, DESPR, collaborated with staff from the NIDA Office of Science Policy and Communications to plan a **Virtual Town Hall** meeting in Washington, DC and Camden, ME, to discuss implementation of evidence-based drug abuse prevention and new findings from the Community Youth Development Study, which is testing the efficacy of the Communities That Care operating system for delivery of tested and effective prevention interventions within communities. The Virtual Town Hall was held on September 9, 2009 and included the Directors of the National Institute on Drug Abuse, the Office of National Drug Control Policy, the SAMHSA Center for Substance Abuse Prevention, and the Principal Investigator of the Community Youth Development Study at the Washington, DC site, and program staff and community partners in the five-town implementation site that gathered in Camden, ME as well as participants from Illinois and Washington.

Dr. James Bjork, DCNBR, in collaboration with Dr. Lis Nielsen at NIA, organized

Planned Meetings

Publications

Staff Highlights

Grantee Honors

a meeting on **Aging, Motivation, and Addiction**, which was held on October 5 and 6, 2009 in Washington D.C. The meeting was co-sponsored by the Office of Science Policy and Communications (OSPC), with additional funding by NIA. The major purpose was to assess the state of knowledge about how advanced aging may interact with drug use to affect cognition and decision-making.

Drs. Bethany Deeds, Liz Ginexi, and Thomas Brady of DESPR collaborated with colleagues in the NIH's Office of Behavioral and Social Sciences Research (OBSSR), the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to host NIDA's **Exploring Interconnections: A Network Dynamics Workshop for Understanding and Preventing Adolescent and Young Adult Substance Abuse** on January 13th and 14th, at NIH. Objectives of the meeting were to describe state-of-the-art methodological advances in the field of social network research; identify and discuss obstacles and opportunities for stimulating and integrating scientific advancements in social network analysis for epidemiology, prevention, and services research in adolescents and young adult substance use; and discuss strategies for promoting the translation of social network research findings to improve prevention and treatment of substance use among adolescents and young adults, including the support of ongoing recovery.

Drs. Cecelia Spitznas, Lisa Onken, Jessica Chambers and Debra Grossman, all of DCNBR, organized a meeting held September 21, 2009 in Bethesda MD entitled, **Developing an Innovative Mobile Therapy: Twitter for Tobacco "Tweetment."** The conference brought together treatment development experts, Twitter Developers, and smoking cessation researchers to examine the utility of using the novel microblogging service Twitter as well as other social networks for addressing addiction to nicotine.

The National CTN Steering Committee Meetings were held October 20-22, 2009 in Bethesda, MD. The following meetings/committees convened:

- CTP and PI Caucuses
- Invest Fellow Meeting
- Executive Committee
- Research Utilization Committee
- Research Development Committee
- Node Coordinator Workgroup
- Steering Committee
- Pharmacotherapy Special Interest Group
- CTN 0027 START Study Team
- CTN 0031 STAGE 12 Study Team
- CTN 0037 STRIDE Study Team
- CTN 0044 Web-based Study Team
- CTN 0046 S-CAST Study Team
- CTN 0047 SMART ED Study Team
- CTN 0048 CURB Study Team

Three workshops were held during the CTN Steering Committee Meetings:

- **Cost-Effectiveness Evaluation in Addiction Treatment Clinical Trials Mini-Workshop** The purpose of this workshop was to give a brief overview of the discussion and conclusions from the NIDA CTN-sponsored workshop held July 30-31, 2009 - "Cost-Effectiveness Evaluation in Addiction Treatment Clinical Trials."
- **Synthesizing Results Across Studies: Meta-Analysis in Plain English**

A CTN Design and Analysis Workshop on "Synthesizing Results Across Studies: Meta-Analysis in Plain English", was held Tuesday, October 20, from 3:00 pm to 5:00 pm. The workshop provided a non-technical introduction to meta-analysis, its key elements, logic, and benefits.

- **Methods for Disseminating Evidence-Based Treatments from the Frontlines of Community Treatment Programs: October 2009 Edition** On October 20, 2009, the Research Utilization Committee convened its second implementation workshop, titled, "Methods for Disseminating Evidence-Based Treatments from the Frontlines of Community Treatment Programs: October 2009 Edition." CTP representatives from seven CTN Nodes described efforts to implement empirically supported treatments in CTPs. These presentations underscored implementation innovations, successes, and lessons learned. This workshop was an extension of the first dissemination workshop held at the March 2009 CTN SC meeting. The first workshop was recorded and will soon be available on the CTN Dissemination Library website, along with the opportunity to take a knowledge quiz to earn credit hours. The CTN Library and NATTC are coordinating this effort.

The second and third **2009 CTN Regional Dissemination Workshops** were held October 28-29, 2009 in Pittsburgh, PA and November 2, 2009 in Charleston, SC, respectively.

CCTN staff organized a NIDA Science Meeting sponsored by NIDA's Office of Science Policy and Communications on December 15-16, 2009 in Bethesda, MD. The title of the two-day conference was **Clinically Meaningful Substance Abuse Treatment Outcome Measures for Effectiveness Trials**. The main objective of the meeting was to explore current thinking by leaders in the drug abuse field regarding appropriate primary drug abuse/use outcomes, measures and approaches for clinical effectiveness trials in drug abuse treatment research.

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "National Institute on Drug Abuse: Institute Update" at the American Psychiatric Association (APA) Annual Fall Hill Briefing on Advances in Psychiatric and Substance Use Research on Capitol Hill on September 30, 2009.

Dr. Timothy P. Condon provided welcoming remarks at the NIDA Primary Care Meeting in Rockville, Maryland on October 1, 2009.

Dr. Timothy P. Condon led a "Discussion with the NIDA Deputy Director" at the SPO Joint Minorities Work Group Meeting in Bethesda, Maryland on October 15, 2009.

Dr. Timothy P. Condon presented "Advances in Drug Abuse and Addiction Research" at the Society for Neuroscience Addiction Studies Program in Chicago, Illinois on October 16, 2009.

Dr. Timothy P. Condon presented "NIDA Progress, Priorities & Plans for the Future" at the US-Netherlands Collaborative Research Meeting in Washington, D.C. on October 22, 2009.

Dr. Timothy P. Condon participated on a plenary panel and presented "Opportunities and Priorities for Addiction Health Services Research at NIDA" at the Addiction Health Services Research Conference 2009 Health Care Reform, Parity, and Continuing Care Models: A Forum for a New Era in Addiction Services Research, in San Francisco, California on October 30, 2009.

Dr. Timothy P. Condon presented opening welcome remarks at the NIDA T32 Directors Meeting in Bethesda, Maryland on November 2, 2009.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt -- The Neuroscience of Addiction" and participated in at the National

Chief and Presiding Judges Symposium, Advancing Systems Change: Enhancing Court System Efficiencies Through Emerging Addiction Science, in Savannah, Georgia on November 5, 2009.

Dr. Timothy P. Condon was a panelist and presented on "Drug Abuse Research Update: Communica-ting Science Fact, Not Science Fiction" at the Red, White & True: Journalism Education Association/ National Scholastic Press Association Fall National High School Journalism Convention Covering Health Issues: What You Need to Know Before You Publish a Health Related Story in Washington, D.C. on November 13, 2009.

Dr. Timothy P. Condon chaired the MIEDAR II, Blending Handoff Meeting on Computerized Motivational Incentives in Washington, DC on December 8, 2009.

Dr. Timothy P. Condon served as a panelist in the CSAT Road to Recovery webcast Ignoring Instructions: The Importance of Using Prescription and Over-the-Counter Medications Correctly in Rockville, Maryland on December 17, 2009.

Dr. Cindy Miner, Deputy Director, OSPC presented the Keynote "Neurobiology of Addiction" at the Sussex County Substance Abuse Conference on October 2, 2009 in Sussex, New Jersey.

Dr. Cindy Miner presented the Keynote "Advances in Drug Abuse and Addiction Implementation Research: Implications for Prevention" at the 5th Annual Conference on Alcohol, Tobacco, Other Drug Abuse and Violence on October 9, 2009 in St. Cloud, Minnesota.

Dr. Cindy Miner presented "Science of Addiction" at the Science of Drug Abuse in Schools and Colleges 2009 Conference on October 20, 2009 in Athens, Georgia.

Dr. Cindy Miner participated in the NIDA/NIMH Grantwriting Workshop and Mock IRG Panel at the American Academy of Child & Adolescent Psychiatry Conference on October 28, 2009 in Honolulu, Hawaii.

Dr. Cindy Miner participated in a panel discussion of the AACAP-NIDA Career Development Award, K12 Program at the American Academy of Child & Adolescent Psychiatry Conference on October 28, 2009 in Honolulu, Hawaii.

Dr. Cindy Miner represented NIDA at the Jeanne Spurloch Minority Medical Student Research Fellowship presentations at the AACAP Young Leaders Awards Luncheon at the AACAP Conference on October 28, 2009 in Honolulu, Hawaii.

Dr. Denise Pintello, OD, participated in an NIH panel titled: "Social Work Research Career Opportunities at NIH and CDC" presented at the Society for Social Work Research on January 13, 2010 in San Francisco, California.

Dr. Ruben Baler organized and co-chaired a panel entitled "Modafinil: revisited" at the 2009 ACNP Annual meeting in Hollywood, FL.

Dr. Ruben Baler presented the lecture "Neuroscience of Addiction" at the World Congress on Addictions" September 23-25, 2009, Mexico City, Mexico

On November 8 and 9, 2009, Elisabeth Davis, OSPC, attended the annual meeting of the American Association of Medical Colleges in Boston to launch the first wave of curriculum resources for medical students, resident physicians, and faculty developed by NIDA's Centers for Excellence for Physician Information. NIDA Press Officer Jeff Levine also attended the meeting to encourage media attention of the resources.

As part of a panel presentation entitled: Innovative Strategies to Improve Physician Screening and Referral of Substance Use Disorders in

Medical/Surgical Patients at the annual meeting of the Academy of Psychosomatic Medicine in Las Vegas in November 2009, Elisabeth Davis, OSPC, presented alongside representatives from NIDA's Centers for Excellence for Physician Information on the newly released medical education resources for students, resident physicians and faculty.

Dr. Lula Beatty, Director, Special Populations Office, participated in the careers in psychology forum on November 21, 2009 held at Trinity College in Washington, D.C., sponsored by the D. C. Chapter of the Association of Black Psychologists.

Dr. Lula Beatty presented a session on health disparities at NIDA's Training Directors meeting on November 2, 2009 in Bethesda, Maryland.

Dr. Lula Beatty served as a discussant at two sessions, "Making Drug Abuse Services Work for Vulnerable Populations in the 21st Century" and "HIV/AIDS research: Unmasking disparities in the 21st century," at the American Public Health Association conference on November 10-11, 2009 in Philadelphia, Pennsylvania.

Ana Anders, M.S.W., Public Health Analyst, SPO, represented NIDA at the Latino Behavioral Health Institute (LBHI) annual conference on September 24-26, 2009 in Los Angeles, California.

Ana Anders attended the National Hispanic Science Network (NHSN) annual conference on October 28-30, 2009 in Miami, Florida.

Dr. Teri Levitin, Director, OEA, attended the American Academy of Family Physicians meeting in October 2009 and served as a resource for questions about changes in NIH review policies and procedures.

Lyle Furr, OEA, participated in the 60th AALAS National Meeting in Denver, CO, November 8-12, 2009.

Dr. Gerald McLaughlin, OEA, was an invited discussant at the Systems Biology of Human Aging Symposium at the Biomedical Research Center, Baltimore, MD, December 8 and 9, 2009.

Dr. Meena Hiremath, OEA, gave a presentation on Enhancing Peer Review Changes at the Addiction Health Services Research Conference, San Francisco, CA October 28-30, 2009.

Dr. David Shurtleff gave a presentation: "Overview of NIDA's Genetics Program" for the NIDA Science of Genetics Council Review meeting in Bethesda, MD, Nov. 23, 2009.

Drs. Steve Grant, DCNBR, and David Shurtleff co-organized and co-chaired a symposium entitled "Impulse Control Disorders in Parkinson's Disease: What do we Know and What do we do About it?" at the Annual Meeting of the American College of Neuropsychopharmacology, December 9, 200 in Hollywood FL. Speakers included Drs. Daniel Weintraub; Anthony A. Grace; Mark A. Gluck; Isabelle Boileau; Wendy R. Galpern.

Dr. Vishnu Purohit, DBNBR, presented a seminar on Cannabinoid and Liver Inflammation at the North Eastern University, Boston, MA, September 24, 2009.

Dr. Vishnu Purohit organized a symposium on Mother-to-Child Transmission of HIV and Drugs of Abuse: Post-HAART Era, Rockville, Maryland, October 26-27, 2009.

Dr. Cora Lee Wetherington, DBNBR, and Coordinator, Women and Sex/Gender Differences Research Program, participated in the Office of Research on Women's Health (ORWH) workshops, "Strategic Planning: Updating the

Women's Health Research Agenda for the Coming Decade," held at Brown University, Providence, RI, September 21-2, 2009 and at Northwestern University, Chicago, IL, October 14-16, 2009.. The meeting was co-hosted by the Women & Infants Hospital of Rhode Island and The Warren Alpert Medical School of Brown University.

Dr. Cora Lee Wetherington gave an invited talk, "Evidence for Gender-Specific Addiction Risk," at the American Society for Addiction Medicine's Course on the State of the Art in Addiction Medicine in Washington, DC, October 22-24, 2009.

Dr. Cora Lee Wetherington was a session chair at the NIH Office of Research on Women's Health's Sixth Annual Interdisciplinary Women's Health Research Symposium held at Lipsett Auditorium, Bethesda, MD, November 17, 2009.

Dr. Samia Noursi, DBNBR, Deputy Coordinator, Women and Sex/Gender Differences Research Program, represented NIDA at the "Think Tank Meeting" of the National Partnership to End Interpersonal Violence across the Lifespan (NPEIV) and the 14th International Conference on Violence, Abuse and Trauma, September 23-26, 2009 in San Diego, CA. NPEIV is an overarching group of organizations, agencies, coalitions, and groups that embraces a national, multi-disciplinary and multicultural commitment to violence prevention across the lifespan.

Dr. Samia Noursi, together with Dr. Nicolette Borek, DCNBR, organized and co-chaired a symposium, "New Directions in Research on Prenatal Nicotine Exposure: Early Neurobehavioral Outcomes, Genetic Influences, and Treatment for Pregnant Women Who Smoke," at the annual meeting of the American Academy of Child and Adolescent Psychiatry (AACAP), October 27-November 2, 2009 in Honolulu, Hawaii. Panelists were Lisa Stroud (Brown University), Sandra Wiebe (University of Nebraska-Lincoln), Jenae Neiderhiser (The Pennsylvania State University), and Steve Higgins (University of Vermont).

Dr. Samia Noursi participated in the National Conference sponsored by the Office of Research on Women's Health in Chicago, October 14-16, 2009. This was the fourth in a series of public hearings and scientific workshops to update the Women's Health Research Agenda at the NIH for the coming decade. The meeting was co-hosted by the Northwestern University, Feinberg School of Medicine and Northwestern Memorial Hospital. Dr. Noursi served on the ORWH Panel that received public testimonies from over 17 representatives of national advocacy organizations. She also participated in the "Under-Studied and Under-Represented Populations" working group.

Dr. Minda Lynch, DBNBR, gave three invited lectures at the NASW/Alaska Chapter Annual Meeting in Anchorage, AK, during October 2009. The talks included: "Under Construction: Addiction, Risk, and Adolescent Brain Development", "Not Your Grandfather's Genes: The Brave New World of Genetics in Mental Health" and "Inhalant Abuse: Nothing to Huff About!"

Dr. Susan Volman, DBNBR, was invited to co-chair a session on "Multi-Level Measurement and Technological Advances" at the NIH meeting "Facilitating Interdisciplinary Research: Methodological and Technological Innovation in the Behavioral and Social Sciences" on October 8, 2009 in Bethesda.

Dr. Allison Hoffman, DBNBR, was invited to participate in a DHHS working group subcommittee on Tobacco Product Regulation.

Dr. Allison Hoffman participated on the Planning Committee for an NCI workshop on "Cigarette Warning Labels, Packaging, & Product Labeling: Current Science & Practice to Identify Research Priorities", October 20-21, 2009, Rockville, Maryland.

Dr. Allison Hoffman participated on the Planning Committee for the National Hispanic Science Network Annual Meeting, Miami, FL (October 29-31, 2009).

Theme: Tobacco.

Dr. Allison Hoffman participated on the Planning Committee for the 2nd Menthol Conference, held in Atlanta, GA on October 19-20, 2009.

Dr. Allison Hoffman participated on the Planning Committee for the 1st Annual Schroeder Institute Consensus Conference: Integrating Social Network Analysis and Informatics Technology into Behavior Change and Tobacco Control, November 30, December 1, 2009.

Dr. Jonathan D. Pollock, DBNBR, attended the Treatment of Hepatitis C Virus in Patients on Opiate Agonist Treatment, Cornell Weill Medical Center, New York City, New York, November 13, 2009.

Dr. Jonathan D. Pollock participated in the Knockout Mouse Project and Mouse Phenotyping Meeting, Bethesda, MD, October 28-29, 2009.

Dr. Jonathan D. Pollock attended the Annual Meeting of the American Society for Human Genetics, Honolulu, HI, October 20-24, 2009.

Dr. Da-Yu Wu, DBNBR, attended the Rat Genomics and Models meeting at the Cold Spring Harbor Laboratory from December 2 to December 5, and held discussions there with several groups of researchers from UK and US on developing rat genetics and genomics research for drug addiction. A web based work shop is being organized at NIDA on this topic.

Dr. John Satterlee, DBNBR, gave a presentation: "Overview of NIDA Epigenetics and Roadmap Epigenomics Programs" at the NIDA Science of Genetics Council Review, Bethesda, MD, November 23, 2009.

Dr. John Satterlee chaired the session: "Epigenetics, Central Nervous System Function and Disease" at the NIDA Mini-Convention: Frontiers in Addiction Research, Chicago, Illinois, October 16, 2009.

Dr. Satterlee attended the NHGRI sponsored "Genomics of Gene Regulation Planning Workshop" on October 27-28, 2009 in Gaithersburg, MD.

Dr. Satterlee attended the Roadmap Epigenomics Program Investigators Meeting on November 5-6, in Bethesda, MD. He moderated the session "Technology Development in Epigenetics" and co-moderated a panel discussion on "Integration of Program Components".

Dr. Joni Rutter, DBNBR, co-chaired the Roadmap Epigenomics Program Investigators Meeting on November 5-6, 2009 in Bethesda, MD.

Drs. Laurence Stanford and Joseph Frascella, DCNBR, participated in the "Workshop on Understanding and Preventing Adolescent Risk Behavior: Integrating Findings Across Domains of Influence" sponsored by the National Research Council Institute of Medicine of the National Academies on December 14, 2009 in Washington, DC.

Dr. Laurence Stanford gave a presentation on NIDA's Exploratory Centers for Translational Research on the Clinical Neurobiology of Drug Addiction to the NIH Office of Behavioral and Social Sciences Research Coordinating Committee on November 14, 2009.

Drs. Joseph Frascella, Laurence Stanford, Lisa Onken, Nicolette Borek, Cheryl Boyce and Steven Grant, all of DCNBR, participated in NIDA Chat Day on November, 10, 2009.

Dr. James M. Bjork, DCNBR, gave a lecture: "Impulsivity and incentive processing in alcoholism: Behavior and brain investigations at the NIH" at the NIH main campus on January 5, 2010. This was part of the "Fall in Love with NIH" lecture series.

Dr. Steven Grant, DCNBR, organized, chaired and served as the discussant for a panel on "Convergent Evidence Linking Functional Brain Imaging to Dopamine Signaling" at the annual meeting of the American College of Neuropsychopharmacology held December 6-10, 2009 in Hollywood, FL.

Dr. Steven Grant and Dr. David Shurtleff, DBNBR co-organized and co-chaired a panel on "Impulse Control Disorders in Parkinson's Disease: What Do We Know and What do We Do About It?" at the annual meeting of the American College of Neuropsychopharmacology held in December 6-10, 2009 in Hollywood, FL.

Dr. Steven Grant served as a discussant on a panel titled "Are Neuronal Consequences of Recreational MDMA (3,4-Methylenedioxy-Methamphetamine; Ecstasy) Use Still a Problem? Recent Neuroimaging Findings" at the annual meeting of the American College of Neuropsychopharma-cology held in December 6-10, 2009 in Hollywood, FL

Dr. Yu (Woody) Lin of DCNBR and Dr. David Thomas of DBNBR co-organized a meeting entitled "Pain Measurement Scale: Current Issues and Future Direction", co-sponsored by NIDA, NIDA Prescription Opioid and Pain Workgroup and Office of Research and Development, the Department of Veterans Affairs. It was held on January 27, 2010 at North Bethesda Marriott Conference Center.

Dr. Yu (Woody) Lin organized a seminar sponsored by the Division of Clinical Neuroscience and Behavior Research by Dr. Ajay Wasan, a K23 grantee at Brigham and Women's Hospital and Harvard Medical School. Dr. Wasan spoke on "The Impact of Negative Affect on Chronic Pain Treatment Outcomes, Including Prescription Opioid Misuse" on January 26, 2010 at the NIH Neuroscience Building.

Dr. Nicolette Borek, DCNBR, and Dr. Samia Noursi, DBNBR co-organized the symposium "New Directions in Research on Prenatal Nicotine Exposure: Early Neurobehavioral Outcomes, Genetic Influences, and Treatment for Pregnant Women Who Smoke" at the American Academy of Child and Adolescent Psychiatry annual meeting October 24-31st, 2009 in Honolulu, HI. Dr. Borek also presented a talk on NIDA Child and Adolescent Research Opportunities during the NIDA-NIMH sponsored NIH Grant Writing Workshop.

Dr. Nicolette Borek, DCNBR, chaired the annual meeting of the Maternal Lifestyles Study Steering Committee. The meeting was held November 17-18, 2009 in Bethesda, MD.

Dr. Cheryl Anne Boyce, DCNBR, presented an "Update on Federal Research on Child Neglect" at the Translational Research on Child Neglect Consortium Annual Meeting: "Enhancing the Validity of Research on Neglect with Ethnically and Culturally Diverse Populations," held at the University of Southern California, Los Angeles, CA, on September 10 -11, 2009.

Dr. Cecelia Spitznas, DCNBR, participated in organizing the m-Health Summit, a meeting on mobile devices for health which was held October 29 & 30, 2009 in Washington, D.C. The meeting was sponsored by the Foundation for NIH and Microsoft, and included NIH, The Rockefeller Foundation, the Vodaphone Foundation, The Robert Wood Johnson Foundation and the UN Foundation as partners. The conference provided an opportunity for chipmakers, handset makers, telecom providers and researchers as well as DHHS leaders and global health experts and policy makers to start developing an agenda for m-health research. Dr. Nora Volkow participated in a "Visionaries" panel at the summit.

Dr. Shoshana Kahana, DCNBR, served as the chair for the Strategies for Integrating Behavioral and/or Pharmacological Treatments for Substance Abuse and Psychiatric Comorbidities panel at the November 20-22, 2009 meeting of

the Association for Behavioral and Cognitive Therapies.

Dr. Will M. Aklin, DCNBR, chaired a meeting entitled, "Targeting Behavioral and Neurobehavioral Mechanisms in Substance Abuse Treatment" at the Association for Behavioral and Cognitive Therapies conference in November, 2009.

At the December, 2009 American College of Neuropsychopharmacology (ACNP) meeting, Dr. Ahmed Elkashef (DPMCDA) chaired and Dr. David McCann (DPMCDA) served as the discussant for a symposium entitled "Development of Immunological and Catabolic Agents for the Treatment of Drug Addiction Disorders." Presentations covered vaccines for tobacco and drug addiction treatment (Dr. Paul Pentel), monoclonal antibodies for drug overdose and drug addiction treatment (Dr. Michael Owens), cocaine catalytic antibodies (Dr. Kim Janda), and a cocaine hydrolase engineered from human butrylcholinesterase (Dr. Liora Sklair-Tavron).

Dr. Ivan Montoya, DPMCDA, chaired a symposium at the annual meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) entitled "Early Intervention of Psychiatric Disorders in Adolescents to Prevent the Initiation and Progression of Drug Use Disorders". It included the following presentations Psychiatric risk and protective factors for initiation and progression of drug use among adolescents (Dr. Gerardo Gonzalez), Interventions for Impulsive/Explosive Behaviors to Prevent the Initiation and Progression of SUDs in Adolescents (Dr. Stephen Donovan), The influence of ADHD on the trajectory of SUDs (Dr. Paula Riggs), Treatment of bipolar disorders in adolescents at risk for SUDs (Dr. Melissa DelBello), and Early Detection and Treatment of Psychotic Disorders and the Progression of Marijuana Use in Adolescents (Dr. Alan Green).

Dr. Ivan Montoya presented at the 46th Session of the Inter-American Drug Abuse Control Commission in Miami, FL. The title of the presentation was "Progress in Developing Medications and Vaccines for Drug Addiction Treatment".

Dr. Wilson M. Compton, Director, DESPR, participated in the DSM-V Task Force and DSM-V Substance Use Disorders Workgroup meetings, Arlington, Virginia, September 22-23 and November 16-17, 2009.

Dr. Wilson M. Compton presented on Mainstreaming Addictions in Medicine at the American Society of Addiction Medicine 2009 Review Course in Addiction Medicine, Washington, DC, October 22, 2009.

Dr. Wilson M. Compton presented on Understanding Addiction as a Brain Disease to the Workshop of the 11th Federal Circuit Court Judges, November 3, 2009.

Dr. Wilson M. Compton participated in the ONDCP Inter-agency Workgroup for Demand Reduction. Meetings have been held on an ongoing basis since March 2009.

Dr. Wilson M. Compton chaired a panel on Drug Use Disorders in the United States: NESARC Study Results at the Annual Meeting of the American Academy of Addiction Medicine, Los Angeles, CA, December 3-6, 2009.

Dr. Kevin Conway, Mark Brodsky and Dr. Wilson M. Compton, all of DESPR, presented on Illicit Drug Outcomes at 3-Years in a Large National Sample at the Annual Meting of the American College of Neuropsychopharmacology, December 6-10, 2009.

Dr. Eve Reider and Dr. Belinda Sims in the Prevention Research Branch, DESPR, are members of the program planning committee for the 18th Annual Society for Prevention Research Annual Meeting that will be held June 1-4, 2010 in Denver, Colorado. Dr. Reider is also an organizer and theme reviewer

for the 3rd Annual NIDA International Poster Session that will be held June 1, 2010 at the SPR Meeting.

Dr. Eve Reider was a NIDA representative at a meeting held September 22, 2009 for the Office of National Drug control Policy (ONDCP) Military, Veterans and their Families Working Group.

Dr. Eve Reider represented NIDA as a member of the Military, Veterans and their Families Working Group at the Demand Reduction Interagency Working Group Meeting July 8, 2009 and November 5, 2009 for the Office of National Drug Control Policy.

Dr. Eve Reider represented NIDA on November 3, 2009 at a meeting of the Interagency Coordinating Committee on the Prevention of Underage Drinking.

Dr. Redonna Chandler, DESPR, presented a plenary address titled: "Addressing adolescent drug abuse: Effective treatment and principles" during a meeting of the Inter-American Development Bank held in San Jose, Costa Rica on October 8, 2009.

Dr. Redonna Chandler presented a plenary address for the National Chief and Presiding Judges Training in Savannah, GA, titled, "Science informed judicial decision making" on November 5, 2009.

Dr. Redonna Chandler gave a plenary address titled, "Evidence based drug abuse treatment in criminal justice settings," at the 16th Annual TASC Conference on Drugs & Crime in Charlotte, NC, on September 24, 2009.

Dr. Elizabeth Ginexi in the Prevention Research Branch, DESPR, served as a panel moderator at the Interagency federal methodological meeting titled "Subgroup analysis in prevention and intervention research" September 14-15, 2009 at the Doubletree Hotel Bethesda, MD.

Dr. Aleta Meyer, in the Prevention Research Branch, DESPR spoke as a panelist for the Virginia Family Impact Seminar titled "Substance Abuse Prevention: Policies, Programs, and Strategies that can Work for Virginia's Youth" on September 23, 2009 at the Capitol of Virginia. Co-panelists were Dr. Anthony Biglan of the Oregon Research Institute and Dr. Patrick Tolan of the University of Virginia.

Dr. Aleta Meyer spoke at the Prevention Research Center at Pennsylvania State University on October 21, 2009. The title of her presentation was "Thinking about Adoption, Implementation, and Sustainability on the Front-End of Research."

Dr. Aleta Meyer represented NIDA as a member of the Workforce-Related Working Group at the Demand Reduction Interagency Working Group Meeting November 5, 2009 for the Office of National Drug Control Policy.

Dr. Augusto Diana in the Prevention Research Branch, DESPR, organized and moderated a panel at the National Prevention Network meeting in Anaheim, CA, September 17, 2009. The panel was titled, "Translational Research: Dissemination Efforts at NIDA." Three NIDA grantees, Drs. Luanne Rohrbach, Richard Spoth and Chris Ringwalt, were the invited panelists who spoke about their NIDA-funded research.

Dr. Augusto Diana organized a symposium as part of the CSAP-NIDA Innovations in Prevention Symposium Series in Rockville, MD, October 7, 2009. The speaker was Dr. Richard Spoth, who discussed his NIDA-funded research on the PROSPER model.

Dr. Augusto Diana organized and moderated a panel at the National Prevention Network meeting in Anaheim, CA, September 17, 2009. The panel was titled, "Translational Research: Dissemination Efforts at NIDA."

Dr. Aria Crump in the Prevention Research Branch, DESPR, presented on "Perspectives On Peer Review: What Makes a Critique Useful For Program Officials?" for the NIH Peer Review Workshop held by the Center for Scientific Review on September 21, 2009 in Bethesda, MD.

On October 14, 2009, Dr. Aria Crump gave a presentation entitled "Prevention Research at NIDA" for the Joint Workgroups Meeting convened by the NIDA Special Populations Office in Bethesda, MD.

On October 26, 2009, Drs. Aria Crump and Belinda Sims led a workshop on career development, training opportunities, and mentoring for the NIH Partners in Research Investigator Meeting at the Natcher Center on NIH's main campus.

On November 2, 2009, Dr. Aria Crump participated on a panel discussing the future of T32 programs for the NIDA Research Training Directors' Meeting held in Bethesda, MD.

On November 10, 2009, Dr. Aria Crump participated in a federal panel entitled "Surging Towards Equality: Health Disparities Research" at the Annual Meeting of the American Public Health Association in Philadelphia, PA.

Dr. Belinda Sims represented NIDA as a member of the Prevention and Education Working Group at the Demand Reduction Interagency Working Group Meeting November 5, 2009 for the Office of National Drug Control Policy.

Dr. Peter Hartsock, DESPR, gave a presentation on HIV/AIDS and drug abuse research funded by NIDA that focus on the U.S.-Mexico border, including studies that involve advanced mathematical modeling, applied epidemiology, and research training, as part of a research symposium and site visit at the University of Texas School of Public Health, in Houston, TX, September 17-18, 2009.

Dr. Peter Hartsock participated in the Georgetown University conference celebrating the 50th anniversary of the University's founding of its Russian Area Studies Program, November 21st, 2009 in Washington, D.C. Dr. Hartsock presented on some notable milestones in drug abuse and HIV/AIDS resulting from NIDA support and collaborations over the past 20 years.

Dr. LeShawndra Price, DESPR, along with Dr. Cheryl Boyce, DCNBR, and colleagues from NICHD and NIMH, presented and participated in the Third Annual Translational Research on Child Neglect Consortium at the University of Southern California in Los Angeles September 11-12, 2009. This year's focus explored health disparities in child neglect and trauma.

Dr. LeShawndra Price, with Dr. Cheryl Boyce, presented and participated in the Family Research Consortium Fall Institute at Yale University on September 20-23, 2009. This year's focus explored the co-occurrence of psychiatric and addictive disorders with a perspective on the family.

Dr. Dionne Jones, DESPR, organized, planned and moderated two symposia "HIV/AIDS Research: Unmasking Disparities in the 21st Century" and "Making Drug Abuse Services Work for Vulnerable Populations in the 21st Century" at the American Public Health Association Annual Meeting in Philadelphia, PA, October 7-11, 2009.

Dr. Tom Brady, DESPR, organized an October 29th, 2009 symposium, "Continuing Care Models for Adolescents in Addiction Treatment: Questions for Future Research", at the Addiction Health Services Research Conference in San Francisco, CA.

Drs. Tom Brady and Wilson Compton developed and presented a NIDA Workshop at the American Psychiatric Association Institute on Psychiatric Services, October 9, 2009 in New York, NY. The workshop was titled "Screening

and Brief Interventions for Substances in Medical Settings: Implications for Psychiatry."

Dr. Dionne Jones, DESPR, gave a presentation on "Health Disparities Research at NIH: Towards Health Equity" for a panel she organized and planned entitled "Surging Toward Equality: Health Disparities Research" at the American Public Health Association Annual Meeting in Philadelphia, PA, October 7-11, 2009.

Dr. Dionne Jones served as a mentor at the NIDA Researchers and Scholars Joint Workgroup Meeting, Bethesda, MD, October 14-15, 2009.

Dr. Harold Perl, CCTN, participated in the Third Annual Drug Facts Chat Day 2009.

Dr. Amy Newman, IRP, was invited to give a lecture at the University of Maryland School of Pharmacy, Baltimore, Maryland, in October 2009.

Dr. Jonathan Katz, IRP, was invited to give a lecture to the Behavioral Pharmacology Research Unit, Johns Hopkins University Medical School, Baltimore, MD, October, 2009.

Dr. Jonathan Katz was invited to chair a Nanosymposium on Sigma Receptors at the 39th annual meeting of the Society for Neuroscience, October, 2009.

Dr. Elliot Stein, IRP, was a featured speaker at Mapping the Brain of the Violent, Psychopathic, Criminal Defendant, 2009 ASTAR Judges Science School. He spoke to state supreme court and appellate court judges about imaging, lie detection, drug abuse and psychopathy in Chicago, November, 2009.

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Media and Education Activities

Monitoring the Future 2009

The results of this year's Monitoring the Future (MTF) survey were unveiled at a press conference December 14, 2009, at the National Press Club in Washington, D.C. Featured speakers included NIDA Director Nora D. Volkow, M.D., Director of the Office of National Drug Control Policy R. Gil Kerlikowske, and the study's principal investigator, Lloyd D. Johnston, Ph.D. In addition, a local high school senior gave remarks about the importance of the MTF survey to students. Coverage of the event was extensive and included print, broadcast and web stories from the following outlets (among numerous others): NBC, MSNBC, CBS, CNN, National Public Radio, *Associated Press, Reuters, Los Angeles Times, Dow Jones Newswire and Healthday News.* In addition, Dr. Volkow answered questions about the survey results for the web blog "Addiction Inbox," a highly-popular and well-regarded blog which has over 7,000 websites that link to it.

Town Hall Event

To promote community-wide involvement in drug abuse prevention efforts, NIDA hosted a live virtual town hall meeting to showcase effective evidence-based drug abuse prevention approaches. The webcast was viewed by health, science and justice reporters to learn how effective approaches are changing U.S. communities. The virtual town hall offered top federal prevention experts a chance to interact with citizens and local representatives who have seen impressive results in their own communities. This event followed the September 7 release of results from the Community Youth Development Study, the first randomized trial of the model for implementing prevention programs known as Communities That Care. The study was supported by a research grant from NIDA with co-funding from other NIH Institutes and from the Center for Substance Abuse Prevention.

Teleconference on Cocaine Vaccine

On October 5, PILB held a teleconference discussion with national, local, and trade reporters to discuss the findings of a NIDA-funded study in the October issue of Archives of General Psychiatry evaluating the safety and efficacy of a vaccine to treat cocaine addiction. Dr. Volkow and the study's lead investigator, Dr. Thomas Kosten, led the discussion and answered questions from the media. The teleconference was well attended, with nearly 30 media outlets participating, including the *New York Times*, Reuters, NBC News, *Los Angeles Times, Houston Chronicle, McClatchy Newspapers, BBC, Addiction magazine, Scientific American,* and *Medscape Psychiatry*.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

NIDA Drug Facts Chat Day

NIDA sponsored its third annual NIDA Drug Facts Chat Day on November 10, 2009. The purpose of this chat was to provide an opportunity for students and teachers in classrooms across the United States to ask questions of the Nation's top experts in the field of drug abuse and addiction. Despite efforts to limit registration, more than 13,000 questions came into Chat Day central as moderators Dr. Cindy Miner and Dr. Gaya Dowling screened and sent hundreds of queries to more than 40 NIDA scientists and science writers. Working as quickly as they could, the NIDA team answered close to 1,400 questions from 50 schools in 23 states. Among the participants was NIDA Director Dr. Nora Volkow, who herself answered more than 100 questions. An informal review of the incoming questions revealed that queries on marijuana more than doubled this year.

Press Releases

September 4, 2009 -- **Drug Czar, Top Federal Experts Use Virtual Town Hall to Announce Success of Major Community Based Drug Prevention Effort.** To promote community-wide involvement in drug abuse prevention efforts, NIDA hosted a live, virtual town hall meeting to showcase effective evidence-based drug abuse prevention approaches (see details above).

September 7, 2009 -- **Innovative Community-Based Prevention Dramatically Reduces Risky Behavior in 10-14 Year Olds.** A randomized trial of Communities That Care (CTC), an evidence-based, substance-use, community-focused prevention system, showed significant reductions in the initiation of alcohol use, tobacco use, binge drinking, and delinquent behavior among middle schoolers as they progressed from the fifth through the eighth grades. The positive results, published in the September 7 *Archives of Pediatrics and Adolescent Medicine,* demonstrate that community-based coalitions using customized evidence-based approaches can prevent the early initiation of substance abuse and delinquent behavior among youth.

September 21, 2009 -- **NIDA's 2009 Avant-Garde Awards for Innovative HIV/AIDS Research Announced.** Four scientists have been selected as this year's winners of the Avant-Garde Award for HIV/AIDS research, NIDA announced. The annual award competition, now in its second year, is intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in drug abusers. Winning scientists receive $500,000 per year, plus associated facilities and administrative costs, for five years to support their research.

October 1, 2009 -- **Teleconference Discussion of Results from Cocaine Vaccine Study.** Drs. Nora Volkow and Thomas Kosten discussed the findings of a study in the October issue of *Archives of General Psychiatry* evaluating the safety and efficacy of a vaccine to treat cocaine addiction. Currently there is no FDA-approved medication for treating cocaine addiction.

October 5, 2009 -- **Cocaine Vaccine Shows Promise for Treating Addiction.** Immunization with an experimental anti-cocaine vaccine resulted in a substantial reduction in cocaine use in 38 percent of vaccinated patients in a clinical trial supported by NIDA. The study, published in the October issue of *Archives of General Psychiatry,* is the first successful, placebo-controlled demonstration of a vaccine against an illicit drug of abuse.

October 30, 2009 -- **Federal Stimulus Grant Supports Crucial Study of Anti-Nicotine Vaccine.** Efforts to develop a vaccine capable of preventing tobacco addiction got a $10-million shot in the arm in the form of an American Recovery and Reinvestment Act grant. The award to Nabi Biopharmaceuticals of Rockville, MD, was funded by NIDA. The Recovery Act funds will help pay for

the first pivotal phase III trial of NicVAX, an injectable vaccine intended to help people quit smoking and prevent them from relapsing. The grant enables Nabi to retain its current staff as well as support 150 jobs at NicVAX research sites around the country.

November 6, 2009 -- **NIDA Launches New Substance Abuse Resources to Help Fill Gaps in Medical Education.** The rigors of medical training sharpen a doctor's ability to diagnose and treat a wide variety of human afflictions. However, drug abuse and addiction are often insufficiently covered in medical school curricula, despite the fact that drug use affects a wide range of health conditions and drug abuse and addiction are themselves major public health issues. To improve drug abuse and addiction training of future physicians, NIDA unveiled a series of new teaching tools, through its Centers of Excellence for Physician Information Program (NIDA CoEs), at the Association of American Medical Colleges 2009 Annual Meeting's "Innovations in Medical Education" Exhibit in Boston.

November 19, 2009 -- **NIDA Stimulus Grant to Assess the Benefits of Counseling with HIV.** Public health experts encourage everyone between the ages of 13 and 64 to be HIV tested. Researchers at the University of Miami Miller School of Medicine and the San Francisco Department of Public Health will determine whether receiving a rapid HIV test and counseling offers healthier outcomes than rapid testing alone, with a $12.3 million grant awarded through the American Recovery and Reinvestment Act. The grant is being funded by NIDA.

December 14, 2009 - **Teen Methamphetamine Use, Cigarette Smoking at Lowest Levels in NIDA's 2009 Monitoring the Future Survey.** Methamphetamine use among teens appears to have dropped significantly in recent years, according to NIDA's annual Monitoring the Future (MTF) survey, released at a news conference at the National Press Club in Washington. However, declines in marijuana use have stalled, and prescription drug abuse remains high, the survey reported.

December 15, 2009 -- **NIDA Director Honored By French Government With Top Science Award For Addiction Research.** Dr. Nora D. Volkow, Director of NIDA, was awarded the International Prize from the French Institute of Health and Medical Research (Inserm) for her pioneering work in brain imaging and addiction science. Dr. Volkow will receive the award at a December 17, 2009 ceremony at the College of France learning center in Paris.

Research News

Full NewsScans can be seen at http://www.nida.nih.gov/NIDANews.html#newsscan.

September 11, 2009 - **NIDA NewsScan #63** - Research News

- Disparities, Variability Found in Methadone Maintenance Dosing Patterns
- Brain Receptors Underlie Sex Differences Observed in Morphine Analgesia
- Marijuana Prevention Campaigns May Have Undesired Effects on Marijuana Use
- Crack Cocaine Use Hastens Progression of HIV Infection to AIDS
- Few U.S. High Schools Use Evidence-Based Drug Prevention Curricula
- Gene Changes Linked to Nicotine Dependence and Success With Smoking Cessation
- Electronic Diary Captures Moods and Cues Leading to Heroin and Cocaine Use
- Aging Population of Steroid Abusers May Face Underrecognized Health

Problems

December 11, 2009 - **NIDA NewsScan #64** - Research News

- Imaging Study Correlates Areas of Brain Activity with Sensation Seeking
- Suppressing Glial Cell Activity Reduces Rewarding Effects of Morphine and Withdrawal in Rats
- Imaging Study Shows Awareness Deficit in Marijuana Abusers
- Ibudilast and Minocycline Reduce Symptoms of Withdrawal from Two Different Opioid Drugs
- Salvinorin A Causes Rapid, Short-Lasting Sedation in Non-Human Primates
- Traumatic Brain Injury is an Understudied Risk Factor for Drug Abuse
- Marijuana Use Associated with a Subtype of Testicular Cancer
- CREB Protein Activity in the Nucleus Accumbens Shell Mediates Environmental Cues Associated with Nicotine

Highlights of Interviews & Articles of Interest

March 26, 2009 - *Los Angeles Times* - Interview with Dr. Nora Volkow about studies on obesity for a story about bad habits and how hard it is to break them.

September 15, 2009 - *Washington Post* - Dr. Volkow was interviewed about a study in the Journal of the American Medical Association regarding dopamine and ADHD.

September 22, 2009 - *Everydayhealth.com* - Dr. Compton was interviewed about the difference between tolerance and addiction.

September 25, 2009 - *Wall-to-Wall Productions* - Dr. Volkow was interviewed for a National Geographic series called "A Biography of Drugs."

October 1, 2009 - *Scientific American* - Dr. Volkow was interviewed for a cover story about cognitive enhancing drugs.

October 2, 2009 - *Discovery Health* - Dr. David Shurtleff was interviewed about the effects of LSD on the body and the brain for a program called "Dr. G: America's Most Shocking Cases."

October 26, 2009 - *New York Times* - Dr. Volkow was interviewed for a column about dopamine.

November 17, 2009 - *CBS "60 Minutes"* - Dr. Volkow was interviewed by Katie Couric for an upcoming segment on cognitive-enhancing drugs. The interview took place at Brookhaven National Laboratory, where Dr. Volkow conducts her brain imaging research.

November 19, 2009 - *AOL.com* - Dr. Compton was interviewed about the problem of abuse of pain medication among general population and youth.

November 21, 2009 - *New York Times* - Dr. Volkow was interviewed for a story about the use of marijuana to treat psychiatric conditions, including ADHD.

November 30, 2009 - *Bigthink.com* - Dr. Volkow was interviewed for a story on the science of addiction.

A research study by Dr. Yun Wang, IRP, was highlighted in Reuters Health (2009-06-23) by Megan Rauscher. Title: Delayed treatment with p53 inhibitor enhances stroke recovery in rats.

Outreach Activities

NIDA Scientists Star in Web Videos

NIDA has expanded the video library on its Teen Website with three creative new videos on prescription drug abuse and painkillers. The videos feature NIDA scientists Dr. Cindy Miner, Dr. Joni Rutter, and Dr. Wilson Compton talking about the facts and dangers of prescription drug abuse, as well as the safe use of prescription painkillers.

NIDA Distributes Media Guide to Reporters Nationwide

PILB has produced a new *NIDA Media Guide: How to Find What You Need to Know about Drug Abuse and Addiction.* The guide is designed to provide journalists with fast and user-friendly access to the latest scientific information on drug abuse and addiction. It includes basic and behavioral science research that addresses fundamental and essential questions relevant to drug abuse and addiction, ranging from their causes and consequences to treatment and prevention. More than 300 hard copies of the guide have been distributed to print and broadcast reporters to date, and additional copies are being distributed to professional journalist organizations and in press rooms of national science and health conferences. An online version of the guide will be periodically updated.

Rally for Recovery

Dr. Volkow joined 10,000 others in the second annual Rally for Recovery walk across the Brooklyn Bridge on September 12, 2009 sponsored by the partners of National Alcohol and Drug Addiction Recovery Month and A&E Entertainment. Other key participants included New York Governor David Paterson, Drug Czar Gil Kerlikowske, SAMHSA's Dr. Westley Clark, A&E President and General Manager Bob DeBitetto, Dr. Tom McLellan, Deputy Director of the White House Office of National Drug Control Policy, along with addiction specialists from the A&E show *Intervention*. Jane Velez-Mitchell, CNN anchor, served as the event emcee.

Recent and Upcoming Conferences/Exhibits

National Medical Association Annual Convention and Scientific Assembly July 25-30, 2009 -- Las Vegas, NV

American Association of Medical Colleges Annual Meeting
November 6-11, 2009 -- Boston, MA

American Public Health Association 137th Annual Meeting and Exposition
November 7-11, 2009 -- Philadelphia, PA

National Association for the Education of Young Children 2009 Annual Conference and Expo
November 18-20, 2009 -- Washington, DC

Community Anti-Drug Coalitions of America National Leadership Form XX
February 8-11, 2010 -- National Harbor, MD

National Science Teachers Association National Conference on Science Education
March 18-21, 2010 -- Philadelphia, PA

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Planned Meetings

NIDA will host the 8th Blending Conference in partnership with the University of New Mexico, the University of Arizona, and the University of California, San Francisco on April 22-23, 2010, in Albuquerque, New Mexico. The **Blending Addiction Science and Practice: Evidence-Based Treatment and Prevention in Diverse Populations and Settings** Conference will present innovative, science-based approaches that have been proven to be effective in the prevention and treatment of drug abuse and addiction. This two-day event has evolved into NIDA's signature conference and is designed to narrow the "translational gap" by disseminating science-based findings to treatment providers. NIDA's Deputy Director, Dr. Timothy Condon, is overseeing all conference planning activities and Drs. Cindy Miner (OSPC) and Denise Pintello (OD) are working closely with the two CTN Node PIs co-hosting the Blending Conference: Drs. James Sorenson (California-Arizona Node) and Michael Bogenschutz (Southwest Node).

The National Institute on Drug Abuse (NIDA) is collaborating with the **American Psychiatric Association (APA) to hold a major research based track at the APA Annual Meeting in New Orleans, LA, May 22-26, 2010.** The first major NIDA/APA track was held at the 1998 APA meeting in Toronto, and then again at the 2004 APA meeting in New York City and San Diego in 2007. NIDA has organized a number of diverse subject matter sessions for the upcoming track, including 12 symposia and 1 workshop. NIDA Director, Dr. Nora Volkow will lead an interactive session for residents and medical students on *Addiction and the Brain,* and give an invited Frontiers of Science Lecture titled, *Addiction: Conflict between Brain Circuits.* NIDA anticipates another highly successful program at the meeting in 2010.

For the May, 2010 **American Psychiatric Association** meeting in New Orleans, Dr. David McCann, DPMCDA, has organized a symposium entitled "Update on Medications Development: Promising New Treatments for Drug Addiction." Presentations will cover modafinil for cocaine addiction treatment (Dr. Charles O'Brien), d-cycloserine for cocaine and nicotine addiction treatment (Dr. Kathleen Brady), bupropion for methamphetamine addiction treatment (Dr. David McCann), dronabinol for cannabis addiction treatment (Dr. Frances Levin), and NicVax for tobacco dependence treatment (Dr. Raafat Fahim).

Wilson Compton, DESPR, and Ivan Montoya, DPMCDA, will co-chair a symposium entitled "Innovations in Integrated Treatment of Substance Use and Psychiatric Disorders" at the 2010 annual meeting of the **American Psychiatric Association**. It will include presentations by Drs. Paul Rohde (Simultaneous Treatment of Depression and Substance Use Disorders in Adolescents), Kathleen Brady (Post-Traumatic Stress Disorder and Drug Abuse: Etiology and Treatment Linkages), Roger Weiss (Group Therapy Treatment of

Bipolar Disorder and Addiction), Edward Nunes (Advances in Pharmacotherapy for Comorbid Depression and Cocaine Addiction), Alan Green (Concurrent Treatment of Cannabis Dependence in Patients with Schizophrenia), and Stan Sacks who will serve as the discussant.

Ivan Montoya and Herb Kleber will co-chair a workshop entitled "Maintenance Treatment for Opiate Dependence: Terminable or Interminable?" at the 2010 annual meeting of the **American Psychiatric Association**. The workshop will include the following topics: Deciding between opiate maintenance and detoxification (Dr. Steve Batki), Methadone maintenance: stop and go criteria (Dr. Robert Schwartz) and Optimal Duration of Contingency Management Interventions during Opiate Maintenance (Dr. Kenzie Preston).

Drs. Susan Volman, DBNBR, and James Bjork, DCNBR, have organized a NIDA-sponsored symposium for the May 2010 American Psychiatric Association Annual Meeting. The symposium, entitled **Reward Neurocircuitry in Substance Dependence and Other Psychiatric Disorders: What Does Brain Research Tell Us?** will feature presentations by Drs. Susan Sesack, Mauricio Delgado, Wayne Drevets and James Swanson.

Drs. Minda Lynch, Mary Kautz and "Woody" Lin, DCNBR, have organized a NIDA-sponsored symposium for the May 2010 American Psychiatric Association Annual Meeting. The symposium, entitled **Executive Function as a Brain System for Self-control: The Neurocircuitry of Psychiatric Disorders and Addiction** and will feature presentations by Drs. Karen Berman, B.J. Casey, Earl Miller, Todd Hare, Kevin Ochsner and Trevor Robbins.

Drs. Cora Lee Wetherington, DBNBR, and Shelly F. Greenfield (Harvard Medical School) co-organized and will co-chair 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, May 22-27, 2010, in New Orleans, LA. The speakers will be 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. Minda Lynch and David Shurtleff, DBNBR, are organizing a half-day, NIDA-sponsored satellite for the June 2010 CPDD meeting. The session is entitled: **Application of Genetic Aproaches to Understand Drug Abuse and Addiction.**

The National Institute on Drug Abuse (NIDA) is organizing 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 are involved in organizing and/or presenting on a wide range of session topics. NIDA will also co-sponsor an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

The next **National CTN Steering Committee Meetings** will be held April 19-21, 2010 in conjunction with the NIDA Blending Conference in Albuquerque, New Mexico.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

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

Publications

NIDA Publications

NIDA Publishes New Mind Over Matter
In response to the growing problems with abuse of prescription drugs, NIDA has just published a new Mind Over Matter on Prescription Drugs. The 9th in the Mind Over Matter series, this publication explores how prescription drugs act in the brain in a colorful and engaging manner appropriate for middle school children.

NIDA Reprints "Brain Power! NIDA Junior Scientists"
NIDA has updated and reprinted it's highly successful program for kindergarten and first grade, "Brain Power! NIDA Junior Scientists". This publication provides teachers with lesson that span a week and cover the brain and how to keep it healthy.

Epidemiologic Trends in Drug Abuse Highlights and Executive Summary June 2009, Volume I -- NIH Pub. No. 10-7421 (Print Date TBD)
This report provides descriptive information on the most recent significant trend, emerging problems and populations at risk within and across areas participating in the Community Epidemiology Work Group. This report provides program administrators and officials with specific indicator data in tabular and graphic format, and ethnographic information on current patterns and trends as well as emerging problems.

Epidemiologic Trends in Drug Abuse Highlights and Executive Summary June 2009, Volume II -- NIH Pub. No. 10-7422 (Print Date TBD)
This volume contains the edited research reports submitted by the Work Group participants. It provides an in-depth analysis of the epidemiologic trends and special reports for a limited audience made up primarily of drug abuse researchers who utilize this volume to identify potential areas for further research.

Research Report Series: Tobacco Addiction (Spanish) NIH Pub. No. 10-4342(S) (Print Date TBD)
This report describes what tobacco is, presents current epidemiological research data regarding its use, and reports on the medical consequences of tobacco use. It emphasizes the effects on the brain as well as current research findings about use during pregnancy. It also includes treatment approaches.

Research Report Series: Cocaine Abuse (Spanish) NIH Pub. No. 10-4166(S) (Print Date TBD)
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

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also reports on several pharmacological compounds currently being tested for their potential use in treating cocaine addiction.

Principles of Drug Addiction Treatment: A Research-Based Guide (Rev.) (Spanish)
NIH Pub. No.: 10-4180(S) (Print Date TBD)
This guide will communicate the latest research-based information about the treatment of drug addiction to a vast audience. In question and answer format this guide explains the various treatment approaches developed through NIDA-supported research and helps to explain some of the medical, social, and economic benefits associated with drug addiction treatment.

NIDA NOTES

***NIDA NOTES,* Vol. 22, No. 4 - NIH Pub. No.09-6459**
The lead story reports data identifying chromosome sites linked with nicotine addiction in two racial groups. The issue also features a mouse model for mania; a program that reduces girls' delinquent behavior; evidence that a dopamine receptor complex triggers cellular signaling; and an intervention that shows long-term benefits in children with disruptive behavior disorder. The Director's Perspective emphasizes the importance of treating addiction as a chronic disease.

***NIDA NOTES,* Vol. 22, No. 5 - NIH Pub. No. 09-6460**
The lead story describes how computer-based interventions can promote drug abstinence by reinforcing and expanding the well-established benefits of therapy delivered by a counselor. The story presents three groundbreaking examples of interactive multimedia therapies that may reduce costs and extend access to treatment. Also included in the issue are features reporting an immunotherapy that shows promise as a treatment for methamphetamine overdose; evidence that a person's genetic makeup influences success in quitting smoking and also which smoking cessation technique works best; and a new technique that uses dime-size arrays of tiny needles to painlessly deliver naltrexone and other medications. Another feature explores how extended cocaine exposure impairs attention in rats. In the Director's Perspective, Dr. Nora Volkow describes NIDA coalition with other federal agencies to assess and find solutions to the problems of substance abuse among service men and women, veterans, and members of military families.

***NIDA NOTES,* Vol. 22, No. 6 - NIH Pub. No. 10-7440**
This issue begins with a description of research from several laboratories that links contrasting smoking patterns with variations in half a dozen genes that dictate the structure of the brain receptor to which nicotine binds. The results suggest that genes for several receptor subunits drive different aspects of the multi-step process of nicotine addiction. Also included in the issue is a feature reporting that a checkup system provided after treatment for substance abuse may be especially beneficial for clients with co-occurring mental disorders. Another feature presents evidence that highly active antiretroviral therapy (HAART) is as useful in combating HIV in people who use illicit injection drugs as in other people infected with the virus. The issue also includes a report that proliferation of a rare receptor may underlie the intensification of craving that cocaine abusers experience during their first weeks of abstinence. In the Director's Perspective, Dr. Nora Volkow notes NIDA's 35th Anniversary, listing the Institute's major accomplishments and describing current challenges.

CTN-Related Publications

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 20 CTN trials are now available on the CTN Data Sharing Web Site. Over 300 research scientists have downloaded one or more data sets. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap.

International Program-Related Publications

New INVEST/CTN Fellowship Flyer Available
NIDA IP has developed a new flyer to help expand recruitment efforts for its INVEST/CTN Research Fellowship program. The colorful flyer describes the goals of the program and answers commonly asked questions about what the fellowship includes, who is eligible, how to find a mentor, and how and when to apply. A downloadable PDF version of the flyer is available on the International Program's Web site at http://www.international.drugabuse.gov/research/PDFs/CTN_flyer_110909.pdf.

Other Publications

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

Staff Highlights

Staff Honors and Awards

Dr. Cheryl Anne Boyce, DCNBR, received the American Psychological Association (APA) Meritorious Research Service Citation at the December 4, 2009 APA Board Meeting in Washington, DC.

Dr. Jag Khalsa, DPMCDA, received the Distinguished Service Award from ISAM for his contributions to the Society.

Dr. Harold Perl, CCTN, was elected as a Fellow in the American Psychological Association (APA) for his commitment and outstanding contribution in the field of psychology, effective September 2009.

Quandra Scudder, CCTN, along with Christie Espinoza, DBNBR, and the NIH Tracking and Inclusion Committee received the NIH Merit Award for outstanding achievements and dedication to the efforts to support the NIH tracking and inclusion policies and reporting. The 2009 OD Honor Awards Ceremony was held January 8, 2010.

Dr. Amy Newman, IRP, was elected to be a member of the American College of Neuropsychopharmacology in December 2009.

Dr. Amy Newman was invited to be a member of the Editorial Advisory Board of the new journal ACS Medicinal Chemistry Letters.

Erin Karschner and **Teresa Gray**, doctoral students of Dr. Huestis' from the University of Maryland, received Educational Research Awards from the Society of Forensic Toxicology for their research on cannabinoids and in utero drug exposure, respectively.

Staff Changes

Phil Skolnick, Ph.D., D.Sc. (hon.), a leader in the worlds of corporate and academic drug research, has been appointed Director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA). Prior to his assuming this position Dr. Skolnick was a research professor of psychiatry at New York University Langone Medical Center. He served as Chief Scientific Officer at DOV Pharmaceutical, Inc., from 2001-2009. Under his leadership, DOV discovered and developed novel reuptake inhibitor platforms, including the first triple (norepinephrine, serotonin, and dopamine) reuptake inhibitor tested in humans. These compounds can be targeted to a wide variety of neuropsychiatric disorders ranging from depression and attention deficit hyperactivity disorder, to pain and obesity. At NIDA, he will lead a team that stimulates and conducts all phases of medications development from synthesis

and screening of potential drug entities to preparing submissions for New Drug Applications. Dr. Skolnick's appointment marks a return to the NIH community. He first joined NIH in 1972 as a staff fellow under Dr. John W. Daly in the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD), now the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). After a brief stint as a senior investigator at the National Institute on Alcohol Abuse and Alcoholism, he returned to NIAMDD in 1978. In 1983, he became Chief of the Section on Neurobiology, and in 1986, Chief of the Laboratory of Neuroscience. After a celebrated career as an NIH neurobiologist and more than 500 papers published, Dr. Skolnick retired from government service in 1997 when he accepted a position as a Lilly Fellow in Neuroscience at Eli Lilly. Dr. Skolnick will take the Division helm from Acting DPMCDA Director David McCann, Ph.D. who has shown a strong and dynamic vision over the past year in leading the Division's programs and activities.

Dr. John SJ Anderson has joined the Office of Bioinformatics and Information Management as NIDA's new Chief Technology Officer (CTO). Dr. Anderson holds a Ph.D. in Molecular and Cellular Biology from the University of Arizona, and joins NIDA after working as a Lead Systems Architect at the Bureau of the Census on projects involving web-based electronic data collection. Prior to his work at the Census, he was a Principal Systems Analyst at the National Center for Biotechnology Information (NCBI; part of the National Library of Medicine) for several years, assisting with a variety of challenging projects. John brings extensive expertise in managing teams, IT projects, computer systems, and modern software development. As the NIDA CTO, Dr. Anderson will provide expert leadership and advice for information technology and management systems utilized by the Institute. Within the Office of Bioinformatics and Information Management, Dr. Anderson will coordinate and lead the development of bioinformatics software projects to assist and expand NIDA's mission of understanding and combating drug addiction.

Dr. Marsha Lopez has been promoted to the position of Branch Chief of the Epidemiology Research Branch in DESPR. As Branch Chief, Dr. Lopez will be responsible for a complex and diverse portfolio of national and international research on the prevalence, incidence and etiology of drug abuse and addiction, including a large program on HIV/AIDS. Dr. Lopez completed a Ph.D. in epidemiology at Johns Hopkins University. She was working as a supervising data analyst in the Department of Defense when she joined NIDA approximately 5 years ago as a Program Official in the Epidemiology Research Branch (ERB). Since joining NIDA, Dr. Lopez has managed a portfolio of national epidemiology studies and methodological projects. In particular, she has served as Program Official for the Monitoring the Future (MTF) study. Most recently, during the past 4 months, she has served as Acting Branch Chief for ERB and, in this position, working with colleagues, she has developed an innovative new initiative for secondary data release and analysis.

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Grantee Honors

Dr. Joanna S. Fowler, a senior chemist and Director of the Radiotracer Chemistry, Instrumentation and Biological Imaging Program at the U.S. Department of Energy's Brookhaven National Laboratory, was awarded the National Medal of Science at a White House ceremony on October 7, 2009. She is one of nine researchers named by President Barack Obama to receive the nation's highest award for lifetime achievement in science. The National Medal of Science was created by statute in 1959 and is administered for the White House by the National Science Foundation. The annual award recognizes individuals who have made outstanding contributions to science and engineering. Nominees are selected by a committee of Presidential appointees based on their advanced knowledge in, and contributions to, the biological, behavioral/social, and physical sciences, as well as chemistry, engineering, computing and mathematics.

NIDA grantee **Dr. Margaret L. Brandeau**, of Stanford University, was elected a Fellow of the Institute for Operations Research and Management Sciences (INFORMS) at the INFORMS annual conference, October 20-23, 2009, "For expanding the recognition and understanding of OR/MS in healthcare and for developing methods to inform public policy and to improve the effective control and treatment of disease and the distribution of critical resources."

Dr. Carrie Oser received the American Sociological Association (ASA) Alcohol, Drug, & Tobacco section, Junior Scholar Award, 2009.

Dr. Vivek Shetty of UCLA received the Laskin Award for the year's most outstanding article on Comparative Effectiveness Research, a subject of high priority in the Obama Administration. The article was published in the Journal of Oromaxillary and Facial Surgery. This NIDA-funded research is paving the way for a bill on methamphetamine and associated oral/dental consequences that the US Congress is considering.

Lawrence S. Brown, Jr., MD, MPH, FASAM, Executive Senior Vice President, Addiction Research and Treatment Corporation and Principal Investigator for the Infections and Substance Abuse Study (CTN 0012) has been named Addiction Physician of the Year by Karen M. Carpenter-Palumbo, Commissioner of the Office of Alcoholism and Substance Abuse Services (OASAS) in New York. This award is given to "a physician who has earned widespread recognition from his/her peers, and whose work reflects the highest level of professional conduct and dedication to serving individuals and families suffering from alcoholism and/or substance abuse."

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