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

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

Research Findings - Basic Neuroscience Research

Temporally Precise In Vivo Control of Intracellular Signaling

In the study of complex mammalian behaviors, technological limitations have prevented spatiotemporally precise control over intracellular signaling processes. Here Dr. Deisseroth of Stanford University and his research team report the development of a versatile family of genetically encoded optical tools ('optoXRs') that leverage common structure-function relationships among G-protein-coupled receptors (GPCRs) to recruit and control, with high spatiotemporal precision, receptor-initiated biochemical signaling pathways. In particular, they have developed and characterized two optoXRs that selectively recruit distinct, targeted signaling pathways in response to light. The two optoXRs exerted opposing effects on spike firing in nucleus accumbens in vivo, and precisely timed optoXR photostimulation in nucleus accumbens by itself sufficed to drive conditioned place preference in freely moving mice. The optoXR approach allows testing of hypotheses regarding the causal impact of biochemical signaling in behaving mammals, in a targetable and temporally precise manner. Airan RD, Thompson KR, Fenno LE, Bernstein H, Deisseroth, K. Temporally precise in vivo control of intracellular signalling. Nature. 2009; March 18; 1-5. Epub ahead of print.

Intracerebral BDNF Administration Prevents Cocaine-induced Increases in Glutamate Release and Cocaine Self-administration

Glutamatergic neurons originating from the dorsomedial prefrontal cortex (dmPFC) and projecting to the nucleus accumbens core (NAc) form a critical component of the reward circuitry that underlies reinstatement to cocaine-seeking behavior. Brain-derived neurotrophic factor (BDNF) activity is important for synaptic plasticity, is expressed by and modulates PFC-NAc neurons, and by itself enhances glutamatergic transmission. Cocaine also enhances glutatmate release. BDNF infusion into the dmPFC attenuates reinstatement to cocaine-seeking behavior, as well as some cocaine-induced molecular adaptations within the NAc. In the present study, it is demonstrated that a single intra-dmPFC infusion of BDNF prevents cocaine-induced increases in extracellular glutamate levels within the NAc. These data suggest that intra-PFC BDNF attenuates reinstatement to cocaine-seeking behavior and it does so by normalizing cocaine-induced neuroadaptations that alter glutamate neurotransmission within the NAc. Berglind, WJ, Whitfield, TW, LaLumiere, RT, Kalivas, PW, McGinty, JF. A single intra-PFC infusion of BDNF prevents cocaine-induced alterations in extracellular glutamate within the nucleus accumbens. J Neurosci, 2009;29(12):3715-19.

A Sensitizing D-Amphetamine Regimen Induces Long-Lasting Spinophilin Protein Upregulation in the Rat Striatum and Limbic

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Forebrain

Morphologic studies show that chronic regimens of psychostimulants increase dendritic length, branching, and overall spine density in the rat striatum. These long-term structural alterations in spines of striatal neurons may underlie sensitization-related alterations that contribute to addiction. The present study examined psychostimulant-induced changes in the levels of spinophilin, a protein found abundantly in dendritic spines, in brain regions implicated in psychostimulant-induced neuroplasticity. Rats received an escalating (1-8 mg/kg ip) regimen of d-amphetamine (twice daily) for 5 weeks, were tested for locomotor sensitization, and euthanized 28 days later. This amphetamine dosing regimen induced a significant sensitization of locomotor activity in these rats. Western blotting and radioimmunocytochemistry showed that spinophilin protein was upregulated in the striatum of the amphetamine-treated rats. Additionally, radioimmunocyto-chemical analyis revealed that spinophilin was also increased in the septum, hippocampus, amygdala, and cingulate cortex, but was unchanged in sensorimotor cortices. Because it binds to F-actin and protein phosphatase-1, spinophilin has been proposed as a protein linking synaptic transmission to changes in spine morphology.
Radioimmunocytochemistry for spinophilin provides a novel approach to identification of brain regions whose neurons undergo dendritic change after chronic exposure to drugs of abuse. Boikess SR, Marshall JF. A sensitizing D-amphetamine regimen induces long-lasting spinophilin protein upregulation in the rat striatum and limbic forebrain. European Journal of Neuroscience. 2008;28:2099-2107.

Nucleus Accumbens CREB is Essential for Nicotine-Induced Conditioned Reward

Dr. Marina Picciotto and her colleagues at Yale University have continued their studies on the adaptive changes in brain and behavior that accompany repeated exposure to nicotine, including projects aimed at a better understanding of the role of transcription factor cyclic AMP-response element binding protein, or CREB. This factor is thought to be important for new gene transcription and in the phosphorylated form (pCREB) to promote long-term changes in synaptic strength. Earlier studies have associated nucleus accumbens (NAc) CREB activity with the modulation of cocaine and morphine reward, and have also revealed that nicotine conditioned place preference (CPP) is associated with NAc CREB activation. The present study showed that nicotine context conditioning led to elevated pCREB levels in the NAc shell, but not in the core of mice following placement in a nicotine-paired chamber in the absence of nicotine. To test if CREB activity in the NAc shell contributed to cue-induced responses that precipitate nicotine-seeking, Dr. Picciotto and her colleagues used viral-mediated gene transfer of a dominant-negative CREB construct in the NAc shell of C57BL/6J mice and found that disruption of CREB activation before training blocked nicotine place preference across a range of doses. Dr. Picciotto interpreted these studies to indicate that the NAc shell is a brain region where CREB activity is essential for nicotine CPP. Brunzell DH, Mineur YS, Neve RL, Picciotto MR. Nucleus accumbens CREB activity is necessary for nicotine conditioned place preference.
Neuropsychopharmacology. 2009; Feb 11 [E-pub ahead of print]

Authentic Rat Embryonic Stem Cell Lines Established

The creation of knockout and knockin mice using mouse embryonic stem cells since the early 1980s has had tremendous impact on biological research. Now, Dr. Austin Smith and his group at the University of Cambridge, supported by NIDA funding, have demonstrated the ability to generate germline competent rat ES cells that will permit the creation of rats deficient in a gene of interest.

Because the rat is a more tractable organism for physiology and pharmacology and is widely used in models of psychiatric and addiction disorders, this breakthrough will enable researchers in the field to generate transgenic rat models for these studies, and significantly advance the field. In addition, the new knowledge gained in generating these authentic stem cell lines will have high impact on human stem cell research. This research paves the way to targeted genetic manipulation in this important biomedical model species and provides a new test bed for cell therapies based on pluripotent stem cells. Buehr M, Meek S, Ure J, McLay R, Silva J, Yang J, Hall J, Blair K, Ying QL, Smith A. Authentic embryonic stem cells isolated from rat blastocysts. Cell. 2008;135:1287-98.

Maternal High-Fat Diet and Fetal Programming: Increased Proliferation of Hypothalamic Peptide-Producing Neurons That Increase Risk for Overeating and Obesity

Recent studies in adult and weanling rats show that dietary fat, in close association with circulating lipids, can stimulate expression of hypothalamic peptides involved in controlling food intake and body weight. Dr. Leibowitz of the Rockefeller University and her research team examined the possibility that a fat-rich diet during pregnancy alters the development of these peptide systems in utero, producing neuronal changes in the offspring that persist postnatally in the absence of the diet and have long-term consequences. The offspring of dams on a high-fat diet (HFD) versus balanced diet (BD), from embryonic day 6 to postnatal day 15 (P15), showed increased expression of orexigenic peptides, galanin, enkephalin, and dynorphin, in the paraventricular nucleus and orexin and melanin-concentrating hormone in the perifornical lateral hypothalamus. The increased density of these peptide-expressing neurons, evident in newborn offspring as well as P15 offspring cross-fostered at birth to dams on the BD, led them to examine events that might be occurring in utero. During gestation, the HFD stimulated the proliferation of neuroepithelial and neuronal precursor cells of the embryonic hypothalamic third ventricle. It also stimulated the proliferation and differentiation of neurons and their migration toward hypothalamic areas where ultimately a greater proportion of the new neurons expressed the orexigenic peptides. This increase in neurogenesis, closely associated with a marked increase in lipids in the blood, may have a role in producing the long-term behavioral and physiological changes observed in offspring after weaning, including an increase in food intake, preference for fat, hyperlipidemia, and higher body weight. Chang GQ, Gaysinskaya V, Karatayev O, Leibowitz SF. Maternal high-fat diet and fetal programming: increased proliferation of hypothalamic peptide-producing neurons that increase risk for overeating and obesity. J Neurosci. 2008;28(46):12107-19.

Optical Deconstruction of Parkinsonian Neural Circuitry

Deep brain stimulation (DBS) is a therapeutic option for intractable neurological and psychiatric disorders, including Parkinson's disease and major depression. Because of the heterogeneity of brain tissues where electrodes are placed, it has been challenging to elucidate the relevant target cell types or underlying mechanisms of DBS. Dr. Deisseroth of Stanford University and his team employed optogenetics and solid-state optics to systematically drive or inhibit an array of distinct circuit elements in freely moving Parkinsonian rodents, and found that therapeutic effects within the subthalamic nucleus can be accounted for by direct selective stimulation of afferent axons projecting to this region. In addition to providing insight into DBS mechanisms, these results demonstrate an optical approach for dissection of disease circuitry, and define the technological toolbox needed for systematic deconstruction of disease circuits by selectively controlling individual components. Gradinaru V, Mogri M, Thompson KR, Henderson J, Deisseroth K. Optical deconstruction of

Parkinsonian neural circuitry. Sciencexpress. 2009; March 19; 1-13. Epub.

Gabapentin Acts within the Locus Coeruleus to Alleviate Neuropathic Pain

Gabapentin recruits descending inhibition to produce analgesia after nerve injury, but whether this is a local action in the brainstem is not known. It was hypothesized that gabapentin activates noradrenergic neurons in the locus coeruleus (LC) by a local action. Male rats underwent L5-L6 spinal nerve ligation (SNL) and received drugs by intra-LC or systemic routes for behavior testing, immunohistochemistry in the LC, and microdialysis in the spinal dorsal horn. In other studies, brainstem slices from normal and SNL animals were used for immunohistochemistry. SNL increased phosphorylated cyclic adenosine monophosphate response element binding protein (pCREB)-expressing nuclei bilaterally in the LC, and increased noradrenaline release in the spinal dorsal horn. Gabapentin, whether in isolated brainstem slices or in conscious or anesthetized animals, increased pCREB-expressing nuclei in the LC. The net increase in pCREB expression by gabapentin did not differ between normal and SNL conditions. This gabapentin-induced pCREB activation in LC neurons was abolished by an AMPA receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). Intra-LC-injected gabapentin reduced hypersensitivity in SNL rats in a dose-dependent manner. Both intra-LC coadministration of CNQX and intrathecal administration of the alpha2-adrenoceptor antagonist idazoxan blocked antihypersensitivity by intra-LC gabapentin. Intravenous gabapentin induced noradrenaline release in the spinal dorsal horn. The net amount of noradrenaline release by gabapentin is larger in SNL rats compared with the normal condition, although the percentage increases from the baseline were the same. These results suggest that gabapentin acts directly in the brainstem via a glutamate-dependent mechanism to stimulate descending inhibition to produce antihypersensiti-ity after peripheral nerve injury. Hayashida K, Obata H, Nakajima K, Eisenach JC. Gabapentin acts within the locus coeruleus to alleviate neuropathic pain. Anesthesiology. 2008;109:1077-84.

Differential Effects of Methylphenidate and Cocaine on Dendritic Spines and Delta-FosB in the Striatum

Methylphenidate marketed as Ritalin is one of the most frequently used prescriptions for treating attention deficit hyperactivity disorder (ADHD). Both methylphenidate and cocaine are psychostimulants and like cocaine, methylphenidate can be abused when injected intravenously. This has raised concerns about whether long term treatment of children diagnoses as ADHD are at risk of developing substance abuse disorder. However, meta-analysis of ADHD children treated with methylphenidate suggests that these children are protected from developing subsequent substance abuse. Studies in juvenile rats also suggest that treatment with methylphenidate does not increase drug seeking behavior when these rats become mature. This raises the question of whether the actions of methylphenidate are different from those of cocaine. Dr. Paul Greengard and his colleagues compared the effect of chronically administered methylphenidate for two weeks with chronically administered cocaine for two weeks on medium spiny neurons in the striatum of transgenic mice. The medium spiny neurons expressing the DRD1 or DRD2 dopamine receptors in these transgenic mice are tagged with a fluorescent tag that allows the neurons to be identified. DRD1 expressing neurons are medium spiny neurons that project from the striatum to the ventral tegmental area and DRD2 expressing neurons are medium spiny neurons that project from the striatum to pallidum. Dr. Greengard and his colleagues report that both chronic cocaine and chronic methylphenidate increase the number of dendritic spines and delta-FosB in medium spiny neurons but the patterns observed in three regions of the striatum (dorsal striatum, nucleus accumbens shell, and nucleus

accumbens core) are different for methylphenidate and cocaine. Chronic cocaine but not methylphenidate increased the density of spines in the dorsal striatum of DRD1 and DRD2 expressing spiny neurons. In the shell but not the core of the accumben both cocaine and methylphenidate increased the density of short dendritic spines in DRD2 expressing medium spiny neurons. Both methylphenidate and cocaine increase the density of dendritic spines in the shell and core of the accumbens. In contrast to cocaine, which increases the number of delta-FosB positive staining DRD1 and DRD2 neurons, methylphenidate increased only the number of delta-FosB positive DRD1 medium spiny neurons in all regions of the striatum. These results suggest that methylphenidate and cocaine produce different neuronal adaptations. Further work is needed to determine whether these differences can explain the reason that treatment of children with methylphenidate appears to decrease the risk of developing substance abuse disorder. Kim Y, Teylan MA, Baron M, Sands A, Nairn AC, Greengard P. Methylphenidate-induced dendritic spine formation and DeltaFosB expression in nucleus accumbens. Proc Natl Acad Sci U S A. 2009;106(8):2915-20.

D2 Dopamine and Type 1 Cannabinoid Receptors Both Target Downstream cAMP/PKA Signaling to Effect Neuroplasticity (Long-Term Depression)

Short- and long-term synaptic depression (LTD) are forms of neuroplasticity that are mediated by endogenous cannabinoid (eCB) signaling) in many brain regions. Endocannabinoid regulation is in turn affected by D(2) dopamine receptors, which show cooperativity with group I metabotropic glutamate receptors (mGluRs), ultimately inducing eCB-mediated LTD of glutamatergic excitatory and GABAergic inhibitory (I-LTD) synaptic transmission. Because D(2) receptors and group I mGluR agonists can induce the release of eCBs, it was widely accepted that D(2) receptors contributed to neuroplasticity (LTD) by regulating the release of eCBs. This paper challenges this hypothesis by showing that D(2) receptor activation does not enhance CB(1) receptor activation. Instead, D(2) receptor activation facilitates I-LTD induction via direct inhibition of cAMP-dependent protein kinase A (PKA) signaling. The authors demonstrate that the cAMP/PKA signaling pathway is the downstream effector for CB(1) receptors and is required for eCB-mediated I-LTD induction. Importantly, these results suggest that D(2) receptors and CB(1) receptors target the same downstream effector cAMP/PKA signaling pathway resulting in neuroplasticity (I-LTD). Further, D(2) receptor activation facilitates eCB-mediated I-LTD in dopamine neurons without enhancing CB(1) receptor activation. Pan B, Hillard CJ, Liu QS. D2 dopamine receptor activation facilitates endocannabinoid-mediated long-term synaptic depression of GABAergic synaptic transmission in midbrain dopamine neurons via cAMP-protein kinase A signaling. J Neurosci. 2008;28(52):14018-30.

Structure-Activity Relationships for a Novel Series of Dopamine D2-like Receptor Ligands Based on N-Substituted 3-Aryl-8-azabicyclo[3,2,1]octan-ol

Dopamine receptors, specifically D2-like receptors (D2R), have received particular attention in psychostimulant abuse because their availability has been shown to be related to cocaine's pleasurable effects in both human and primate studies. Although antipsychotic medications targeting the D2-like receptors have been clinically utilized for over half a century, an understanding of the complex relationship between dopamine receptor subtype activity, clinical efficacy, and side effects remains incomplete. Hence, D2R are clearly involved in drug reinforcement and addiction, and D2R selective antagonists have recently shown efficacy in animal models of drug abuse without incapacitating motor side effects. Continued study of the D3-like receptors

(D3R) using selective ligands has proven critical for the understanding of dopamine receptor related mechanisms, yet it remains unclear which subtypes are necessary and have the most potential to target in medication discovery. Given D2-like receptor antagonism has been implicated in the origin of cataleptic and other motor side effects, the narrow therapeutic window of non-selective D2R antagonists might be improved with a critical ratio of D2R/D3R selectivity. Thus the discovery of subtype selective ligands with which to determine specific roles of each of these receptor targets has been an imperative step toward the development of more effective medications for the treatment of schizophrenia, Parkinson's disease, obesity, and substance abuse. To provide tools with which to further explore the role of the dopamine receptor system, Dr. Paul and his colleagues developed high affinity D2R and D3R selective ligands by chemically modifying the lead chemical template, D2R-selective antagonist, by replacing piperidine with a tropane ring that reversed the selectivity as seen in the parent compound. Further exploration of both N-substituted and aryl ring-substituted analogs resulted in the discovery of several high affinity D2R/D3R ligands with 3-benzofurylmethyl-substituents, that induced high affinity not achieved in similarly N-substituted piperidine analogues and significantly (470-fold) improved D3R binding affinity compared to the parent ligand, L741,626. X-ray crystallographic data revealed a distinctive spatial arrangement of pharmacophoric elements in the piperidinol vs. tropine analogues, providing clues for the discovery in SAR at the D2 and D3 receptor subtypes. Paul NM, Taylor M, Kumar R, Deschamps J, Luedke R, Newman AH. Structure-activity relationships for a novel series of dopamine D2-like receptor ligands based on N-Substituted-3-Aryl-8-azabicyclo[3,2,1]octan-3-ol. Journal of Medicinal Chemistry. 2008;51:6095-6109.

Predicting Nicotine Dependence

The genetics of nicotine dependence (ND) have been elusive because no single factor is likely to explain a large proportion of the complex trait of dependence. Genome-wide association studies (GWAS) have been a powerful tool to help identify important genetic factors for ND, and subsequent replications have provided strong confirmation of the association between particular genetic variants and ND. Dr. Ramoni and his group have moved beyond individual single nucleotide polymorphism (SNP) associations to identify predictive models of the ND phenotype. Predictive modeling is a logical complement to the association-based approach because predictive measures are 1) amenable to translation into clinical practice where they can be used in risk communication and counseling, and 2) are able to address some of the challenges of the analysis and interpretation of genome-wide data. Dr. Ramoni and his colleagues used Bayesian networks, which are multivariate dependency models that account for simultaneous associations and interactions among multiple factors, to build the predictive models. Out of the original 73 SNPs identified by the Bierut et al. 2007 study, 60 were incorporated into the model, along with age and sex. SNP rs2836823 alone had the highest single predictive accuracy on fitted values of 54.4% ($P=0.002$). However, combined with the network of the other variables, the model achieved a predictive accuracy on fitted values of 75% ($P<0.0001$). This modeling approach is an iterative process of developing an understanding of the genetic basis of ND, in which weak associations are successively improved upon by generating hypotheses on the basis of subgroups and assessing them in new cohorts. As new information is uncovered, data can be added to the model to help define etiology driven definitions of ND and to reveal new targets for ND treatments. Ramoni RB, Saccone NL, Hatsukami DK, Bierut LJ, Ramoni MF. A testable prognositic model of nicotine dependence. J. Neurogenetics. 2009; Jan 31:1-10 [Epub ahead of print].

Morphine Leads to an Inhibition of CXCR4 Signaling in Neurons via a Ferritin Heavy Chain Mechanism

Dr. Olimpia Meucci and colleagues at Drexel University, Columbia University, and Washington University have been investigating the effects of μ-opioid receptor agonists on CXCR4 signaling in neurons, and the mechanisms involved in regulation of neuronal CXCR4 by opiates. CXCR4 is a CXCL12 chemokine receptor that promotes neuronal survival, plays a critical role in neuronal development, can be regulated by phosphorylation, and acts as a coreceptor for HIV envelope protein gp120. Opioids and chemokine systems can reciprocally influence the other's function, but the mechanism by which μ-opioid agonists modulate CXCR4 signaling is unknown. To that end, investigators tested whether opioid and chemokine receptors directly interact in neurons, using a glia-free neuronal culture system and treating with DAMGO (μ-opioid agonist) or morphine. They found that both drugs blocked CXCL12-induced phosphorylation in neurons and inhibited CXCL12-dependent signaling. They also tested whether in vivo morphine treatment alters CXCL12 responses and found that morphine transiently inhibited CXCL12-induced G-protein activation. Moreover, neither of the findings described above are due to a reduction in CXCR4 expression, as determined by RT-PCR and Westerns. The next set of experiments revealed that pretreatment with morphine completely abolished CXCR4 phosphorylation induced by CXCL12, suggesting that opioids may alter neuronal CXCR4 signaling by interfering with receptor activation, internalization, and recycling. Additional findings suggest that opioid treatment induced long-term adaptations in neurons that require de novo protein synthesis and resulted in deficits of CXCR4 signaling. To understand the mechanism underlying a decrease in CXCL12-induced phosphorylation, they sought to determine if Ferritin Heavy Chain (FHC), which has been shown to inhibit CXCR4 signaling, is increased by opioid exposure and thus inhibits receptor signaling. DAMGO and morphine caused a time-dependent increase in neuronal FHC levels, and an increase in FHC protein was also reported in the cortex of morphine-treated animals. The onset and decay of FHC upregulation inversely correlated with CXCR4 activation. These results point to a crucial role of FHC in mediating the effect of opioids on neuronal CXCR4. Lastly, in FHC-deficient cells, DAMGO pretreatment did not affect the phosphorylation induced by CXCL12. These data provide strong evidence that the upregulation of FHC levels is an important factor in the inhibition of CXCR4 signaling by opioids, and may be a potential mechanism by which opioids reduce the neuroprotective functions of CXCR4 and lead to increased susceptibility to infectious disorders. Sengupta R, Burbassi S, Shimizu S, Cappello S, Vallee RB, Rubin JB, Meucci O. Morphine increases brain levels of ferritin heavy chain leading to inhibition of CXCR4-mediated survival signaling in neurons. Journal of Neuroscience. 2009;29:2534-44.

Mechanism of Persistent Enhanced Synaptic Strength in Nucleus Accumbens

The nucleus accumbens (NAc) plays a central role in mediating motivated behaviors related to natural rewards and drugs of abuse. Ninety percent of the neurons in the NAc are "medium spiny" neurons (MSNs); MSNs project from the NAc, and are an interface from limbic to motor systems. MSNs receive inputs related to motivational state from dopamine (DA) neurons originating in the ventral mesencephalon and from glutamate neurons originating in the prefrontal cortex (PFC) and limbic regions such as the hippocampus and amygdala. Before we can understand the mechanisms underlying addiction, we must understand how the DA and glutamate inputs interact at MSNs. Marina Wolf's group tackled this problem by developing an in vitro system consisting of rat NAc neurons co-cultured with labeled PFC neurons obtained from enhanced cyan fluorescent protein-expressing mice. The cortical neurons fluoresce and provide excitatory input to NAc neurons and can be distinguished from the NAc neurons in culture. They first showed that brief DA D1 agonist exposure increased AMPA receptor (AMPAR) insertion onto extrasynaptic

regions of MSN processes through a mechanism requiring protein kinase A. This facilitated the Ca2+/calmodulin dependent protein kinase II (CaMKII)-dependent synaptic incorporation of AMPAR in response to subsequent NMDA glutamate receptor (NMDAR) stimulation. Through this mechanism, DA may promote reward- and drug-related plasticity in the NAc. Then, to model effects of repeated in vivo cocaine exposure, they treated the co-cultures with DA on days 7, 9 and 11 in culture. On day 15, MSNs exhibited increased synaptic AMPAR levels. This required CaMKII activation during the 4-day "withdrawal" period. Further, D1 agonist exposure on day 15 no longer increased AMPAR surface expression. NMDAR surface expression was not altered by acute or repeated DA receptor stimulation. Since it is known that the ratio of AMPAR to NMDAR determines persistent synaptic strength, the present results suggest that psychomotor stimulants, by increasing DA levels, may initially facilitate plasticity in the NAc, perhaps contributing to learning of drug-seeking behaviors. After drug withdrawal, NAc MSNs may be more responsive to glutamate inputs that trigger drug seeking. Sun X, Milovanovic M, Zhao Y, Wolf ME. Acute and chronic dopamine receptor stimulation modulates AMPA receptor trafficking in nucleus accumbens neurons cocultured with prefrontal cortex neurons. J Neuroscience. 2008;28:4216-30.

Expression and Adhesion Profiles of SynCAM Molecules Indicate Distinct Neuronal Functions

Cell-cell interactions through adhesion molecules play key roles in the development of the nervous system. Synaptic cell adhesion molecules (SynCAMs) comprise a group of four immunoglobulin (Ig) superfamily members that mediate adhesion and are prominently expressed in the brain. Although SynCAMs have been implicated in the differentiation of neurons, there has been no comprehensive analysis of their expression patterns. Here Dr. Biederer of Yale University examines the spatiotemporal expression patterns of SynCAMs by using reverse transcriptase-polymerase chain reaction, in situ hybridization, and immunohistological techniques. SynCAMs 1-4 are widely expressed throughout the developing and adult central nervous system and are present in both excitatory and inhibitory neurons. Each SynCAM has a distinct spatiotemporal expression pattern in all regions analyzed in developing and mature mouse brain and it is particularly notable in the cerebellum, where SynCAMs display highly distinct expression in cerebellar granule and Purkinje cells. These unique expression profiles are complemented by specific heterophilic adhesion patterns of SynCAM family members, as shown by cell overlay experiments. Three prominent interactions are observed, mediated by the extracellular domains of SynCAMs 1/2, 2/4, and 3/4. These expression and adhesion profiles of SynCAMs together with their previously reported functions in synapse organization indicate that SynCAM proteins contribute importantly to the synaptic circuitry of the central nervous system. Thomas LA, Akins MR, Biederer T. Expression and adhesion profiles of SynCAM molecules indicate distinct neuronal functions. J Comp Neurol. 2008;510(1):47-67.

CREB Regulation of Channel Gene Expression Underlies Rapid Drug Tolerance

Dr. Nigel Atkinson and co-workers exploit the genetically powerful fruit fly model system to investigate the molecular basis of inhalant tolerance. Previously, Dr. Atkinson has shown that a single exposure to inhalant can lead to epigenetic changes in the chromatin (the DNA/protein complex in the nucleus of a cell) near the "slowpoke" potassium channel gene, leading to altered expression of the slowpoke gene and reduced sensitivity (tolerance) to additional inhalant exposures. These studies are based on the observation that animals become tolerant to sedation by organic solvents, which can be abused as inhalants, and this reduced sensitivity to inhalant requires increased expression of the slowpoke potassium channel which in turn alters neuronal

function. The epigenetic changes involved are believed to lead to a more "open" chromatin conformation, allowing transcription factors to bind to DNA elements more readily. Which transcription factors are important in this process? In this follow up study, Dr. Atkinson and co-workers investigate the role of the transcription factor CREB which has been previously linked to processes critical for addiction. Sedation with benzyl alcohol leads to increased expression of positively acting CREB isoforms and reduced expression of negatively acting CREB isoforms (including dCREB2). Specifically the dCREB2 isoform shows increased occupancy at the slowpoke promoter immediately after benzyl alcohol sedation in a chomatin immunopreciptation assay. Animals with a knockout in dCREB2 no longer have increased benzyl alcohol induced slowpoke gene expression and also no longer develop tolerance to this organic solvent. Overall this work provides insight into the precise mechanisms by which exposure to an inhalant can lead to gene expression changes of a single gene, resulting in altered neuronal function and altered behavioral responses of an animal to future inhalant exposure. Although this work investigated an inhalant, analogous mechanisms may be utilized for responses to other drugs of abuse. Wang Y, Ghezzi A, Yin JCP, Atkinson NS. CREB regulation of BK channel gene expression underlies rapid drug tolerance. Genes, Brain and Behavior. 2009; Feb 9. [Epub ahead of print].

Sister Neurons Prefer Sister Neurons: Preferential Synaptic Formation Between Sister Neurons in the Radial Column of the Developing Cortex

Cortical neurons are often organized into columns in function. In many situations a single neuron in a column almost selectively communicates only with neurons above or below the column, but not the adjacent neurons. Such functional organization is pivotal for critical cortical information processing, such as seen in ocular dominance columns. However, how this selective communication within a column is established in cortical development is not known. Dr. Song-Hai Shi, a NIDA supported neurobiologist at Memorial Sloan Kettering and Cornell University, reports in Nature that sister neurons derived from the same mother radial glial cell during cortical formation migrate radially into destined cortical layers in the same column, and preferentially form functional excitatory synapses between each other within the column. The research team labeled ontogenetic radial clones of excitatory neurons in the mouse neocortex by in utero intraventricular injection of enhanced green fluorescent protein (EGFP)-expressing retroviruses around the onset of the peak phase of neocortical neurogenesis. The columns of sister neurons are then identified by the EGFP expression. Multiple-electrode whole-cell recordings were performed to probe synapse formation among these EGFP-labeled sister excitatory neurons in radial clones and the adjacent non-siblings during postnatal stages. They found that radially aligned sister excitatory neurons have a propensity for developing unidirectional chemical synapses with each other rather than with neighboring non-siblings. Moreover, these synaptic connections display the same interlaminar directional preference as those observed in the mature neocortex. These results indicate that specific microcircuits develop preferentially within ontogenetic radial clones of excitatory neurons in the developing neocortex and contribute to the emergence of functional columnar microarchitectures in the mature neocortex. Yu YC, Bultje RS, Wang X, Shi SH. Specific synapses develop preferentially among sister excitatory neurons in the neocortex. Nature. 2009;458:501-5.

The G-protein Coupled Receptor, Neurokinin 1, Mediates Opioid-Induced Endocytosis and Desensitization of Mu-Opioid Receptors

Mu-Opioid receptors (MORs) are G-protein-coupled receptors (GPCR) that mediate the physiological effects of endogenous opioid neuropeptides and opiate drugs such as morphine. MORs are coexpressed with neurokinin 1

receptors (NK1Rs) in several regions of the CNS that control opioid dependence and reward, and NK1R activation itself affects opioid reward. However, how NK1Rs regulate the mu opiate system is unknown. These researchers report that ligand-induced activation of NK1Rs mediates an NK1R-dependent sequestration of arrestins on endosome membranes that results in the cell-autonomous and nonreciprocal inhibition of MOR endocytosis. NK1R-mediated regulation of MOR trafficking was associated with a reduction in the usual opioid-induced desensitization of adenylyl cyclase signaling in striatal neurons. Additionally, heterologous regulation of MOR trafficking was observed in both amygdala and locus coeruleus neurons that naturally coexpress these receptors. These results identify a cell-autonomous mechanism that may underlie the highly specific effects of NK1R on opioid signaling and suggest, more generally, that receptor-specific trafficking of arrestins may represent a fundamental mechanism for coordinating distinct GPCR-mediated signals at the level of individual CNS neurons. Yu YJ, Arttamangkul S, Evans CJ, Williams JT, von Zastrow M. Neurokinin 1 receptors regulate morphine-induced endocytosis and desensitization of mu-opioid receptors in CNS neurons. J Neurosci. 2009;29(1):222-33.

Pro-Opiomelanocortin Gene Variation Related to Alcohol or Drug Dependence: Evidence and Replications Across Family- and Population-based Studies

Opioidergic neurotransmission is critical in many, possibly all, forms of substance dependence. Several opioid-system genes have been shown to be associated with substance dependence disorders. The pro-opiomelanocortin gene (POMC) encodes several peptides important for endogenous opioidergic neurotransmission. The investigators tested whether POMC genetic variation affects risk for substance dependence. Five noncoding single nucleotide polymorphisms spanning POMC were examined in independent family and case-control samples. Family-based studies included 854 subjects from 319 African American (AA) families and 761 subjects from 313 European American (EA) families. Each family had a pair of siblings affected with cocaine and/or opioid dependence. Case-control studies included 791 cases (455 AAs and 336 EAs) affected with alcohol, cocaine, and/or opioid dependence and 682 control subjects (199 AAs and 483 EAs). Family-based analyses revealed an association of rs6719226 with opioid dependence in AA families and rs6713532 with cocaine dependence in EA families ($p = .010$-$.044$). Case-control analyses demonstrated an association of rs6713532 with alcohol or cocaine dependence in EAs (p(allele-wise) $= .003$-$.008$). Moreover, the minor allele of rs1866146 was found to be a risk factor for cocaine or opioid dependence in AAs (p(allele-wise) $= .010$-$.017$) and for alcohol, cocaine, or opioid dependence in EAs (p(allele-wise) $= .001$-$.003$). Logistic regression analyses in which sex and age were considered and population stratification analyses confirmed these findings. Additionally, specific haplotypes increased risk for cocaine dependence ($p = .023$) in AAs and opioid dependence ($p = .012$) in EAs. Given these replicated results, the authors concluded that variation in POMC confers vulnerability to multiple forms of substance dependence. Zhang H, Kranzler HR, Weiss RD, Luo X, Brady KT, Anton RF, Farrer LA, Gelernter J. Pro-Opiomelanocortin gene variation related to alcohol or drug dependence: evidence and replications across family- and population-based studies. Biol Psychiatry. 2009; Feb 12 [Epub ahead of print].

Mu Opioid and Cholecystokinin Receptor Complexes

Dr. Philip Portoghese of the University of Minnesota and Dr. Laurence Miller of the Mayo Clinic in Arizona are investigating the physical association of the mu receptor (MOR) with the cholecystokinin receptor (CCK2) in the central nervous system. These two receptors have been shown to overlap in certain brain areas, particularly in medullary neurons shown to co-express the CCK2R and

the MOR. By analogy with heterodimeric associations in the lipid cell membrane found for other GPCRs, such as MOR/DOR, MOR/CB1, KOR/DOR, this study attempts to show whether homodimers and heterodimers of CCK2 and MOR exist, and whether a bifunctional ligand containing a CCK2 antagonist pharmacophore linked to a MOR agonist could serve the dual purpose of treating pain, and reducing the tolerance developing with chronic administration of a MOR agonist. In this case, the MOR agonist oxymorphone was used as the MOR pharmacophore, and the CCK2 antagonist L-365,260 as the second pharmacophore, separated by a linker of 9, 16, 18, or 22 atoms. The basis of examination was the use of BRET technology (bioluminescence resonance energy transfer) in COS cells between recombinant receptors tagged either with luminescent Rluc (renilla luciferase enzyme, energy donor) or yellow fluorescent protein (YFP, energy acceptor), as well as equilibrium binding (radiolabeled CCK or DAMGO), calcium mobilization assay, and in-vivo measure of tolerance in the mouse tail-flick assay. In brief, the investigators found BRET signals as evidence of heteordimers of CCK2-MOR "induced" only in the presence of bivalent ligands with a spacer of 16, 18, or 22 atoms. Evidence for constitutive homodimers of CCK2 or MORs was also found, in the absence of any ligands, and the bivalent ligands did not affect these observed homodimers. Monovalent ligands containing only one of the two pharmacophores competed with the bivalent ligands (reducing the BRET signals) only in the case of the CCK2 ligand, but not the monovalent MOR ligand. Equilibrium binding Ki values measured in CHO cell membranes co-expressing MORs and CCK2s were comparable to the values found in cells expressing only the MOR receptor, but the binding to the CCK2 receptor was improved in the system expressing both receptors. Moderate intracellular calcium mobilization as a functional test was observed in CHO cells co-expressing the MOR and CCK2 receptors, for one bivalent ligand (18 atom spacer) and for the MOR monovalent ligand. Tolerance in the radiant heat tail-flick assay (in terms of effective dose) was not seen for any of the three bivalent ligands given to mice by the icv route. This paper suggests that use of bivalent ligands to observe heteromeric associations between different GPCRs continues to be a useful technique. Information about the effects of bivalent ligands on receptor dimeric conformations, their signaling pathways, and their therapeutic possibilities awaits further work. Zheng Y, Akgun E, Harikumar KG, Hopson J, Powers MD, Lunzer MM, Miller LJ, Portoghese PS. Induced association of mu opioid and cholecystokinin (CCK2) receptors by novel bivalent ligands. J Med Chem. 2009;52(2):247-58.

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

Research Findings - Basic Behavioral Research

Progesterone's Attenuation of Cocaine-Primed Reinstatement in Freely Cycling Female Rats is Estrous Cycle Dependent

Cocaine self-administration has been shown to vary with the estrous cycle, and studies in which females are ovariectomized or estrogen is pharmacologically blocked clearly show that ovarian hormones play a role. Estrogen has been shown to have a facilitative effect on cocaine self-administration, including acquisition, escalation (which is commonly used to model the transition from moderate drug use to addiction), and reinstatement (a commonly used model of relapse). In contrast, progesterone has been shown to prevent escalation of cocaine self-administration and to have an inhibitory effect on reinstatement of cocaine-seeking behavior in females. Recently Drs. Matthew Feltenstein and Ron See at the Medical University of South Carolina found an inverse relationship between cocaine-primed reinstatement and plasma progesterone levels in freely cycling female rats across the estrous cycle. In a follow-up study, they directly assessed progesterone's effects on cocaine-primed reinstatement and examined whether its effects varied with the stage of estrous. They found that when administered during diestrus or proestrus, when progesterone is already high, progesterone had no effect. But, when administered during estrus, when progesterone is low, the additional progesterone attenuated cocaine reinstatement. These results complement NIDA-supported laboratory investigations with women showing that cocaine cue-induced craving is inversely related to circulating plasma progesterone levels in women and that experimentally administered progesterone decreases the positive subjective effects cocaine in women but not men. This line of research points to the potential clinical use of progesterone or related compounds in the treatment of cocaine use and addiction. Feltenstein MW, Byrd EA, Henderson AR, See RE. Attenuation of cocaine-seeking by progesterone treatment in female rats. Psychoneuroendocrinology. 2009;34(3):343-52. Epub 2008 Nov 1.

Sex and Age Differences in Sensitivity to Cocaine Conditioned Reward

Cocaine self-administration studies with adult rats have shown that females, compared to males, acquire self-administration faster, show greater escalation of self-administration, greater cocaine-primed reinstatement, and higher motivation for cocaine as measured by the progressive ratio procedure. Recent NIDA-supported research also reveals that female adolescents also acquire cocaine self-administration more rapidly than adolescent males. More recently, Dr. Sari Izenwasser and colleagues at the University of Miami have found that cocaine conditioned reward, as measured by the conditioned place procedure, also is greater in female adolescents than male adolescents, and is greater in

adult females than adult males with the order of sensitivity being adolescent females > adult females > adolescent males > adult males. These findings complement other findings showing that the greater sensitivity to cocaine's reinforcing and conditioned reinforcing effects observed in adult females compared to males is not a difference seen only in adulthood, but is present earlier during development, in adolescence. Ongoing research by these investigators is aimed at understand the neurobiological basis of these sex differences. Zakharova E, Wade D, Izenwasser S. Sensitivity to cocaine conditioned reward depends on sex and age. Pharmacol Biochem Behav. 2009;92(1):131-4. Epub 2008 Nov 12.

Gonadal Steroids Mediate Opposite Changes in Cocaine-induced Locomotion across Adolescence in Male and Female Rats

Studies have consistently shown that female rats exhibit greater sensitivity to stimulants than males. This sex difference, however, has not been examined developmentally. Dr. Cynthia Kuhn and her colleagues at Duke University have now characterized the emergence of this difference across development and have examined the role of prepubertal gonadal hormones. In the first study, cocaine was administered at postnatal days 28, 42 and 65. On each of those days, rats received cocaine according to an escalating dose procedure, (designed to simulate binge cocaine effects), and effects on behavioral activation were assessed. In a second experiment with the same protocol intact adults were compared with adults that had been gonadectomized in puberty. Results indicated that across puberty, cocaine responsivity changed in opposite directions in males and females, decreasing in males and increasing in females. Among adults, gonadectomy also had opposite effects in males and females: castration resulted in increased responsivity in males at the highest cocaine dose and ovariectomy decreased responsivity in females at the lower doses. The authors suggest that these data may indicate important organizational effects of testosterone and estrogen during puberty and that these effects may be responsible for sex differences in cocaine responsivity observed in adulthood by virtue of their influence on developing brain dopamine systems. Parylak SL, Caster JM, Walker QD, Kuhn CM. Gonadal steroids mediate the opposite changes in cocaine-induced locomotion across adolescence in male and female rats. Pharmacol Biochem Behav. 2008;89(3):314-23. Epub 2008 Jan 16.

mGlu2/3 Receptors As Targets For Ameliorating Stress-Associated Relapse Risk

Stress is a significant risk factor both in the initiation of drug taking and in relapse to drug use in abstinent drug addicts. Pharmacotherapies with anxiolytic properties therefore offer potential benefit in reducing relapse rates. Dr. Weiss and his colleagues focused their research on group II metabotropic glutamate receptor subtypes (mGluR2/3). They investigated the effects of the selective mGluR2/3 agonist LY354740 (LY), which previous research had demonstrated to have anxiolytic properties, on the shock-probe defensive burying model of anxiety. In this model, the primary index of stress or anxiety is the time spent by rats burying an electrified probe, with increased burying time indicating elevated stress reactivity or anxiety. Weiss and his colleagues tested rats that had been self-administering cocaine under conditions of short or long access to cocaine. The long access condition provides an escalation model of dependence and offers an opportunity to study the behavioral and neurobiological effects of cocaine under conditions that mimic cocaine abuse in humans. The results of three experiments were reported. In Experiment 1, rats were trained to self-administer cocaine, under short (ShA, 1-h) or long (LgA, 6-h) access conditions, or noncaloric food pellets (Ctrl, 1-h), and following 1, 14, 42, or 84 days of abstinence were tested for stress reactivity in the shock-probe defensive burying test. In Experiment 2, experimentally naive rats receiving the mGlu2/3 receptor agonist LY (0, 0.3, 1.0, or 3.0 mg/kg) were

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tested in the defensive burying test to establish its anxiolytic efficacy in this model. In Experiment 3, rats with a history of ShA vs LgA cocaine self-administration, or a history of operant responding reinforced by noncaloric food pellets, were tested in the defensive burying test, following administration of these same doses of LY at 14 days of abstinence. LgA rats exhibited a two- to threefold increase in defensive burying at 1, 14, and 42 days of abstinence compared to ShA or control animals. LY at 3.0 mg/kg reduced burying in all groups, whereas the 1.0 mg/kg dose reduced burying only in the LgA group. These results reveal that a robust and enduring increase in stress reactivity developed in rats with a history of daily 6-h access to cocaine. They also support the hypothesis that chronic cocaine use produces an increase in stress reactivity that may play a significant role in susceptibility to stress-induced relapse. Finally, these data indicate that mGlu2/3 receptors may be promising treatment targets for stress-induced relapse in cocaine addiction. Aujla H, Martin-Fardon R, Weiss F. Rats with extended access to cocaine exhibit increased stress reactivity and sensitivity to the anxiolytic-like effects of the mGluR 2/3 agonist LY379268 during abstinence. Neuropsychopharmacology. 2008;33:1818-26.

The Dorsal Subiculum and Conditioned Reinstatement of Cocaine-Seeking

Drug associated environmental cues are known to be important elicitors of drug seeking behavior and have a well-documented role in human craving and relapse. Similarly, in animal models, drug-associated cues have been shown to be potent elicitors of drug self-administration in the reinstatement model of relapse. Environment-drug associations typically are established in experiments using multiple drug-cue pairings, but it has now been demonstrated that robust associations, lasting up to one year, can be established after a single 2 hr conditioning session in rats. This persistence of conditioned associations suggests that drug-related learning during an initial cocaine experience may be an important element contributing to continued desire for drug once drug use has begun. Weiss and his colleagues sought to identify brain regions mediating the rapid acquisition of cue conditioning. It is well known that the hippocampus and its major projection, the subiculum play a critical role in the neural substrate for goal-directed behavior. Weiss et al. hypothesized that the subiculum mediates associative learning and plays an important role in behavior controlled by environmental stimuli conditioned with drugs of abuse. The present study investigated whether transient inactivation of the ventral (VSUB) or dorsal (DSUB) subiculum would interfere with the development of cue-induced cocaine-seeking. This hypothesis was tested by reversibly inactivating the VSUB and DSUB with tetrodotoxin (TTX) prior to conditioning rats during a single 2-h period of access to intravenous cocaine. Rats were given 2 h of response-contingent access to intravenous cocaine or saline in the presence of distinct stimuli that served as contextual stimuli associated with the availability and subjective effects of cocaine (S+) versus saline (S-). Before onset of the sessions, rats received bilateral microinjections of TTX into the VSUB or DSUB. Following extinction, rats were subjected to reinstatement tests in which exposure to the cocaine-, but not saline-associated stimulus produced strong recovery of responding. This effect was completely abolished in rats with transient TTX inactivation of the DSUB during the conditioning session. TTX inactivation of the VSUB during conditioning did not alter the response-reinstating effects of the cocaine cue. The results suggest that functional integrity of the DSUB, but not VSUB, is critical for the acquisition of conditioned cocaine-seeking controlled by contextual stimuli under conditions where such learning occurs during a single conditioning trial. These findings have implications for the transition from initial drug use to addiction and implicate the DSUB as an important neural substrate for the acquisition of drug-related contextual memory, at least during the early stages of this process. Martin-Fardon R, Ciccocioppo R, Aujla H, Weiss F. The dorsal

subiculum mediates the acquisition of conditioned reinstatement of cocaine-seeking. Neuropsycho-pharmacology. 2008;33:1827-34.

Novel Approach to Blocking the Toll-like Receptor 4 may be useful in the Treatment of Chronic Pain

Toll-like receptors are an integral part of the immune system and are important in the response to both exogenous and endogenous danger signals. Recently, the toll-like receptor 4 (TLR4) has emerged as a target for the treatment of various diseases, including chronic pain. In a recent study, NIDA-grantee Dr. Linda Watkins and colleagues used a chemical biology approach to disrupt the TLR4-myeloid differentiation factor 2 (MD2) interaction, thereby blocking TLR4 signaling. They demonstrated that short peptides, corresponding to the TLR4-binding loop, can prevent MD2 from binding to TLR4, and that this inhibits the release of proinflammatory cytokines. Proinflammatory cytokine release is responsible for some forms of chronic pain. By specifically blocking the TLR4-MD2 interaction, a cascade of events leading to chronic pain, can be inhibited. Thus, the development of clinically viable small peptides that interfere with the TLR4-MD2 interaction may be clinically useful for treating chronic pain and other disease conditions. Slivka PF, Shridhar M, Lee G, Sammond DW, Hutchinson MR, Martinko AJ, Buchanan MM, Sholar PW, Kearney JJ, Harrison JA, Watkins LR, Yin H. A peptide antagonist of the TLR4-MD2 interaction. ChemBioChem. 2009;10:645-9.

Mechanism for Sex Differences in Pain Perception and Analgesic Responsiveness

Men and women feel pain and respond to analgesics differently. For example, the prototypic analgesic morphine is significantly less effective in women compared with men. In this study, NIDA-grantee Dr. Anne Murphy and colleagues examined some of the potential reasons for this difference in morphine efficacy using a rat model of inflammatory pain. With immunohistochemical techniques, they found that males had a significantly higher expression of mu-opioid receptors (the receptors to which morphine primarily binds) in the ventrolateral periaqueductal gray (PAG) compared with cycling females, and the lowest level of expression was observed in proestrus females. Inflammation of the paw produced thermal hyperalgesia in both males and females that could be significantly reversed in males by a microinjection of morphine into the ventrolateral PAG, whereas this microinjection produced much less analgesia in the proestrus and estrus females. Further, selective lesions of mu-opioid receptor-expressing neurons in the ventrolateral PAG resulted in a significant reduction in the effects of systemic morphine in males only. These data elucidate a mechanism for sex differences in pain perception and analgesic efficacy, and may be of use in the development sex-specific pain treatments. Loyd DR, Wang X, Murphy AZ. Sex differences in mu-opioid receptor expression in the rat midbrain periaqueductal gray are essential for eliciting sex differences in morphine analgesia. J. Neurosci. 2008;28(52):14007-17.

A Sensitizing Regimen of MDMA Causes Enduring Structural Changes in the Accumbens and Prefrontal Cortex

The popular "club" drug MDMA (ecstasy) is a widely used amphetamine derivative, especially by young adults, but relatively little is known about its long-term neurobehavioral effects. A growing body of evidence from animal studies suggests that this drug has neurobiological and behavioral effects that are similar to highly addictive drugs. For example, behavioral studies have shown that repeated MDMA induces behavioral sensitization, conditioned place preference, and drug self-administration. In this study, the investigators gave

rats two daily injections of either MDMA or saline vehicle for 3 consecutive days, followed by 4 drug-free days, and repeated this sequence for a total of 3 weeks. Following a 4-week drug-free period, MDMA-pretreated rats displayed behavioral sensitization characterized by a significantly greater locomotor response to a challenge dose of MDMA. At this same time point, rats were sacrificed and their brains processed by a modified Golgi-Cox method for anatomical analysis. The MDMA-pretreated animals showed large increases in spine density and the number of multiple-headed spines on medium spiny neurons in the core and shell subregions of nucleus accumbens. In medial prefrontal cortex, the prelimbic subregion showed increased spine density, while the anterior cingulate subregion showed a change in the distribution of dendritic material instead. These results indicate that long-lasting locomotor sensitization to MDMA is accompanied by reorganization of synaptic connectivity in limbic-cortico-striatal circuitry. The changes in dendritic structure they observed are similar, although not in all brain areas identical to, those found previously in response to cocaine, amphetamine, and nicotine. These structural adaptations, combined with behavioral evidence, suggest that MDMA use may lead to compulsive drug-seeking and drug-taking behavior. Ball KT, Wellman CL, Fortenberry E, Rebec GV. Sensitizing regimens of (+/-)3, 4-methylenedioxymethamphetamine (Ecstasy) elicit enduring and differential structural alterations in the brain motive circuit of the rat. Neuroscience. 2009; Feb 21. [Epub ahead of print]

Cocaine Produces Behavioral Responses in Honey Bees Indicative of Reward

The role of cocaine as an addictive drug of abuse in humans is hard to reconcile with its ecological role as a natural insecticide that prevents herbivory of coca plants. In the past, this paradox has been explained by proposing a fundamental difference in mammalian and invertebrate responses to cocaine, despite the fact that cocaine similarly increases biogenic amine transmission in insects and mammals, and biogenic amines modulate locomotion and reward sensitivity in insects as well as mammals. The question of whether cocaine has reinforcing effects in insects is of importance because insects, such as the fruitfly Drosophila, provide genetic model organisms for the study of other aspects of the neurobiological effects of cocaine. In this study, the investigators show effects of cocaine in honey bees that parallel human responses. Forager honey bees perform symbolic dances to advertise the location and value of floral resources to their nest mates. Thus, the investigators used this "dance language" as a natural bioassay to study the effect of cocaine on reward assessment. When forager bees were treated with a low dose of cocaine, the likelihood and rate of their dancing after foraging increased, although their general locomotor activity did not. This effect is consistent with an interpretation that cocaine caused the bees to overestimate the value of the food resources they had collected. In addition, the experimenters showed that abrupt cessation of chronic cocaine treatment produced a deficit in learning an odor discrimination, similar to learning deficits that occur after cocaine withdrawal in rats. The authors suggest that these similarities likely occur because in both insects and mammals the biogenic amine neuromodulator systems disrupted by cocaine perform similar roles as modulators of reward as well as of motor systems. These analogous responses also propose an alternative solution to the paradox of cocaine reinforcement: ecologically, cocaine is an effective plant defense compound via disruption of herbivore motor control but, because the neurochemical systems targeted by cocaine also modulate reward processing, the reinforcing properties of cocaine may be produced as a "side effect". Barron AB, Maleszka R, Helliwell PG, Robinson GE. Effects of cocaine on honey bee dance behaviour. J Exp Biol. 2009;212(Pt 2):163-8.

Adolescent Anabolic-Androgenic Steroid Exposure Alters Several

Neurotransmitters Systems in the Hypothalamus

Richard Melloni and his colleagues have established that chronic anabolic-androgenic steroid (AAS) treatment during adolescence facilitates offensive aggression in male Syrian hamsters. Three recent studies by these investigators explored specific alterations in serotonin, dopamine and glutamate systems that correlate with development of this aggressive phenotype. Serotonin (5-HT) is known to modulate aggressive behavior and has been shown to be altered after AAS treatment. In addition, the 5-HT(2A) receptor has been implicated in the control of aggression. In one of their new studies, they showed that 5-HT(2A) receptor levels and the number of cells expressing this receptor subtype were significantly upregulated in the lateral portion of the anterior hypothalamus (LAH), a brain area thought to be involved in control of aggression. A second study investigated the role of the dopaminergic system in the modulation of AAS-induced aggressive behavior. Aggressive AAS-treated animals showed increased tyrosine hydroxylase immunoreactivity in anterior hypothalamic subnuclei and increased dopamine type 2 (D2) receptor levels in the AH, but decreased D2 levels in the ventrolateral hypothalamus (VLH). These results suggest that alterations in dopamine synthesis and function, together with modifications in D2 receptor expression in the AH, may facilitate AAS-induced aggression. In a third study, they found that glutamatergic cells in the LAH showed a lasting activation following adolescent AAS exposure, as evidenced by increased levels of PAG, the rate limiting enzyme for glutamate synthesis. They also found decreases in afferent innervation from the LAH to the VLH. This decreased connectivity may underlie some of the distinct behavioral peculiarities of AAS-induced aggression found in previous studies. Together, these three studies provide evidence for several neuroplastic mechanisms through which chronic adolescent AAS exposure may facilitate aggressive behavior. They also strengthen the hypothesis that a specific nucleus in the AH, the LAH, is a critical hypothalamic sub-region particularly sensitive to AAS-induced neurodevelopmental effects. Schwartzer JJ, Ricci LA, Melloni RH Jr. Adolescent anabolic-androgenic steroid exposure alters lateral anterior hypothalamic serotonin-2A receptors in aggressive male hamsters. Behav Brain Res. 2009;199(2):257-62. Ricci LA, Schwartzer JJ, Melloni RH Jr. Alterations in the anterior hypothalamic dopamine system in aggressive adolescent AAS-treated hamsters. Horm Behav. 2009;55(2):348-55. Carrillo M, Ricci LA, Melloni RH Jr. Adolescent anabolic androgenic steroids reorganize the glutamatergic neural circuitry in the hypothalamus. Brain Res. 2009;1249:118-27.

Nicotine Withdrawal in Mice Disrupts New, But Not Previously Acquired, Contextual Learning

Research suggests a link between nicotine-induced changes in learning and memory processes and nicotine addiction. Nicotine may facilitate the formation of maladaptive drug-context associations that could lead to drug seeking behavior, and nicotine withdrawal-related disruption of cognitive processes may trigger withdrawal. With this in mind, Drs. Portugal and Gould investigated the effects of nicotine withdrawal on contextual learning that occurred prior to withdrawal and learning that occurred during nicotine withdrawal. To test pre-withdrawal learning, a conditioned place preference procedure (CCP) was used to investigate contextual learning. Mice spent significantly more time in the nicotine-paired environment (e.g., drug context), indicating successful contextual learning. Following CPP testing, mice were surgically implanted with osmotic minipumps that released either nicotine or saline for 12 days. After 12 days, the pumps were removed to initiate spontaneous withdrawal and mice were again tested for CPP to assess whether prior contextual learning was still intact. A nicotine place preference was again observed, revealing that the earlier contextual learning persisted during withdrawal. An hour later, they began training in a fear conditioning paradigm to assess fear-cued

conditioning. In this paradigm, freezing in either the training chamber, or a different environment, is used to assess contextual learning. The fear conditioning task paired 30 seconds of a noise cue with mild footshock. Freezing induced by presentation of noise was then used to measure to fear conditioning. Twenty-four hours after training, the mice were tested again, in either the same contextual environment or a different environment and freezing in the absence of noise was recorded. During nicotine withdrawal, only contextual conditioning (assessed on the re-test) was disrupted, with fear conditioning remaining intact. That is, the animals learned the connection between the noise and shock (e.g., fear conditioning), regardless of whether they had been treated with chronic nicotine (and were in withdrawal) or chronic saline (no withdrawal). During the contextual learning assessment (generalized freezing), the animals withdrawn from nicotine displayed less context-dependent freezing. Since the contextual learning that took place prior to nicotine withdrawal remained intact, nicotine withdrawal differentially affected contextual learning depending upon whether acquisition took place before or during withdrawal. This suggests that, during nicotine withdrawal, there are adaptations in neural processes involved in contextual learning. Disruption of learning may play a role in maintaining nicotine addiction, particularly as related to relapse following a period of withdrawal. Portugal GS, Gould TJ. Nicotine withdrawal disrupts new contextual learning. Pharm Biochem Beh. 2009;92:117-23.

Habenula and Interpeduncular α2 and α5 Nicotinic Receptors are Necessary for the Expression of Nicotine Withdrawal

Although it is clear that nicotinic receptors are required for nicotine addiction and subsequent nicotine withdrawal, there are questions as to which nicotinic receptor subtypes, and which brain areas, are involved. Dr. Mariella De Biasi and colleagues investigated the roles of α2 and α5 nicotinic receptors in nicotine withdrawal by comparing mice lacking either α2 or α5 nicotinic receptors with their wildtype littermates. Following chronic nicotine administration via either mini osmotic pump or nicotinated drinking water, systemic administration of mecamylamine (a nicotinic receptor antagonist) was given to precipitate withdrawal. Nicotine withdrawal was calculated using somatic signs, including grooming, scratching, chewing, shaking, cage scratching, head nodding and jumping. While the WT mice displayed significant somatic signs of nicotine withdrawal following mecamylamine administration, neither the α2 nor α5 knockout mice did so. This indicates that α2 and α5 nicotinic receptors are needed for somatic expression of nicotine withdrawal. Investigation into which nicotinic receptor populations in the brain may underlie expression of nicotine withdrawal was then undertaken by administering local injections of mecamylamine following chronic exposure to nicotine. Blocking nicotinic receptors in the habenula or the interpeduncular nucleus precipitated withdrawal as evidenced by somatic withdrawal signs, whereas administration into the cortex, ventral tegmental area or hippocampus did not. This indicates a critical role for nicotinic receptors in the habenulo-interpeduncular system; however conditional KO mice, use of selective ligands, or other targeted technologies are needed to further elucidate the role of particular receptor subtypes. These data suggest that α2 and α5 nicotinic receptors are potential targets for pharmacotherapy for smoking cessation. Salas R, Sturm R, Boulter J, De Biasi M. Nicotinic receptors in the habenulo-interpeduncular system are necessary for nicotine withdrawal in mice. J Neurosci. 2009;29(10):3014-8.

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

Research Findings - Behavioral and Brain Development Research

Prenatal Exposure to Cigarettes, MAOA Genotype, Gender and Antisocial Behavior in Youth

Genetic susceptibility to antisocial behavior may increase fetal sensitivity to prenatal exposure to cigarette smoke. Dr. Laurie Wakschlag and her colleagues tested whether a functional polymorphism in the gene encoding the enzyme monoamine oxidase A (MAOA) interacts with prenatal exposure to predict pathways to adolescent antisocial behavior. One hundred seventy-six adolescents and their mothers participated in a follow-up of a pregnancy cohort with well-characterized exposure. A sex-specific pattern of gene x exposure interaction was detected. Exposed boys with the low-activity MAOA 5' uVNTR genotype were at increased risk for conduct disorder (CD) symptoms. In contrast, exposed girls with the high-activity MAOA uVNTR genotype were at increased risk for both CD symptoms and hostile attribution bias on a face-processing task. There was no evidence of a gene-environment correlation (rGE). Findings suggest that the MAOA uVNTR genotype, prenatal exposure to cigarettes and sex interact to predict antisocial behavior and related information-processing patterns. Future research to replicate and extend these findings should focus on elucidating how gene x exposure interactions may shape behavior through associated changes in brain function. Wakschlag LS, Kistner EO, Pine DS, Biesecker G, Pickett KE, Skol AD, Dukic V, Blair RJ, Leventhal BL, Cox NJ, Burns JL, Kasza KE, Wright RJ, Cook EH Jr. Interaction of prenatal exposure to cigarettes and MAOA genotype in pathways to youth antisocial behavior. Molecular Psychiatry. 2009; March; (Epub ahead of print).

Maternal Methadone Dosing Schedule and Fetal Neurobehavior

Daily methadone maintenance is the standard of care for opiate dependency during pregnancy. Previous research has indicated that single-dose maternal methadone administration significantly suppresses fetal neurobehaviors. The purpose of this study by Dr. Lauren Jansson was to determine if split-dosing would have less impact on fetal neurobehaviour than single-dose administration. Forty methadone-maintained women were evaluated at peak and trough maternal methadone levels on single- and split-dosing schedules. Monitoring sessions occurred at 36- and 37-weeks gestation in a counterbalanced study design. Fetal measures included heart rate, variability, accelerations, motor activity and fetal movement-heart rate coupling (FM-FHR). Maternal measures included heart period, variability, skin conductance, respiration and vagal tone. Repeated measure analysis of variance was used to evaluate within-subject changes between split- and single-dosing regimens. All fetal neurobehavioural parameters were suppressed by maternal methadone administration, regardless of dosing regimen. Fetal parameters at peak were

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significantly lower during single versus split methadone administration. FM-FHR coupling was less suppressed from trough to peak during split-dosing versus single-dosing. Maternal physiologic parameters were generally unaffected by dosing condition. Split-dosed fetuses displayed less neurobehavioral suppression from trough to peak maternal methadone levels as compared with single-dosed fetuses. Split-dosing may be beneficial for methadone-maintained pregnant women. Jansson LM, Dipietro JA, Velez M, Elko A, Knauer H, Kivlinghan KT. Maternal Methadone Dosing Schedule and Fetal Neurobehavior. J Matern Fetal Neonatal Med. 2009;22(1):29-35.

Maternal Smoking during Pregnancy and Newborn Neurobehavior

Dr. Laura Stroud and her colleagues examined effects of maternal smoking during pregnancy on newborn neurobehavior at 10 to 27 days. Participants were 56 healthy infants (28 smoking-exposed, 28 unexposed) matched on maternal social class, age, and alcohol use. Maternal smoking during pregnancy was determined by maternal interview and maternal saliva cotinine and postnatal smoke exposure was quantified by infant saliva cotinine. Infant neurobehavior was assessed through the NICU Network Neurobehavioral Scale. Smoking-exposed infants showed greater need for handling and worse self-regulation and trended toward greater excitability and arousal relative to matched, unexposed infants (all moderate effect sizes). In contrast to prior studies of days 0 to 5, no effects of smoking-exposure on signs of stress/abstinence or muscle tone emerged. In stratified, adjusted analyses, only effects on need for handling remained significant (large effect size). Effects of maternal smoking during pregnancy at 10 to 27 days are subtle and consistent with increased need for external intervention and poorer self-regulation. Along with parenting deficits, these effects may represent early precursors for long-term adverse outcomes from maternal smoking during pregnancy. That signs of abstinence shown in prior studies of 0- to 5-day-old newborns did not emerge in older newborns provides further evidence for the possibility of a withdrawal process in exposed infants. Stroud LR, Paster RL, Papandonatos GD, Niaura R, Salisbury AL, Battle C, Lagasse LL Lester, B. Maternal smoking during pregnancy and newborn neurobehavior: effects at 10 to 27 days. J Pediatr. 2009;154(1):10-6.

Stability of Early Living Arrangements, Behavior Outcomes, and Prenatal Drug Exposure

Dr. Henrietta Bada and her colleagues from the Maternal Lifestyle Study, the largest longitudinal prospective study of prenatal cocaine exposure, evaluated whether living arrangements of children with or without prenatal drug exposure would be associated with their behavior outcomes and adaptive functioning. At age three, 1092 children were evaluated with the Child Behavior Checklist and Vineland Adaptive Behavior Scales. Total and externalizing behavior problems T scores of children in relative care were lower (better) than those in parental care; externalizing behavior scores were lower than those in non-relative care ($p < .05$). Total behavior problem scores increased 2.3 and 1.3 points, respectively, with each move per year and each year of Child Protective Services involvement. Compared to children in non-relative care, those in parental or relative care had higher (better) scores in the Vineland Adaptive Behavior Scales total composite ($p < .023$), communication ($p < .045$), and daily living ($p < .001$). Each caretaker change was associated with a decrease of 2.65 and 2.19 points, respectively, in communication and daily living scores. Children's living arrangements were significantly associated with childhood behavior problems and adaptive functioning. The instability of living situation was also a significant predictor of these outcomes. While family preservation continues to be the goal of the child welfare system, expediting decision toward permanency remains paramount once children are placed in foster care. Bada HS, Langer J, Twomey J, Bursi C, Lagasse L, Bauer CR, Shankaran S, Lester

BM, Higgins R, Maza PL. Importance of stability of early living arrangements on behavior outcomes of children with and without prenatal drug exposure. J Dev Behav Pediatr. 2008;29(3):173-82.

Parenting Stress and Child Behavior Problems in High-Risk Children with and without Prenatal Drug Exposure

This study examined the relationship between early parenting stress and later child behavior in a high risk sample of children exposed and unexposed to cocaine in utero. The study also examined the role of drug exposure on the relationship between parenting stress and child behavior. A subset of child-caregiver dyads (n=607, 221 prenatal cocaine exposure, 386 unexposed) were selected from the Maternal Lifestyle Study (MLS), the largest longitudinal prospective study of prenatal cocaine exposure. Selection was based on the presence of a stable caregiver at 4 and 36 months with no evidence of change in caregiver between those time points. Parenting stress at 4 months significantly predicted child externalizing behavior at 36 months. These relations were unaffected by cocaine exposure suggesting the relationship between parenting stress and behavioral outcome exists for high-risk children regardless of drug exposure history. These results extend the findings of the relationship between parenting stress and child behavior to a sample of high-risk children with prenatal drug exposure and have implications for child outcomes and treatment interventions for high risk children. Bagner DM, Sheinkopf SJ, Miller-Loncar C, LaGasse LL, Lester BM, Liu J, Bauer CR, Shankaran S, Bada H, Das A. The effect of parenting stress on child behavior problems in high-risk children with prenatal drug exposure. Child Psychiatry Hum Dev. 2009;40(1):73-84.

Prenatal Drug Exposure, Caregiving Context and Sustained Visual Attention

Dr. Maureen Black and her colleagues at the University of Maryland, Baltimore, examined three groups of children from low-income, urban environments to determine the effects of prenatal drug exposure (PDE) and caregiving environment on sustained visual attention (SVA) at 7 years of age. Drug-exposed children remaining in maternal care (n = 43), drug-exposed children placed in non-maternal care (n = 45), and community comparison (CC) children (n = 56) were administered a battery of neurocognitive tests, including the Conners' Continuous Performance Test (CPT). PDE children remaining in maternal care displayed more omission errors than CC children. PDE children in non-maternal care had intermediate scores that did not differ significantly from PDE children in maternal care or CC children. There were no group differences with respect to commission errors or reaction time. CPT errors of omission and commission were significantly correlated with parent-reported attention problems and academic achievement scores. PDE in the context of care provided by a maternal caregiver with persistent drug use patterns may contribute to problems in children's SVA at school-age. As parental drug abuse can interfere with the provision of early care, children raised in a drug-using context may be highly vulnerable to problems with self-regulation, including sustained attention. SVA problems may contribute to subsequent academic and behavioral problems as demands for concentration and sustained effort increase throughout childhood. Children who have been prenatally exposed to drugs or raised in a drug-using household may benefit from early intervention services to avoid problems in SVA that may interfere with subsequent neurocognitive functioning and academic performance. Ackerman JP, Llorente AM, Black MM, Ackerman CS, Mayes LA, Nair P. The effect of prenatal drug exposure and caregiving context on children's performance on a task of sustained visual attention. J Dev Behav Pediatr. 2008;29(6):467-74.

Modeling Prenatal Exposure to Cigarettes

While there is a burgeoning body of research linking smoking during pregnancy to problem behavior in offspring, a major criticism of this work has been the measurement of exposure in these studies (e.g. retrospective, self-reported only) that could lead to biased estimates. To address this issue, this study examined a pregnancy cohort with repeated prospective measures of exposure as well as biological assays to generate estimates of exposure patterns using a range of modeling techniques. In this sample the more complex assessments of exposure, including biological measures, generally did not perform better than simple indicators of exposure based on repeated self-report measures, with one exception: a combined self-report cotinine 'best estimate' of third trimester exposure was uniquely associated with lower brain : body ratio. Further study is needed using more sophisticated cotinine assays and testing prediction of a range of outcomes to ascertain whether these findings represent true differences or are specific to the sample, methods and outcomes used. Such research will inform the development of guidelines for adequate exposure characterization in developmental studies. Pickett KE, Rathouz PJ, Dukic V, Kasza K, Niessner M, Wright RJ, Wakschlag LS. The complex enterprise of modeling prenatal exposure to cigarettes: what is 'enough'? Paediatr Perinat Epidemiol. 2009;23(2):160-70.

Pregnancy and Sexual Health among Homeless Young IDUs

Research on pregnancy and sexual health among homeless youth is limited. In this study, qualitative interviews were conducted with 41 homeless young injection drug users (IDUs) in Los Angeles with a history of pregnancy. The relationship between recent pregnancy outcomes, contraception practices, housing status, substance use, utilization of prenatal care, and histories of sexual victimization are described. A total of 81 lifetime pregnancies and 26 children were reported. Infrequent and ineffective use of contraception was common. While pregnancy motivated some homeless youth to establish housing, miscarriages and terminations were more frequent among youth who reported being housed. Widespread access to prenatal and medical services was reported during pregnancy, but utilization varied. Many women continued to use substances throughout pregnancy. Several youth reported childhood sexual abuse and sexual victimization while homeless. Pregnancy presents a unique opportunity to encourage positive health behaviors in a high-risk population seldom seen in a clinical setting. Hathazi D, Lankenau SE, Sanders B, Jackson Bloom J. Pregnancy and sexual health among homeless young injection drug users. J Adolesc. 2009;32(2):339-55.

Distress Tolerance and Early Adolescent Externalizing and Internalizing Symptoms: The Moderating Role of Gender and Ethnicity

A large body of research has examined the development of internalizing and externalizing symptoms in childhood and early adolescence. Notably, there is significant concomitant impairment associated with early adolescent symptomatology, as well as association of these symptoms with future development of psychopathology, poor physical health, self-destructive thoughts and behaviors, criminal behavior, and HIV risk behaviors. Drawing on negative reinforcement theory, the current study sought to examine the potential role of distress tolerance, defined as the ability to persist in goal-directed activity while experiencing emotional distress, as a potential mechanism that may underlie both internalizing and externalizing symptoms among 231 Caucasian and African American youth (M age=10.9 years; 45.5% female; 54.5% Caucasian ethnicity). A series of regressions resulted in significant moderated relationships, such that low distress tolerance conferred

increased risk for alcohol use among Caucasians, delinquent behavior among African Americans, and internalizing symptoms among females. Clinical implications, including the potential role of negative reinforcement models in early intervention with young adolescents, are discussed. Daughters SB, Reynolds EK, MacPherson L, Kahler CW, Danielson CK, Zvolensky M, Lejuez CW. Distress tolerance and early adolescent externalizing and internalizing symptoms: The moderating role of gender and ethnicity. Behav Res Ther. 2009;47(3):198-205.

Gene-Environment Interactions across Development: Exploring DRD2 Genotype and Prenatal Smoking Effects on Self-Regulation

Genetic factors dynamically interact with both pre- and postnatal environmental influences to shape development. Considerable attention has been devoted to gene-environment interactions (G x E) on important outcomes. It is also important to consider the possibility that these G x E effects may vary across development, particularly for constructs like self-regulation that emerge slowly, depend on brain regions that change qualitatively in different developmental periods, and thus may be manifested differently. To illustrate one approach to exploring such developmental patterns, the relation between variation in the TaqIA polymorphism, related to D2 dopamine receptor expression and availability, and prenatal exposure to tobacco was examined in two exploratory studies. First, in 4-week-old neonates, genotype-exposure interactions were observed for attention and irritable reactivity, but not for stress dysregulation. Second, in preschool children, genotype was related to Preschool Trail Making Test task performance on conditions requiring executive control; children with both the A1+ genotype and a history of prenatal tobacco exposure displayed disproportionately poor performance. Despite study limitations, these results illustrate the importance of examining the interplay between genetic and prenatal environmental factors across development. Wiebe SA, Espy KA, Stopp C, Respass J, Stewart P, Jameson TR, Gilbert DG, Huggenvik JI. Gene-environment interactions across development: Exploring DRD2 genotype and prenatal smoking effects on self-regulation. Dev Psychol. 2009;45(1):31-44.

Substance Use and HIV-Risk Behaviors among Young Men Involved in the Criminal Justice System

Dr. Nicholas Freudenberg and his colleagues examined the relationship between substance use and sexual HIV-risk behaviors among young men who have been incarcerated, in order to understand how HIV risks develop for this vulnerable population. A sample of 552 young men in a New York City jail was interviewed at the time of incarceration. Logistic regression was used to examine associations between alcohol and marijuana use and sexual HIV-risk behaviors in the 90 days prior to incarceration. Respondents were predominantly Black (57%) or Latino (37%), with a mean age of 17.4 years. The most common substances used were marijuana (82%) and alcohol (65%). Alcohol use prior to incarceration was significantly associated with having three or more sexual partners in the same time period (OR = 2.40, $p < .001$), as well as with having unprotected sex with a long-term partner (OR = 1.72, $p < .01$). Marijuana use was significantly associated with having multiple sex partners (OR = 1.55, $p < .01$). Heavy alcohol and marijuana use did not result in an increased likelihood of sexual HIV-risk behaviors. High rates of substance use and unprotected sex may have unintended health consequences for incarcerated young men. Severity of substance use is not a significant predictor of risk behaviors, suggesting the importance of contextual and social factors. Results highlight the need for HIV prevention efforts for this population that take into account contextual and social factors. Valera P, Epperson M, Daniels J, Ramaswamy M, Freudenberg N. Substance use and HIV-risk behaviors among young men involved in the criminal justice system. Am J Drug Alcohol

Abuse. 2009;35(1):43-7.

Maternal Brain Response to Own Baby-Cry Affected by Cesarean Section

A range of early circumstances surrounding the birth of a child affects peripartum hormones, parental behavior and infant wellbeing. One of these factors, which may lead to postpartum depression, is the mode of delivery: vaginal delivery (VD) or cesarean section delivery (CSD). To test the hypothesis that CSD mothers would be less responsive to own baby-cry stimuli than VD mothers in the immediate postpartum period, Dr. Linda Mayes and her colleagues conducted functional magnetic resonance imaging, 2-4 weeks after delivery, of the brains of six mothers who delivered vaginally and six who had an elective CSD. VD mothers' brains were significantly more responsive than CSD mothers' brains to their own baby-cry in the superior and middle temporal gyri, superior frontal gyrus, medial fusiform gyrus, superior parietal lobe, as well as regions of the caudate, thalamus, hypothalamus, amygdala and pons. Also, within preferentially active regions of VD brains, there were correlations across all 12 mothers with out-of-magnet variables. These include correlations between own baby-cry responses in the left and right lenticular nuclei and parental preoccupations ($r = .64$, $p < .05$ and $.67$, $p < .05$ respectively), as well as in the superior frontal cortex and Beck Depression Inventory ($r = .78$, $p < .01$). First this suggests that VD mothers are more sensitive to own baby-cry than CSD mothers in the early postpartum in sensory processing, empathy, arousal, motivation, reward and habit-regulation circuits. Second, independent of mode of delivery, parental worries and mood are related to specific brain activations in response to own baby-cry. Swain JE, Tasgin E, Mayes LC, Feldman R, Constable RT, Leckman JF. Maternal brain response to own baby-cry is affected by cesarean section delivery. J Child Psychol Psychiatry. 2008;49(10):1042-52.

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

Research Findings - Clinical Neuroscience Research

Adolescents More Likely to Develop Substance Use Disorder if Preceded by Depression or High Stress

Dr. Uma Rao and her colleagues assessed young adolescents for depression, risk for depression (depressed first degree relatives), and stress (HPA activity as measured by cortisol). Significantly more subjects who were depressed or who were at risk for depression developed substance abuse disorder in one-to-five-year follow-ups. Significantly more of those who had high HPA activity at baseline developed substance abuse disorder compared to those with low HPA activity. However, it was demonstrated that high HPA activity at baseline coupled with later stressful life events increased vulnerability to substance abuse independent of depression. It is speculated that differences in response to antidepressants in treatment of substance abuse (that is, they are ineffective in some individuals) might be related to differences in HPA activity. If so, treatment strategies might be more effective if tailored to differences in stress reactivity. Rao U, Hammen, CL, Poland RE. Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: Interactions between stress and HPA activity. Am J Psychiatry. 2009;166:361-9.

Functional Haplotype Implicated in Vulnerability for Cocaine Dependence

Dr. Mary Jean Kreek and associates at Rockefeller University evaluated the influence of polymorphisms of the prodynorphin gene in cocaine and cocaine/alcohol codependent individuals. Three SNPs in the 3' UTR region comprising a haplotype were significantly associated with cocaine dependence in the Caucasian but not African American subgroup. In post-mortem tissue it was found that there were significantly lower levels for the CCT haplotype of prodynorphin in both the caudate and nucleus accumbens. This study provides evidence that a haplotype in the 3' UTR prodynorphin gene is implicated in vulnerability to develop cocaine addiction and/or cocaine/alcohol codependence due to a lower mRNA expression of the gene in 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. Neuropsychopharmacology. 2008;34:1185-97.

Ecstasy Use Associated with Reduced Brain Activity in Areas Associated with Semantic Processing

Dr. Ron Cowan and associates at Vanderbilt University used fMRI to investigate

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dysfunction of brain processes that may contribute to verbal learning deficits in polydrug users who included MDMA as one of their major drugs of abuse. Using a semantic memory task, specific areas were studied that had been shown previously to be associated with this task. Significant results were reported for a correlation between lifetime use of MDMA and (decreased) activation in the left Brodmann Areas 9, 18, and 21/22 for semantic recognition but not accuracy or response time. Since polydrug users were assessed, there was evidence that these results were also due to cannabis and cocaine use. Together with previous evidence that there is reduced gray matter in these same areas, it is concluded that MDMA users' verbal memory impairments are due to neuronal changes due to use. Raj V, Liang HC, Woodward ND, Baurenfeind AL, Lee J, Dietrich MS, Park S, Cowan RL. MDMA (Ecstasy) use is associated with reduced BOLD signal change during semantic recognition in abstinent human polydrug users; a preliminary fMRI study. J Psychopharmacol. 2009; March 20; doi: 10.1177/026988109103203.

The Wake-Promoting Drug Modafinil Blocks Dopamine Transporters

Drs. Joanna Fowler, Nora Volkow and colleagues at Brookhaven National Laboratories used PET to assess the effects of therapeutic doses of Modafinil on extracellular dopamine and on dopamine transporters. The drug is used clinically to treat narcolepsy, but is also used as a cognitive enhancer. Results demonstrated increased extracellular dopamine in the caudate, putamen, and nucleus accumbens as well as blockade of the dopamine transporters. It is concluded that since drugs that increase dopamine in the nucleus accumbens have abuse potential, caution is advised in therapeutic uses. Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, Wang G-J, Jayne M, Hooker JM, Wong C, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog-Torres K. Effects of Modafinil on dopamine and dopamine transporters in the male human brain. JAMA. 2009;301(11):1148-54.

Ability to Inhibit Responses and Reaction Time Variability of Continuous Attention Served as ADHD Endophenotypes

Dr. Scott Kollins and colleagues at Duke University examined the molecular genetic substrate underlying attention performance in children having attention deficit hyperactivity disorders (ADHD) and in their family members. Haplotype-tagging SNP analyses were conducted to identify SNPs from 10 candidate genes involved in monoaminergic function and their association with quantitatively measurable cognitive performance that requires continuous attention and represents different aspects of executive function. Four different components of performance analyzed in the study were Errors of Omission (not responding to a target stimulus) that indexed sustained attention, Errors of Commission (responding to a non-target stimulus) that indexed the ability to inhibit response, Reaction Time and Reaction Time Variability that indexed attention regulation. After correction for multiple comparisons and controlling for multiple individuals from the same family, it was found that SNPs in dopamine D2 receptor gene were associated with commission errors on the continuous attention task. Polymorphisms in the norepinephrine transporter gene (NET) were related to reaction time variability in ADHD children and their families, supporting the heritability of these processes. These results suggest that commission errors and reaction time variability are related to NE transmission and may serve as ADHD endophenotypes. Kollins SH, Anastopoulos AD, Lachiewicz AM, FitzGerald D, Morrissey-Kane E, Garrett ME, Keatts SL, Ashley-Koch AE. SNPs in dopamine D2 receptor gene (DRD2) and norepinephrine transporter gene (NET) are associated with continuous performance task (CPT) phenotypes in ADHD children and their families. Am J Med Genet B Neuropsychiatr Genet. 2008;147B(8):1580-8.

Planned Meetings

Publications

Staff Highlights

Grantee Honors

White Matter Tract Injury and Cognitive Impairment in HIV+ Individuals

Dr. Igor Grant and colleagues at the University of California, San Diego, investigated the relationship of white matter integrity to cognitive impairment and antiretroviral treatment variables using diffusion tensor imaging and a comprehensive neuropsychological evaluation. Approximately half of those infected with the human immunodeficiency virus (HIV+) exhibit cognitive impairment, which has been related to cerebral white matter damage. Despite the effectiveness of antiretroviral treatment, cognitive impairment remains common even in individuals with undetectable viral loads. One explanation for this may be subtherapeutic concentrations of some antiretrovirals in the central nervous system (CNS). Diffusion tensor imaging indices were mapped onto a common whole-brain white matter tract skeleton, allowing between-subject voxel wise comparisons. The total HIV-infected group exhibited abnormal white matter in the internal capsule, inferior longitudinal fasciculus, and optic radiation; whereas those with AIDS exhibited more widespread damage, including in the internal capsule and the corpus callosum. Cognitive impairment in the HIV-infected group was related to white matter injury in the internal capsule, corpus callosum, and superior longitudinal fasciculus. White matter injury was not found to be associated with HIV viral load or estimated CNS penetration of antiretrovirals. Relationships between diffusion alterations in specific white matter tracts and cognitive impairment support the potential utility of diffusion tensor imaging in examining the anatomical underpinnings of HIV-related cognitive impairment, especially in individuals with more advanced HIV infection. The study also confirms that CNS injury is evident in persons infected with HIV despite effective antiretroviral treatment. Gongvatana A, Schweinsburg BC, Taylor MJ, Theilmann RJ, Letendre SL, Alhassoon OM, Jacobus J, Woods SP, Jernigan TL, Ellis RJ, Frank LR, Grant I. White matter tract injury and cognitive impairment in human immunodeficiency virus-infected individuals. J Neurovirol. 2009;22;1-9.

Vulnerability to Pain Persisted Following Opioid Detoxification in Chronic Pain Patients

Dr. Sean Mackey and colleagues at Stanford University investigated how patients receiving opioids to relieve chronic pain may paradoxically experience more pain over time as a result of prolonged administration of opioid analgesic. The need for dose escalation of analgesic can be due to desensitization of antinociceptive mechanisms (tolerance to opioids) or elevated sensitization of pain (opioid-induced hyperalgesia). The outcome of this study suggested that prolonged use of opioids results in a reduced tolerance to pain. The study was conducted in chronic pain patients who voluntarily titrated downward their opioids using an individualized biopsychosocial intervention and who had successfully and completely withdrawn from opioid. The association of tapered dose of opioid with subjective perception and tolerance to cold pain were assessed at admission to and discharge from the inpatient opioid detoxification program. Patients who relied upon a higher dose of opioid analgesic and who had experienced higher reduction in daily opioid use became less tolerant to pain. In these individuals, reduced tolerance threshold, but not perception to cold pain, persisted even though quality of life and daily function were significantly improved after a successful detoxification. In contrast, patients managed under lower dose of opioid analgesic before the detoxification had improved pain tolerance. Therefore, increased sensitivity to pain may sustain following opioids cessation, and greater tapering the dose of opioid strongly correlated with less pain tolerance. The lowered tolerance to pain contributes to the difficulty of tapering opioid medications even when classic withdrawal symptoms appear to be well-managed. Younger J, Barelka P, Carroll I, Kaplan K, Chu L, Prasad R, Gaeta R, Mackey S. Reduced cold pain tolerance in chronic pain patients following opioid detoxification. Pain Med. 2008;9(8):1158-63.

Abnormal Glutamate Metabolism in Neurocognitively Asymptomatic HIV+ Patients

Dr. Pom Sailasuta and colleagues at the California Institute of Technology evaluated the concentration of glutamate, the major excitatory neurotransmitter in the frontal cortex and posterior cingulate gyrus, in HIV-seropositive patients. HIV-seropositive patients taking antiretroviral medication may continue to develop cognitive deficits even if the infection is controlled and immune status is recovered. Biomarkers of neural abnormality at an early stage of HIV progression may predict neurocognitive changes in presymptomatic HIV+ patients. A novel MRS method, TE-averaged MRS, was used to differentiate glutamate from glutamine. Glutamate concentration, but not N-acetyl-aspartate or creatine, was significantly lower in the frontal white matter in HIV+ patients. No reduction was identified in frontal grey matter. In contrast, both glutamate and N-acetyl-aspartate concentrations were increased in the frontal white matter in a control group of abstinent methamphetamine users. Sailasuta N, Shriner K, Ross B. Evidence of reduced glutamate in the frontal lobe of HIV-seropositive patients. NMR Biomed. 2009;22(3):326-31.

Critical Review of Challenges Associated with Treatment of Comorbid Substance Use and Posttraumatic Stress Disorder

Dr. Kathleen Brady and colleagues at the Medical College of South Carolina investigated whether individuals with substance use disorders (SUDs) meet criteria for comorbid posttraumatic stress disorder (PTSD). Co-occurrence of SUD and PSTD may be of increasing importance in veterans of the Iraq and Afghanistan conflicts. Clinicians (N = 423) from four national organizations completed an anonymous questionnaire regarding sources of difficulty and gratification in treatment. Comorbid SUD/PTSD was rated as significantly more difficult to treat than either disorder alone. The most common challenges associated with treating SUD/PTSD patients included knowing how to best prioritize and integrate treatment components, patient self-destructiveness and severe symptomatology, and helping patients abstain from substance use. This comorbidity confers a more complicated clinical presentation that carries with it formidable treatment challenges for practitioners. The findings increase understanding of SUD/PTSD treatment challenges, and may be useful for enhancing therapist training programs, supervision effectiveness, and designing optimal SUD/PTSD interventions. Back SE, Waldrop AE, Brady KT. Treatment challenges associated with comorbid substance use and posttraumatic stress disorder: clinicians' perspectives. Am J Addict. 2009;18(1):15-20.

DAT Genotype Modulates Brain and Behavioral Responses Elicited by Cigarette Cues

Dr. Theresa Franklin and colleagues at the University of Pennsylvania tested whether the variable number of tandem repeats (VNTRs) polymorphism in the DA transporter (DAT) SLC6A3 gene influences DA transport, where brain and behavioral responses may be enhanced in probands carrying the 9-repeat allele. To test this hypothesis, they obtained perfusion fMR images during cue exposure in 19 smokers genotyped for the 40 bp VNTR polymorphism in the SLC6A3 gene. Contrasts between groups revealed that individuals with the 9-repeat polymorphism (9-repeats) had a greater response to smoking (vs nonsmoking) cues than smokers homozygous for the 10-repeat allele (10/10-repeats) in the interconnected ventralstriatal/pallidal/orbitofrontal cortex regions (VS/VP/OFC) of both sides. Activity was increased in 9-repeats and decreased in 10/10-repeats in the VS/VP/OFC ($p<0.001$ for all analyses). Brain activity and craving was strongly correlated in 10/10-repeats in these regions

and others (anterior cingulate, parahippocampal gyrus, and insula; $p<0.001$ in all regions). There were no significant correlations between brain and behavior in 9-repeats. There were no differences in cigarette dependence, demographics, or resting baseline neural activity between groups. These results provide evidence that genetic variation in the DAT gene contributes to the neural and behavioral responses elicited by smoking cues. Franklin TR, Lohoff FW, Wang Z, Sciortino N, Harper D, Li Y, Jens W, Cruz J, Kampman K, Ehrman R, Berrettini W, Detre JA, O'Brien CP, Childress AR. DAT genotype modulates brain and behavioral responses elicited by cigarette cues. Neuropsychopharmacology. 2009;34(3):717-28.

Social Discounting Demonstrated in a Public Goods Game

Dr. Howard Rachlin and colleagues at the State University of New York, Stony Brook examined the extent to which a human social discount function can measure the value to a person of a reward to another person at a given social distance. Just as delay discounting is a hyperbolic function of delay, and probability discounting is a hyperbolic function of odds-against, social discounting is a hyperbolic function of social distance. Experiment 1 obtained individual social, delay, and probability discount functions for a hypothetical $75 reward; participants also indicated how much of an initial $100 endowment they would contribute to a common investment in a public good. Steepness of discounting correlated, across participants, among all three discount dimensions. However, only social and probability discounting were correlated with the public-good contribution; high public-good contributors were more altruistic and also less risk averse than low contributors. Experiment 2 obtained social discount functions with hypothetical $75 rewards and delay discount functions with hypothetical $1,000 rewards, as well as public-good contributions. The results replicated those of Experiment 1; steepness of the two forms of discounting correlated with each other across participants but only social discounting correlated with the public-good contribution. Most participants in Experiment 2 predicted that the average contribution would be lower than their own contribution. Jones BA, Rachlin H. Delay, probability, and social discounting in a public goods game. Neuropsychopharmacology. J Exp Anal Behav. 2009;91(1):61-73.

Low Prefrontal Perfusion Linked to Depression Symptoms in Methadone-Maintained Opiate-Dependent Patients

Clinically depressed patients without substance use disorders, compared to controls, exhibit significantly lower resting regional cerebral blood flow (rCBF) in the prefrontal cortex (PFC). In this study, Langleben and colleagues, at the University of Pennsylvania, examined the link between resting rCBF in the PFC and current depressive symptoms in methadone-maintained opiate-dependent (MM) patients with or without major depression. The relationship between the Beck Depression Inventory (BDI) score and resting rCBF was examined in a single regression analysis. The BDI scores ranged between 0 and 18 ($m=7.0$, $S.D.=4.8$), and 30% of the sample had mild to moderate depression symptoms according to BDI scores. A negative correlation was observed between BDI scores and relative rCBF in the bilateral ventrolateral prefrontal cortex, and middle frontal gyri. The inverse relationship between prefrontal paralimbic rCBF and depression scores suggests a link between reduced fronto-limbic activity and depressive symptoms in MM patients. A significant subgroup of opiate-dependent patients has clinical or sub-clinical depression that is often undetected; these data identify brain substrates of depression symptoms that may also be a potential marker of relapse in this population. Treatment strategies targeting these brain regions may improve outcomes in depressed substance abusers. Suh JJ, Langleben DD, Ehrman RN, Hakun JG, Wang Z, Li Y, Busch SI, O'Brien CP, Childress AR. Drug Alcohol Depend. 2009;99(1-3):11-7.

The Relationship between Recreational Gambling and Substance Abuse/Dependence: Data from a Nationally Representative Sample

Dr. Marc Potenza and colleagues at the Yale University School of Medicine investigated the co-occurrence of substance abuse and recreational gambling. Logistic regression analyses were performed on data from a nationally representative sample from the Gambling Impact and Behavior Study. Substance-abusing recreational gamblers, as compared to non-substance-abusing ones, differed in gambling motivations, began gambling at earlier ages, reported heavier gambling, and preferred and performed strategic forms of gambling. As compared with non-substance-abusing gamblers, substance-abusing gamblers demonstrated different gambling profiles including heavier gambling. These findings suggest the need for additional research on whether and how substance use might promote gambling and vice versa. Liu T, Maciejewski PK, Potenza MN. Drug Alcohol Depend. 2009;100(1-2):164-8.

Ventral Striatal Dopamine Release in Response to Smoking a Regular vs a Denicotinized Cigarette

Prior studies have demonstrated that both nicotine administration and cigarette smoking lead to dopamine (DA) release in the ventral striatum/nucleus accumbens. In tobacco-dependent individuals, smoking denicotinized cigarettes leads to reduced craving, but less pleasure, than smoking regular cigarettes. Using denicotinized cigarettes and (11)C-raclopride positron emission tomography (PET) scanning, Brody and colleagues, at UCLA, sought to determine if nicotine is necessary for smoking-induced DA release. Sixty-two tobacco-dependent smokers underwent (11)C-raclopride PET scanning, during which they smoked either a regular or denicotinized cigarette (double-blind). Change in (11)C-raclopride binding potential (BP) in the ventral striatum from before to after smoking was used as an indirect measure of DA release. Cigarette craving, anxiety, and mood were monitored during scanning. Smoking a regular cigarette resulted in a significantly greater mean reduction in ventral striatal (11)C-raclopride BP than smoking a denicotinized cigarette. Although both groups had reductions in craving and anxiety with smoking, the regular cigarette group had a greater improvement in mood. For the total group, change in BP correlated inversely with change in mood, indicating that greater smoking-induced DA release was associated with more smoking-related mood improvement. Thus, nicotine delivered through cigarette smoking appears to be important for ventral striatal DA release. Study findings also suggest that mood improvement from smoking is specifically related to ventral striatal DA release. Brody AL, Mandelkern MA, Olmstead RE, Allen-Martinez Z, Scheibal D, Abrams AL, Costello MR, Farahi J, Saxena S, Monterosso J, London ED. Neuropsychopharmacology. 2009;34(2):282-9.

Brain Nicotinic Acetylcholine Receptor Occupancy: Effect of Smoking a Denicotinized Cigarette

Brody and colleagues, at UCLA, recently reported that smoking a regular cigarette (1.2-1.4 mg nicotine) resulted in 88% occupancy of brain alpha4beta2* nicotinic acetylcholine receptors (nAChRs). However, this study did not determine whether nicotine inhalation or the many other pharmacological and behavioral factors that occur during smoking resulted in this receptor occupancy. If nicotine is solely responsible for alpha4beta2* nAChR occupancy from smoking, then (as estimated from previous data) smoking a denicotinized (0.05 mg nicotine) or a low-nicotine (0.6 mg nicotine) cigarette (commonly used for research and clinical purposes) would result in substantial 23% and 78% alpha4beta2* nAChR occupancies, respectively, and

a plasma nicotine concentration of 0.87 ng/ml would result in 50% alpha4beta2* nAChR occupancy (EC50). Twenty-four positron emission tomography sessions were performed on tobacco-dependent smokers, using 2-[F-18]fluoro-A-85380 (2-FA), a radiotracer that binds to alpha4beta2* nAChRs. 2-FA displacement was determined from before to 3.1 hours after either: no smoking, smoking a denicotinized cigarette, or smoking a low-nicotine cigarette. Analysis of these PET data revealed that smoking a denicotinized and a low-nicotine cigarette resulted in 26% and 79% alpha4beta2* nAChR occupancies, respectively, across three regions of interest. The EC50 determined from this dataset was 0.75 ng/ml. Given the consistency of findings between a previous study with regular cigarettes and the present study, nicotine inhalation during smoking appears to be solely responsible for alpha4beta2* nAChR occupancy, with other factors (if present at all) having either short-lived or very minor effects. Brody AL, Mandelkern MA, Costello MR, Abrams AL, Scheibal D, Farahi J, London ED, Olmstead RE, Rose JE, Mukhin AG. Int J Neuropsychopharmacol. 2009;12;(3):305-16.

MAO-A Genotype Does Not Modulate Resting Brain Metabolism

Dr. Alia-Klein and colleagues at Brookhaven National Laboratory used a combination of brain imaging and genotyping to investigate whether polymorphisms in the MAO-A gene in humans have functional effects on cerebral metabolism. Variation in the monoamine-oxidase-A (MAO-A) gene has been associated with volumetric changes in corticolimbic regions with differences in their response to relevant emotional tasks. However, no differences in baseline regional brain metabolism were observed as a function of genotype. These results suggest that unchallenged, corticolimbic activity is not modulated by the MAO-A genotype. Alia-Klein N, Kriplani A, Pradhan K, Ma J, Logan J, Williams B, Craig I, Telang F, Tomasi D, Goldstein R, Wang G, Volkow N, Fowler J. The MAO-A genotype does not modulate resting brain metabolism in adults. Psychiatry Research-Neuroimaging. 2008;164(1):73-6.

Nonlinear Neurobiological Probability Weighting Functions for Aversive Outcomes

Dr. Greg Berns and colleagues at Emory University used fMRI to investigate what brain processes generate the tendency for people to overestimate the likelihood of improbable events and underestimate the likelihood of probable events. They presented individuals during fMRI with a series of situations that differed with respect to the intensity of a impending (mild) cutaneous electric shock and the probability with which the shock would be received. During the anticipatory phase, prior to the delivery of the shock, activity in a circumscribed network of brain regions including the anterior cingulate, visual, parietal, and temporal cortices was proportional to the probability of the expected outcome. However, the degree of neuronal activity did not scale linearly with the probability of the shock, rather most of these regions displayed responses to probabilities consistent with nonlinear probability weighting. The neural responses to passive situations predicted 79% of subsequent decisions when individuals were offered choices between different situations. More importantly, the prior neuronal activation was a better predictor of later choices than prior behavioral choices near the indifference point. These results indicate that brain activity is a sensitive index of later choices that involve assessment of aversive outcomes. Berns GS, Capra CM, Chappelow J, Moore S, Noussair C. Nonlinear neurobiological probability weighting functions for aversive outcomes. Neuroimage. 2008;39(4):2047-57.

Neurobiological Regret and Rejoice Functions for Aversive Outcomes

Dr. Greg Berns and colleagues at Emory University used fMRI to investigate the neural basis of why winning a bet when winning was unlikely is a more positive experience than when winning was highly probable - even if the absolute amount of the outcome is the same. In this study, "regret" was defined as a choice that results in a more adverse outcome than a different choice would have yielded, whereas "rejoice" when a choice resulted in better outcome than a different choice. Unlike previous studies, non-monetary outcomes were used, consisting of mild electrical shocks to the foot. Subjects were asked to make the choices which allowed for the possibility of avoiding the shocks. It was hypothesized that the neural response to a painful outcome would not only reflect the intensity of the shock, but would also reflect the degree of regret as measured by the likelihood that alternative choices would not have yielded the same adverse outcome. Similarly, when an individual avoided a potential shock, the neuronal response would reflect the degree of rejoicing proportional to the probability he had of receiving the shock. Activation of a cortical network, consisting of the medial orbitofrontal cortex, left superior frontal cortex, right angular gyrus, and left thalamus, correlated with the degree of regret. A different network, including the rostral anterior cingulate, left hippocampus, left ventral striatum, and brain stem/midbrain correlated with rejoice. The right inferior orbitofrontal cortex, pre-supplementary motor area, anterior cingulate, and posterior cingulate showed similar patterns of activation with both regret and rejoice, suggesting that these regions may be associated with surprise from the realization of relatively unlikely events. Therefore, distinct, but overlapping networks are involved in the experiences of regret and rejoice. Dysregulation of these networks may contribute to the inability of substance abusers to "regret" adverse outcomes resulting from substance use. Chandrasekhar PVS, Capra CM, Moore S, Noussair C, Berns GS. Neurobiological regret and rejoice functions for aversive outcomes. Neuroimage. 2008;39(3):1472-84.

Abstinence from Chronic Cocaine Self-Administration Alters Striatal Dopamine Systems in Rhesus Monkeys

Dr. Linda Porrino and colleagues at Wake Forest University use ex vivo autoradiography imaging to determine whether changes in dopamine receptors during chronic cocaine self-administration persist after abstinence. Male rhesus monkeys self-administered cocaine (0.3 mg/kg per injection, 30 reinforcers per session) under a fixed-interval 3-min schedule for 100 days. This duration of cocaine self-administration has been previously shown to decrease DA D2-like receptor densities and increase levels of D1-like receptors and DA transporters (DAT). Responding by control monkeys was maintained by food presentation under an identical protocol and the same abstinence periods. Following 30 days of abstinence both D1 receptor binding, indexed by [H-3] SCH 23390, and DAT binding, indexed by [H-3] WIN 35 428, was significantly higher in all portions of the striatum, compared to control animals. In contrast, D2 receptor binding indexed by [H-3] raclopride did not differ between the cocaine and control monkeys. Following 90 days of abstinence, DA D1 receptor and DAT binding were not different from control values. These results indicate that there is eventual recovery of the separate elements of the DA system, but highlight the dynamic nature of these components during the initial phases of abstinence from chronic cocaine self-administration. Beveridge T, Smith H, Nader M, Porrino L. Abstinence from chronic cocaine self-administration alters striatal dopamine systems in rhesus monkeys. Neuropsychopharmacology. 2009;34(5):1162-71.

Transdermal Nicotine Administration and the Electroencephalographic Activity of Substance Abusers in Treatment

Dr. Sara Nixon and colleagues at the University of Florida examined the effects

of nicotine on patterns of electroencephalographic (EEG) activity in smokers who concurrently were dependent on other substances. Subjects were regular smokers who were also either alcohol-dependent, stimulant-dependent, or had concurrent alcohol- and stimulant-dependence compared to community controls. After overnight nicotine abstinence, subjects were administered either a high (14 or 21 mg) or low (7 mg) dose transdermal nicotine patch. EEG data were collected during a 2-minute eyes open and 5-minute eyes closed baseline recording session. Results indicated differential pattern of nicotine dose effects by group. There was no difference across nicotine doses in the EEG patterns of controls and concurrent alcohol/stimulant-dependent participants. In contrast nicotine administration in either the alcohol-dependent or stimulant-dependent groups resulted in opposite findings across a range of spectral bands. Although further research is warranted, these data suggest that nicotine-related changes in neurophysiology may be associated with specific drug histories and reinforce the need for caution in generalizing across groups with different drug histories. Ceballos N, Tivis R, Prather R, Nixon S. Transdermal nicotine administration and the electroencephalographic activity of substance abusers in treatment. Journal of Addiction Medicine. 2008;2(4):202-14.

Cognitive Control for Task Sets is the Same for Shifting Spatial Attention and Switching Categorization Rules

Dr. Steven Yantis and colleagues at Johns Hopkins University used fMRI to investigate whether the ability to voluntarily shift in task across different domains of cognitive control (e.g., spatial attention shifts, shifts between categorization rules, or shifts between stimulus-response mapping rules) is associated with separate, domain-specific brain control networks, or whether a common, domain-independent brain source of control initiates shifts in all domains. A rapid event-related fMRI paradigm allowed use of a single paradigm in which subjects were cued to perform both shifts of spatial attention and switches between categorization rules. A conjunction analysis revealed a common transient signal evoked by switch cues in medial superior parietal lobule for both domains of control, revealing a single domain-independent control mechanism. These results suggest that proper functioning of the medial superior partietal lobe may be necessary for drug abusers to be able to shift their attention (and behavior) away from drug-related cues. Chiu Y, Yantis S. A domain-independent source of cognitive control for task sets: shifting spatial attention and switching categorization rules. J Neurosci. 2009;29(12):3930-8.

Striatal Dopamine Predicts Outcome-Specific Reversal Learning and its Sensitivity to Dopaminergic Drug Administration

Dr. Mark D'Esposito and colleagues at the University of California, Berkeley used PET ligand imaging to investigate whether individual variability in reward-based learning is due to quantitative variation in baseline levels of striatal dopamine. Variation in baseline striatal dopamine synthesis capacity measured with 6-[18F]fluoro-L-m-tyrosine (FMT) correlated with reward-based reversal learning. Subjects with high baseline dopamine synthesis in the striatum showed relatively better reversal learning from unexpected rewards than from unexpected punishments, whereas subjects with low baseline dopamine synthesis in the striatum showed the reverse pattern. In addition, baseline dopamine synthesis predicted the direction effects of the D(2) receptor agonist bromocriptine. Bromocriptine improved reward-based relative to punishment-based reversal learning in subjects with low baseline dopamine synthesis capacity, while impairing it in subjects with high baseline dopamine synthesis capacity in the striatum. Finally, this pattern of drug effects was outcome-specific, and driven primarily by drug effects on punishment, but not reward-based reversal learning. These data demonstrate that the effects of D(2) receptor stimulation on reversal learning in humans depend on task demands and baseline striatal dopamine synthesis capacity. Cools R, Frank MJ, Gibbs SE,

Miyakawa A, Jagust W, D'Esposito M. Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. J Neurosci. 2009;29(5):1538-43.

N-Acetylaspartate (NAA) Correlates Inversely with Cannabis Use in Frontal Cortex of MDMA (Ecstasy) Polydrug Users

Dr. Ron Cowen and colleagues at Vanderbilt University used magnetic resonance spectroscopy (MRS) to investigate the relative contributions of Ecstasy (MDMA) or polydrug exposure to reduced verbal memory. Although, Ecstasy users have reduced gray matter in brain regions mediating verbal memory (BA 18, 21 and 45), MRS studies in Ecstasy users have yielded inconsistent results using N-acetylaspartate (NAA) as a neuronal marker and myoinositol (MI) as a glial marker. Therefore it was hypothesized that Ecstasy combined with other polydrug use would be associated with altered NAA or MI in verbal memory brain regions. No effects were seen for MI in seventeen polydrug Ecstasy users, nor were there any statistically significant associations for lifetime use of Ecstasy, alcohol, or cocaine with NAA. However, lifetime cannabis use was significantly associated with BA45 NAA/Cr ($r = -0.687$), but not with NAA in BA 18 or 21. These findings suggest that cannabis use may contribute to altered neuronal integrity in Ecstasy polydrug users in a brain region associated with verbal memory processing. Cowan R, Joers J, Dietrich M. N-acetylaspartate (NAA) correlates inversely with cannabis use in a frontal language processing region of neocortex in MDMA (Ecstasy) polydrug users: A 3 T magnetic resonance spectroscopy study. Pharmacology Biochemistry and Behavior. 2009;92(1):105-10.

Cannabinoid Effects on Brain-Derived Neurotrophic Factor (BDNF) Levels in Humans

Dr. Cyril D'Souza and colleagues at Yale School of Medicine investigated whether delta(9)-tetrahydrocannabinol (delta(9)-THC), the principal active component of cannabis, would alter BDNF levels in humans, similar to effects of THC in pre-clinical studies. In a double-blind, fixed order, placebo-controlled, laboratory study light users of cannabis ($n = 9$) received intravenous administration of delta(9)-THC (0.0286 mg/kg). Serum sampled at baseline, after placebo administration, and after delta(9)-THC administration was assayed for BDNF using ELISA. Delta(9)-THC administration did not increase serum BDNF levels in cannabis users. The doses of delta(9)-THC were pharmacologically active as reflected in produced psychotomimetic effects, perceptual alterations, subjective reports of "high" and spatial memory impairments. The effects of socially relevant doses of cannabinoids on BDNF suggest a possible mechanism underlying the consequences of exposure to cannabis. This may be of particular importance for the developing brain and also in disorders believed to involve altered neurodevelopment such as schizophrenia. However, the effects of cannabinoids on BDNF and other neurotrophins need to be replicated in larger studies. D'Souza D, Pittman B, Perry E, Simen A. Preliminary evidence of cannabinoid effects on brain-derived neurotrophic factor (BDNF) levels in humans. Psychopharmacology. 2009;202(4):569-78.

Impaired Reproduction of Three-Dimensional Objects by Cocaine-Dependent Subjects

Dr. Igor Elman and colleagues at McLean Hospital investigated cognitive impairments in cocaine abusers. Twenty seven cocaine-dependent, 26 marijuana-abusing or dependent, and 33 healthy subjects performed a perceptual-motor task of figure copying. Cocaine-dependent and healthy individuals did not differ in their scores on the copying of a two-dimensional

diamond and a cross. In contrast, cocaine-dependent subjects displayed significantly poorer ability to copy a three-dimensional Necker cube, a smoking pipe, a hidden line elimination cube, a pyramid, and a dissected pyramid. Marijuana users' performance on all copied figures was comparable to that of the healthy comparison subjects. Three-dimensional copying ability has been found to be associated with parietal lobe damage, suggesting a role for parietal lobe dysfunction in the pathophysiology of cocaine dependence. Elman I, Chi W, Gurvits T, Ryan E, Lasko N, Lukas S, Pitman R. Impaired reproduction of three-dimensional objects by cocaine-dependent subjects. Journal of Neuropsychiatry and Clinical Neurosciences. 2008;20(4):478-84.

Expert Financial Advice Neurobiologically "Offloads" Financial Decision-Making Under Risk

Dr. Greg Berns and colleagues at Emory University used fMRI to investigate how the brain processes external information, such as advice, during decision-making. The current experiment investigated the neurobiological basis of the influence of expert advice on financial decisions under risk by having participants make a series of financial choices between a certain (100% probability) payment and an uncertain payment (<100% probability) undergoing fMRI scanning. Choices were made in two conditions: 1) advice from a financial expert about which choice to make was displayed (MES condition); and 2) no advice was displayed (NOM condition). Behavioral results showed a significant effect of expert advice. Specifically, probability weighting functions changed in the direction of the expert's advice. This was paralleled by neural activation patterns. Brain activations showing significant correlations with valuation (parametric modulation by value of lottery/sure win) were obtained in the absence of the expert's advice (NOM) in intraparietal sulcus, posterior cingulate cortex, cuneus, precuneus, inferior frontal gyrus and middle temporal gyrus. Notably, no significant correlations with value were obtained in the presence of advice (MES). These findings were corroborated by region of interest analyses. Neural equivalents of probability weighting functions showed significant flattening in the MES compared to the NOM condition in regions associated with probability weighting, including anterior cingulate cortex, dorsolateral PFC, thalamus, medial occipital gyrus and anterior insula. Finally, during the MES condition, significant activations in temporoparietal junction and medial PFC were obtained. These results support the hypothesis that one effect of expert advice is to "offload" the calculation of value of decision options from the individual's brain. Engelmann JB, Capra CM, Noussair C, Berns GS. Expert financial advice neurobiologically "Offloads" financial decision-making under risk. PLoS ONE. 2009;4(3): e4957.

Prefrontal and Midline Interactions Mediating Behavioural Control

Dr. Hugh Garavan and colleagues at Trinity University used fMRI to determine whether frontal and midline brain areas serve to facilitate interaction of top-down control processes with bottom-up stimulus-driven task demands so as to facilitate the smooth execution of behaviour. This study utilized a GO/NO-GO task with cued and uncued inhibitory events to investigate the effect of cue-induced levels of top-down control on NO-GO trial response conflict. Within-subjects on a trial-for-trial basis, high levels of top-down control, as indexed by left dorsolateral prefrontal activation prior to the NO-GO, resulted in lower levels of activation on the NO-GO trial in the pre-supplementary motor area. These results suggest that prefrontal and midline regions work together to implement cognitive control and reveal that intra-subject variability is reflected in these lateral and midline interactions. Since substance abusers have been shown to have structural and functional dysregulation of prefrontal and midline brain regions, these results provide insight into how brain dysfunction may impede the ability to exert behavioral control on drug use. Fassbender C, Hester R, Murphy K, Foxe JJ, Foxe DM, Garavan H. Prefrontal and midline

interactions mediating behavioural control. Eur J Neurosci. 2009;29(1):181-7.

Structural Brain Differences in Bipolar Adolescents with and without Cannabis Use Disorders

Dr. Igor Elman and colleagues at McLean Hospital used structural MRI (voxel based morphometry) to determine whether there are differences in brain structure between bipolar adolescents with co-occurring cannabis use disorders (CUD) and bipolar adolescents without any substance use disorder. Whole-brain structural magnetic resonance imaging (MRI) scans were obtained from 14 bipolar adolescents. Seven study participants were diagnosed with CUD before and/or shortly after their MRI scan was obtained, and 7 subjects were free of any substance use disorder at the time of their MRI scan as well as during longitudinal follow up. Bipolar adolescents with CUD demonstrate evidence of greater structural abnormalities than adolescents with bipolar disorder alone in frontal and temporal cortical regions, as well as in subcortical areas linked with emotion and motivational regulation. Specifically, bipolar adolescents with co-occurring CUD demonstrated decreased gray matter volume (GMV) in the left fusiform gyrus and increased GMV in the right caudate and precentral gyrus, as well as increased gray matter density in the right middle occipital and fusiform gyri and cerebellar vermis. Although the limited prescan exposure to marijuana in these adolescents tentatively suggests that these findings may reflect underlying differences, the direct effect of cannabis exposure may also be involved. Jarvis K, DelBello M, Mills N, Elman I, Strakowski S, Adler C. Neuroanatomic comparison of bipolar adolescents with and without cannabis use disorders. Journal of Child and Adolescent Psychopharmacology. 2008;18(6):557-63.

Neural Activity During the Stop Signal Task is Related to Risk Taking and Trait Anxiety

Dr. Chiang Li and colleagues at Yale School of Medicine used the stop signal task (SST) and fMRI to examine the "risk-taking" component of the SST. The current study took advantage of variability of go trial reaction time (RT) and compared the post-go go trials that showed a decrease in RT (risk-taking decision) and those post-go go trials that showed an increase in RT ("risk-aversive" decision) in 33 healthy individuals who underwent fMRI scanning during the SST. This contrast revealed robust activation in bilateral visual cortices as well as left inferior parietal and posterior cingulate cortices, amygdala, and middle frontal gyrus. Furthermore, the magnitude of amygdala activity was positively correlated with trait anxiety of the participants. Li CR, Chao HH, Lee T. Neural correlates of speeded as compared with delayed responses in a stop signal task: An indirect analog of risk taking and association with an anxiety trait. Cereb Cortex. 2009;19(4):839-48.

Improvements in a Nonferrous Smoking Device for Self-Administration of Smoked Drugs with Concurrent fMRI Neuroimaging

Lukas and associates at McLean Hospital improved a previously-developed smoke-delivery device to facilitate investigations of the acute neuronal effects of smoked drugs as the improved device does not interfere with the collection of MRI neuroimaging data. The problem with the previous device was that the amount of nicotine delivered to subjects smoking was reduced by approximately 44% compared to nicotine delivered by cigarettes smoked normally. Improvements were made to the smoke delivery component of this apparatus in an attempt to improve drug delivery, while not interfering with collection of MRI data. The improved device does not interfere with typical drug effects produced by normal smoking. Phantom scans revealed that BOLD signal

was not found to be altered by the (in-bore) installation and operation of the improved device. Preliminary data analysis of smoking induced changes in the BOLD response to visual stimulation suggest that this response is not affected by the improved device, the act of smoking, air puffing, nicotine, or other components of cigarette smoke. Lindsey KP, Lukas SE, MacLean RR, Ryan ET, Reed KR, Frederick BD. Design and validation of an improved nonferrous smoking device for self-administration of smoked drugs with concurrent fMRI neuroimaging. Clin EEG Neurosci. 2009;40(1):21-30.

Insular Cortical Activation Reflects both Affective and Sensory Aspects of Touch

Dr. Martin Paulus and colleagues at the University of California, San Diego, used fMRI to examine the contribution of different parts of the insular cortex in the representation of both affective and sensory aspects of touch. Subjects were administered a cued application of touch during functional MRI. Stimulus-related activation occurred in the mid-to-posterior insula, whereas anticipatory related activation was seen mostly in anterior insula. Moreover, the degree of activation in anterior insula during anticipation was correlated with the degree of activation in the posterior insula and caudate during stimulus processing. Finally, the degree of activation in the anterior insula during anticipation was also correlated with experienced intensity of the touch. Taken together, these results are consistent with the hypothesis that the anterior insula is preparing for the sensory and affective impact of touch. This preparatory function has important implications for the understanding of addictive disorders because dysfunctions in anticipatory processing are a fundamental part of the psychopathology. Lovero KL, Simmons AN, Aron JL, Paulus MP. Anterior insular cortex anticipates impending stimulus significance. Neuroimage. 2009;45(3):976-83.

Effect of Impulsivity in Risky Decision-Making

Drs. Laura Martin and Geoffrey Potts at Florida State University used event-related potentials (ERPs) to examine whether sensitivity to reward and punishment modulates impulsivity during risky decision-making in high and low impulsive subjects. The results indicate that the high-risk option appeared to be the default choice of the high impulsives and the low-risk choice the default for the low impulsives since high impulsives had a larger P3 and the low impulsives a smaller P3 when making a low-risk choice. The low, but not the high impulsives, had a larger error-related negativity (ERN) following high-risk choice indicating that the low impulsives evaluated the risky choice as a poor decision. The results indicate that high impulsive individuals are biased towards immediate reward during option evaluation but are less sensitive to the negative consequences of their choices. Since impulsivity is a risk factor for substance abuse as well as a consequence of substance abuse, these results suggest that dysregulation of brain networks in substance abusers bias them to make high risk choices. Martin L, Potts G. Impulsivity in decision-making: An event-related potential investigation. Personality and Individual Differences 2009;46(3):303-8.

Role of the Insula in Compulsive Drug-Taking

Dr. Antoine Bechara at the University of Southern California reviewed the literature indicating that a largely overlooked structure, the insula, plays a crucial part in conscious urges to take drugs. Most prior research on the neurobiology of addiction has focused on the role of subcortical systems, such as the amygdala, the ventral striatum and mesolimbic dopamine system, in promoting the motivation to seek drugs. The insula has been highlighted as a region that integrates interoceptive (i.e. bodily) states into conscious feelings

and into decision-making processes that involve uncertain risk and reward. A heuristic model was proposed in which the processing of the interoceptive effects of drug use by the insula contributes to conscious drug urges and to decision-making processes that precipitate relapse. Naqvi NH, Bechara A. The hidden island of addiction: the insula. Trends Neurosci. 2009;32(1):56-67.

Dual Role of Anterior Cingulate Cortex in Navigating Conflict and Increasing Attentional Focus

Dr. Daniel Weissman of the University of Michigan used a novel cross-modal attentional cueing task during fMRI scans in humans to detect regional specialization for processes that detect conflict and processes that increase attention in the cognitive division of the anterior cingulate cortex (ACC(cd)). Activity in a dorsal subregion was associated with increasing attention to relevant stimuli, correlated with behavioral measures of orienting attention to those stimuli, and resembled activity in dorsolateral prefrontal regions that are also thought to bias attention toward relevant stimuli. In contrast, activity in a rostral subregion was associated only with detecting response conflict caused by irrelevant stimuli. These findings support a 2-component model for minimizing distraction and speak to a longstanding debate over how the ACC(cd) contributes to cognitive control. Orr JM, Weissman DH. Anterior cingulate cortex makes 2 contributions to minimizing distraction. Cereb Cortex. 2009;19(3):703-11.

Decision-Makers Resort to Automated Reactions to Risk while under Stress

Dr. Mauricio Delgado of Rutgers University probed the impact of exposure to acute stress on financial decision making and examined the particular influence of stress on decisions with a positive or negative valence. Participants' choices exhibited a stronger reflection effect when participants were under stress than when they were in the no-stress control phase. This suggests that stress modulates risk taking, potentially exacerbating behavioral bias in subsequent decision making (such as responses to drug-predictive cues). Consistent with dual-process approaches, decision makers fall back on automatized reactions to risk under the influence of disruptive stress. This may have significant explanatory power for compulsive drug use in states of negative affect. Porcelli AJ, Delgado MR. Acute stress modulates risk taking in financial decision making. Psychological Science. 2009;20(3):278-83.

Multimodal Evidence for Similar Subjective and Physiological Responses Between Cocaine Craving and Cocaine Reward

Dr. Leslie Prichep and colleagues at New York University studied subjective, physiological and electroencephalographic (EEG) profiles in cocaine dependent subjects in response to cocaine cue exposure or a dose of smoked cocaine. Both stimuli increased subjective ratings of cocaine high and craving, enhanced negative affect, and boosted plasma ACTH and skin conductance levels. However, cocaine dose produced a greater increase in high and a more prolonged increase in plasma ACTH, while cocaine cue produced a decline in skin temperature. Both stimuli produced increases in absolute theta, alpha and beta EEG power over the prefrontal cortex. However, interhemispheric EEG coherence over the prefrontal cortex decreased during cocaine cue exposure but increased following cocaine dose. Moreover, delta and theta activity were associated with negative affect during cocaine cue exposure, but were associated with cocaine craving and reward following cocaine dosing. In both conditions, alpha activity was a marker for anxiousness but not cocaine high. These data demonstrate similar subjective, physiological responding in clinical laboratory states of cocaine craving and reward. However, differences in EEG

response profiles, and their relationship to function, indicate distinct neurophysiological mediators of cocaine craving and reward within the prefrontal cortex. Reid MS, Flammino F, Howard B, Nilsen D, Prichep LS. Cocaine cue versus cocaine dosing in humans: evidence for distinct neurophysiological response profiles. Pharmacol Biochem Behav. 2008;91(1):155-64.

Can fMRI Predict Substance Abuse Treatment Response

Dr. Martin Paulus of UCSD reviewed evidence supporting the use of functional neuroimaging as a clinical tool to predict outcomes in substance use disorders. The review focused, in part, on the importance of recognizing the clinical heterogeneity of the substance use disorders population. Empirical and theoretical analyses support the idea that the courses of substance use disorders are relatively independent of the types of substance being used. The review also summarized various approaches to the measurement and characterization of the longitudinal courses of substance use disorders as well as reviewing predictors of outcomes and discussing their limitations. Finally, aspects of their work that focus on using functional magnetic resonance imaging to predict outcomes were described. Reske M, Paulus M. Predicting Treatment Outcome in Stimulant Dependence. Addiction Reviews 2008; 1141270-283.

White Matter Abnormalities in Methamphetamine Abusers Correlate with Impaired Stroop Task Performance

Dr. Ruth Salo and colleagues at the University of California, Davis, used Diffusion Tensor Imaging to investigated whether changes in white matter were related to dysregulated cognitive control in methamphetamine abusers (MA). The study related performance on the Stroop selective attention task with indices of WM microstructure obtained from diffusion tensor imaging (DTI) in the callosal genu and splenium of currently abstinent MA abusers and non-substance abusing control subjects. MA abusers exhibited greater Stroop reaction time interference (i.e., reduced cognitive control) compared with control subjects. After correcting for multiple comparisons, fractional anisotropy, a measure of white matter fiber integrity, within the genu correlated significantly with measures of cognitive control in the MA abusers but not in control subjects. There was a trend for group differences in genu but not splenium. The results indicate that methamphetamine abuse alters anterior callosal WM microstructure, but not posterior callosal WM microstructure. Furthermore, white matter alterations indices within the genu but not splenium correlated with measures of cognitive control in chronic MA abusers. Salo R, Nordahl TE, Buonocore MH, Natsuaki Y, Waters C, Moore CD, Galloway GP, Leamon MH. Cognitive control and white matter callosal microstructure in methamphetamine-dependent subjects: a diffusion tensor imaging study. Biol Psychiatry. 2009;65(2):122-8.

Methamphetamine Abusers Exhibited Blunted Error-Elicited Behavior Change and Reduced Activation in Prefrontal Cortex

Dr. Ruth Salo and colleagues at the University California, Davis, employed a fast-event-related functional magnetic resonance imaging design to examine trial-to-trial reaction time (RT) adjustments in 12 methamphetamine (MA)-dependent subjects and 16 non-substance-abusers. A variant of the Stroop task was used to contrast the groups on error rates, RT conflict, and the level of trial-to-trial adjustments seen after incongruent trials. MA abusers exhibited reduced RT adjustments and reduced activation in the right prefrontal cortex compared to controls on conditions that measured the ability to use exposure to conflict situations (i.e., conflict trials) to regulate behavior. The groups did

not differ on accuracy rates or within-trial Stroop conflict effects. The results suggest that deficits in trial-to-trial RT adjustments in methamphetamine abusers may be indicative of an inability of abusers to adapt a behavioral response based on prior experience, which could contribute to further drug-seeking behavior. Salo R, Ursu S, Buonocore MH, Leamon MH, Carter C. Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. Biol Psychiatry. 2009;65(8):706-9.

Adolescents have Reduced Brain Activation in Error-Monitoring Neurocircuitry Compared to Adults

Dr. Goeffery Pearlson and colleagues at the Institute of Living, Yale School of Medicine contrasted functional magnetic resonance imaging (fMRI) data collected from 25 adolescent and 25 adult healthy participants (ages 11-37) performing a visual Go/No-Go task. A whole brain functional connectivity analysis was conducted that contrasted correct versus incorrect button presses using independent component analysis (ICA). Previous studies suggest that the anterior cingulate and other prefrontal brain regions might form a functionally-integrated error detection network in the human brain. Correct responses engaged a network comprising left lateral prefrontal cortex, left postcentral gyros/inferior parietal lobule, striatum, and left cerebellum. In contrast, a similar network was uniquely engaged during errors, but this network was not integrated with activity in regions believed to be engaged for higher-order cognitive control over behavior. A medial/dorsolateral prefrontal-parietal neural network responded to all No-Go stimuli, but with significantly greater activity to errors. ICA analyses also identified a third error-related circuit comprised of anterior temporal lobe, limbic, and pregenual cingulate cortices, possibly representing an affective response to errors. Critically, there were developmental differences in error-processing activity within many of these neural circuits, typically reflecting greater hemodynamic activation in adults. These findings characterize the spatial structure of neural networks underlying error commission and identify neurobiological differences between adolescents and adults that may portend developmental vulnerability to persistent risky behaviors such as substance abuse. Stevens M, Kiehl K, Pearlson G, Calhoun V. Brain network dynamics during error commission. Human Brain Mapping. 2009;30(1):24-37.

Implicit Learning Task Reveals that the Anterior Cingulate Encodes Errors made Outside Awareness

Dr. Stefan Ursu and colleagues at the University of California, Davis used fMRI to investigate whether the caudal anterior cingulate cortex (cACC) is involved in performance monitoring and whether these effects may be differentially modulated by awareness. Subjects performed a dual task: 1) a delayed recognition task and 2) a serial response task (SRT) with an implicit probabilistic learning rule (where the stimulus location followed a probabilistic sequence of which the subjects were unaware). Task performance confirmed that the location sequence was learned implicitly. Even though they found no evidence of awareness for the presence of the sequence, increased cACC activity during correct trials which violated the sequence (high-conflict), relative to trials when stimuli followed the sequence (low conflict), was observed using a rapid event-related fMRI paradigm. Errors made with awareness also activated the same brain region. Their results suggest that the performance monitoring function of the cACC extends beyond detection of errors made with or without awareness, and involves detection of multiple responses even when they are outside of awareness. Ursu S, Clark KA, Aizenstein HJ, Stenger VA, Carter CS. Conflict-related activity in the caudal anterior cingulate cortex in the absence of awareness. Biol Psychol. 2009;80(3):279-86.

Inverse Association Between BMI and Prefrontal Metabolic Activity in Healthy Adults

Dr. Nora Volkow and associates at Brookhaven National Laboratory used PET imaging of regional brain glucose metabolism (2-deoxy-2[F-18] fluoro-D-glucose (FDG)) to assess the relationship between brain activity and obesity, assessed by body mass index (BMI). There was significant negative correlation between BMI and resting metabolic activity in prefrontal cortex and cingulate gyrus but not in other regions. Moreover, baseline metabolism in these prefrontal regions was positively associated with performance on tests of memory (California Verbal Learning Test) and executive function (Stroop Interference and Symbol Digit Modality tests). In contrast, the regional brain changes during performance of the cognitive tasks were not associated with BMI nor with neuropsychological performance. These results further support the concept that obesity and substance abuse involve dysregulation of overlapping neuronal networks. Volkow N, Wang G, Telang F, Fowler J, Goldstein R, Alia-Klein N, Logan J, Wong C, Thanos P, Ma Y, Pradhan K. Inverse association between BMI and prefrontal metabolic activity in healthy adults. Obesity. 2009;17(1):60-5.

Gender Differences in the Ability to Inhibit Brain Activation Elicited by Food Stimulation

Dr. Gene-Jack Wang and associates at Brookhaven National Laboratories assessed the brain activation involved in voluntary inhibition of hunger during food stimulation in 23 fasted men and women. Brain activity was measured using PET assays of regional cerebral glucose metabolism with 2-deoxy-2[(18)F]fluoro-D-glucose ((18)FDG). In men, but not in women, instructions to inhibit responses to food stimulation was associated with significantly decreased activation in regions involved in emotional regulation, conditioning, and motivation, including the amygdala, hippocampus, insula, orbitofrontal cortex, and striatum. The suppressed activation of the orbitofrontal cortex with inhibition in men was associated with decreases in self-reports of hunger, which corroborates the involvement of this region in processing the conscious awareness of the drive to eat. This finding suggests a mechanism by which cognitive inhibition decreases the desire for food and implicates lower ability to suppress hunger in women as a contributing factor to gender differences in obesity. Wang G, Volkow ND, Telang F, Jayne M, Ma Y, Pradhan K, Zhu W, Wong CT, Thanos PK, Geliebter A, Biegon A, Fowler JS. Evidence of gender differences in the ability to inhibit brain activation elicited by food stimulation. Proc Natl Acad Sci U S A. 2009;106(4):1249-54.

Neuropsychology of Cocaine Addiction: Recent Cocaine Use Masks Impairment

Dr. Gene-Jack Wang and colleagues at Brookhaven National Lab examined whether recent cocaine use impairs or improves neuropsychological functions. Drug use was assayed using four measures in subjects with cocaine use disorders (CUD): urine status for cocaine (positive vs negative on study day), cigarette smoking, alcohol consumption, and dysphoria. Compared with healthy control subjects, subjects with CUD exhibited performance deficits on tasks of attention, executive function, and verbal memory (within one standard deviation of controls). Although subjects with CUD with positive urine status, who had higher frequency and more recent cocaine use, reported greater symptoms of dysphoria, these cognitive deficits were most pronounced in the CUD subjects with negative urine status. Cigarette smoking, frequency of alcohol consumption, and dysphoria did not alter these results. These findings suggest that frequent/recent cocaine may mask underlying cognitive (but not

mood) disturbances. These results call for development of pharmacological agents targeted to enhance cognition without negatively impacting mood in individuals addicted to cocaine. Woicik PA, Moeller SJ, Alia-Klein N, Maloney T, Lukasik TM, Yeliosof O, Wang G, Volkow ND, Goldstein RZ. The neuropsychology of cocaine addiction: recent cocaine use masks impairment. Neuropsychopharmacology. 2009;34(5):1112-22.

Gender Effects on Mood and Cigarette Craving During Early Abstinence and Resumption of Smoking

Dr. Arthur Brody and colleagues at the University of California, Los Angeles, investigated whether negative mood, cigarette craving, or other symptoms of nicotine withdrawal may contribute to the higher likelihood that women will relapse after initiating abstinence from cigarette smoking compared to men. The study involved 26 female and 38 male smokers who participated in two sessions; one session began within 1 hr after smoking ad libitum and the other followed overnight abstinence. In the first test block, both men and women reported higher scores after >13 hr abstinence than after <1 hr abstinence on the tension-anxiety and anger-hostility subscales of the Profile of Mood States, and for the craving and psychological symptoms of the Shiffman-Jarvik Withdrawal Scale. Moreover, on the tension-anxiety subscale, women also reported a greater reduction than men from smoking one cigarette after overnight abstinence. The findings indicate that overnight abstinence produces more negative mood symptoms and cigarette craving in female smokers than in males, and that resumption of smoking produces greater relief from these symptoms in female smokers. These differences may contribute to the greater likelihood of relapse when women try to quit smoking. Xu J, Azizian A, Monterosso J, Domier CP, Brody AL, London ED, Fong TW. Gender effects on mood and cigarette craving during early abstinence and resumption of smoking. Nicotine Tob Res. 2008;10(11):1653-61.

Adolescent Subgenual Anterior Cingulate Activity is Related to Harm Avoidance

Dr. Martin Paulus and colleagues at the University of California, San Diego, used fMRI to investigate whether the subgenual anterior cingulate cortex (sgACC) is involved in fundamental mental operations such as affective processing and inhibitory control in adolescents as has been found in adults. Seventeen adolescents, 13-17 years of age, underwent functional magnetic resonance imaging while performing a parametric stop-signal task. Greater harm avoidance levels were significantly associated with increased inhibition-related sgACC activity. These results establish, for the first time, a link between personality and differential sgACC activation in adolescents. These findings suggest that individual differences in sgACC function contribute to personality factors that can serve as risk factors for substance. Yang T, Simmons A, Matthews S, Tapert S, Frank G, Bischoff-Grethe A, Lansing A, Wu J, Paulus M, Iusa P. Adolescent subgenual anterior cingulate activity is related to harm avoidance. Neuroreport. 2009;20(1):19-23.

Dynamic Neural Responses to Cue-Reactivity Paradigms in Heroin-Dependent Users

Dr. Shi-Chiang Li at the Medical College of Wisconsin used fMRI to determine the dynamic neural responses to heroin-related cues. Fifteen heroin-dependent and 12 age-matched non-drug using control subjects participated in this study. Overall, the cue-reactivity paradigms significantly activated the dynamic neural activations in the prefrontal system, and the heroin-cue-induced neural responses within the subregions in the PFC system, including the superior frontal, dorsal lateral prefrontal, and orbitofrontal cortices, were significantly

intercorrelated. In addition to the prefrontal cortex, other brain regions that were significantly activated included the ventral tegmental area (VTA), the left and right amygdala, the left and right fusiform cortex, and the precuneus in the mesocorticolimbic system. These results suggest that the dynamic response patterns in the PFC system characterize the impaired brain control functions in heroin-dependent subjects. Yang Z, Xie J, Shao Y, Xie C, Fu L, Li D, Fan M, Ma L, Li S. Dynamic neural responses to cue-reactivity paradigms in heroin-dependent users: An fMRI study. Human Brain Mapping. 2009;30(3):766-75.

Midbrain Dopamine Receptor Availability is Inversely Associated with Novelty-Seeking Traits in Humans

Dr. David Zald and colleagues at Vanderbilt University used PET ligand imaging to test whether individual differences in dopamine functioning underlie the personality trait of novelty seeking in humans. Novelty-Seeking personality traits were inversely associated with Dopamine D2-like receptor availability indexed by [18]F-Fallypride in the ventral midbrain regions that includes the substantia nigra/ventral tegmental area. This effect remained significant after controlling for age. The investigators speculate that the lower midbrain autoreceptor availability seen in high novelty seekers leads to accentuated dopaminergic responses to novelty and other conditions that induce dopamine release. These findings provide evidence for a neurobiological explanation for how novelty seeking serves as risk-factor for initiation of substance use. Zald DH, Cowan RL, Riccardi P, Baldwin RM, Ansari MS, Li R, Shelby ES, Smith CE, McHugo M, Kessler RM. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. J Neurosci. 2008;28(53):14372-8.

Improved Method for Quantification of Dynamic Radioligand Receptor PET Studies

Dr. Dean Wong and colleagues at Johns Hopkins University developed a new graphical method for PET ligand analysis. This new method is less susceptible to noise-induced negative biases in the estimates of total distribution volume (DV(T)) and binding potential (BP) in the widely used Logan plot. A plasma input function was combined with reference tissue input to estimate DV(T) and BP, followed by an additional condition to ensure that the estimate from the new plot equals DV(T) or BP. It was demonstrated theoretically that 1) the statistical expectations of the estimates from the new plot with given input are independent of the noise of the target tissue concentration measured by PET; and 2) the estimates from the time activity curves of regions of interest are identical to those from the parametric images for the new plot. The computational time for generating DV(T) or BP images in the human studies was reduced by 80% on average by the new plot in contrast to the Logan plot. Overall, the new plot is a consistent and computationally efficient graphical analysis method to improve the quantification of reversible tracer binding in radioligand receptor dynamic PET studies. Zhou Y, Ye W, Brasić JR, Crabb AH, Hilton J, Wong DF. A consistent and efficient graphical analysis method to improve the quantification of reversible tracer binding in radioligand receptor dynamic PET studies. Neuroimage. 2009;44(3):661-70.

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

Research Findings - Epidemiology and Etiology Research

Pathways from Cannabis Availability and Initiation to Abuse

Although previous twin studies have modeled the association between drug initiation and abuse, none has included the obvious risk factor of drug availability. The aim of this study is to determine whether the genetic and environmental risk factors for cannabis availability also generate variation in cannabis initiation and/or progression to DSM-IV symptoms of abuse. The authors used multi-stage modeling, also known as causal-common-contingent (CCC) analysis, to partition the genetic and environmental factors into common and stage-specific components. This report is based on data collected from 1772 adult males ages 24-62 from the Mid Atlantic Twin Registry. The twins participated in two structured interviews which included clinical and non-clinical measures of cannabis abuse as well as retrospective assessments of perceived cannabis availability between ages 8 and 25 years. Cannabis availability explained almost all the shared environmental risks in cannabis initiation and abuse. The influence of availability on the symptoms of abuse was indirect and mediated entirely by cannabis initiation. These findings have begun to elucidate the causal processes underlying the liability to drug use and abuse in terms of putative risk factors. Specifically, they show that the latent shared environmental factors in cannabis initiation and abuse can be explained by measured aspects of the shared environment--those responsible for variation in cannabis availability. Gillespie N, Neale M, Kendler K. Pathways to cannabis abuse: a multi-stage model from cannabis availability, cannabis initiation and progression to abuse. Addiction. 2009;104(3):430-8.

Drug Exposure Opportunities and Use Patterns among College Students: Results of a Longitudinal Prospective Cohort Study

Underage drinking and drug use among college students are major public health concerns, yet few studies have examined these behaviors and their associated risk factors and consequences prospectively. This paper describes the sampling and recruitment methods of a longitudinal study of 1253 college students at a large, mid-Atlantic university. Incoming first-year students were screened during the unique window between high school and college in order to oversample drug users for longitudinal follow-up. Intensive recruitment strategies yielded a 95% cumulative response rate in annual interviews and semiannual surveys. The authors report preliminary results on exposure opportunity, lifetime prevalence, initiation, continuation, and cessation of substance use for alcohol, tobacco, and 10 illicit and prescription drugs during the first 2 years of college. Findings suggest that although some substance use represents a continuation of patterns initiated in high school, exposure opportunity and initiation of substance use frequently occur in college. Implications for prevention and early intervention are discussed. Arria A,

Caldeira K, O 'Grady K, Vincent K, Fitzelle D, Johnson E, Wish E. Drug exposure opportunities and use patterns among college students: results of a longitudinal prospective cohort study. Subst Abuse. 2008;29(4):19-38.

Some Moms Quit Cigarettes, Marijuana, & Alcohol during Pregnancy, but Dads Don't

With the possible exception of cigarette smoking, little attention is paid to substance abuse among men whose partner is pregnant. An understanding of men's patterns of substance use during their partner's pregnancy is necessary to identify critical periods for intervention to reduce children's exposure to paternal substance use. This study examined the relationship between pregnancy or partner's pregnancy and patterns of binge drinking, cigarette use, and marijuana use, desistance, and return to use over a 3-year period from age 21 to 24 years. Data were drawn from the Seattle Social Development Project, a longitudinal study of prosocial and antisocial behavior. 808 (412 male, 396 female) students entering 5th grade in participating schools in the fall of 1985 that consented to participate constitute the sample. Interviews were conducted yearly from ages 10 to 16, at ages 18, 21, and 24. The data used in this study were obtained from age 24 data. Event history calendars were administered at age 24 and were retrospective to 21 years. To provide temporal context, a series of questions about live events, work, and school history were asked. Reports of events were probed to identify the month and year in which they occurred, and repeated events were probed to identify the month and year of each occurrence. Pregnancy was deduced based on the birth date of the child. Men were as likely to binge drink during their partner's pregnancy as they were when their partner was not pregnant. In contrast, women were significantly less likely to binge drink during pregnancy compared with before or after pregnancy. Men were less likely to smoke when their partner was pregnant than they were when their partner was not pregnant. Similarly, women were less likely to smoke during pregnancy than they were before or after pregnancy. Men were as likely to use marijuana during their partner's pregnancy as they were when their partner was not pregnant. Women were less likely to use marijuana when they were pregnant than when they were not pregnant. Because of a return to cigarette smoking among men and to all three forms of substance use among women occurs so soon after birth, the first few months postpartum may provide a critical opportunity for intervention. Men's binge drinking and marijuana use were unaffected by their partner's pregnancy or by the birth of their child suggesting the importance of reaching new fathers-to-be with messages about the importance of stopping substance use during their partner's pregnancy. Reductions in substance use among fathers both during pregnancy and after the birth of their child would likely increase the probability that mothers will desist from substance use during pregnancy, decrease the probability that mothers will relapse to use postpartum, and reduce children's exposure to harmful substance use in the home environment. The first few months postpartum also represent an opportunity for health care practitioners to educate new fathers about the potential effects of their substance-use behavior on their child's development and on the substance-use behavior of their partner. Bailey JA, Hill KG, Hawkins JD, Catalano RF, Abbott RD. Men's and women's patterns of substance use around pregnancy. Birth. 2008;35(1):50-9.

Peer Group Deviance and Cannabis Use: Modeling the Association

Peer group deviance (PGD) is linked strongly to liability to drug use, including cannabis. The aim was to model the genetic and environmental association, including direction of causation, between PGD and cannabis use (CU). Results were based on 1736 to 1765 adult males from the Mid-Atlantic Twin Registry with complete CU and PGD data measured retrospectively from 1994-2004, at three time-intervals between 15 and 25 years using a life-history calendar. At

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all ages, multivariate modeling showed that familial aggregation in PGD was explained by a combination of additive genetic and shared environmental effects. Moreover, the significant PGD-CU association was best explained by a CU-->PGD causal model in which large portions of the additive genetic (50-78%) and shared environmental variance (25-73%) in PGD were explained by CU. These findings question the assumption that PGD was an environmental, upstream risk factor for CU. Rather, they suggest that the liability to affiliate with deviant peers is explained more clearly by a combination of genetic and environmental factors that are indexed by CU which sits as a ''risk indicator '' in the causal pathway between genetic and environmental risks and the expression of PGD. This is consistent with a process of social selection by which the genetic and environmental risks in CU largely drive the propensity to affiliate with deviant peers. Gillespie N, Neale M, Jacobson K, Kendler K. Modeling the genetic and environmental association between peer group deviance and cannabis use in male twins. Addiction. 2009;104(3):420-9.

Needle Exchange and Sexual Risk Behaviors among a Cohort of Injection Drug Users in Chicago, Illinois

Researchers examined the impact of a needle exchange program (NEP) on sexual risk behaviors of injecting drug users (IDUs). Between 1997 and 2000, 889 IDUs in Chicago were recruited from NEPs and an area with no NEP into a cohort study. They were interviewed and tested for HIV at baseline and 3 annual follow-up visits. Random-effect logistic models were used to compare NEP users and nonusers regarding the number of sex partners, number of unprotected sex acts, and frequency of condom use. Compared to NEP nonusers, NEP users had a similar number of sex partners over time, but had 49% higher odds of using condoms with their main partners ($p = 0.047$). At baseline, there was no difference between NEP users and nonusers in episodes of vaginal intercourse, but over time the odds of having a higher number of unprotected instances of vaginal intercourse were reduced by 26% per year for NEP users but only 10% per year for nonusers ($p = 0.02$). These findings suggest that NEP participation may help to reduce the absolute risk of HIV sexual transmission. Huo D, Ouellet L. Needle exchange and sexual risk behaviors among a cohort of injection drug users in Chicago, Illinois. Sex Transm Dis. 2009;36(1):35-40.

Methamphetamine Use Trends among Street-Recruited Gay and Bisexual Males, from 1999 to 2007

Street outreach encounters were used to collect data of reported alcohol and other drug use among gay and bisexual males (N = 11,375) in Hollywood and West Hollywood, California over a 9-year period from January 1999 to December 2007. Analyses were conducted to assess demographic data, self-reported HIV status, and frequency of alcohol and other drug use. Participants averaged 32.3 (SD = 7.7) years, slightly over half were Caucasian/white (53%), and most were identified as gay (85.8%). Self-reported HIV seroprevalence was 20.7%. Observations began January to June 1999, with 46.0% reporting recent methamphetamine use, and ended July to December 2007, with 24.8% reporting recent use of methamphetamine. Percent reporting methamphetamine use peaked in the first half of 2002 at 53% and dipped to a low of 11.1% in the second half of 2006. Findings demonstrate the common use of methamphetamine over the observation period in this high-risk group even in the face of a recent decline in reported use. These data also indicate the need for ongoing methamphetamine abuse and HIV-prevention interventions in this particular high-risk population. Reback C, Shoptaw S, Grella C. Methamphetamine use trends among street-recruited gay and bisexual males, from 1999 to 2007. J Urban Health. 2008;85(6):874-9.

Intranasal Transmission of Hepatitis C Virus: Virological and Clinical Evidence

Intranasal transmission of hepatitis C virus (HCV) via contaminated drug-sniffing implements is a potential but unconfirmed source of viral infection. Researchers were able to demonstrate the virological plausibility of intranasal transmission by confirming that blood and HCV RNA are present in the nasal secretions and drug-sniffing implements of HCV-infected intranasal drug users recruited from a community health clinic in New York City. They conducted an interdisciplinary mixed methods cross-section study involving 86 subjects. Based on 20 qualitative interviews, a quantitative HCV risk survey was then developed and administered to 60 HCV infected drug sniffers. Nasal swabs and drug sniffing implements were collected and tested for the presence of occult blood and HCV RNA. A clinical nasal examination and assessment were also administered. Occult blood was detected in 74% of nasal swabs and 8% of sniffing implements. HCV RNA was detected in 13% of nasal swabs and 5% of sniffing implements. Nasal pathology among chronic drug sniffers was moderate to high, and included epistaxis, rhinitis, rhinorrhea, mucosal lesions, and nasal septal perforations. These findings suggest that intranasal transmission of HCV through contaminated drug-sniffing implements, such as straws or spoons shared by intranasal drug users, may account for the estimated 20% of HCV cases that are otherwise not explained by known primary routes of transmission (ie, injection drug use). Aaron S, McMahon J, Milano D, Torres L, Clatts M, Tortu S, Mildvan D, Simm M. Intranasal transmission of hepatitis C virus: virological and clinical evidence. Clin Infect Dis. 2008;47(7):931-4.

National Comorbidity Survey Replication Adolescent Supplement: I. Background and Measures

This article presents an overview of the background and measures used in the National Comorbidity Survey Replication Adolescent Supplement (NCS-R Adol Supplement). The NCS-R Adol Supplement is a national psychiatric epidemiological survey of adolescents aged 13 to 17 years. The NCS-R Adol Supplement was designed to provide the first nationally representative estimates of the prevalence, correlates, and patterns of service use for DSM-IV mental disorders among U.S. adolescents and to lay the groundwork for follow-up studies of risk and protective factors, consequences, and early expressions of adult mental disorders. The core NCS-R Adol Supplement diagnostic interview, the World Health Organization Composite International Diagnostic Interview, is a fully structured research diagnostic interview designed for use by trained lay interviewers. A multiconstruct, multimethod, and multi-informant battery was also included to assess risk and protective factors and barriers to service use. Design limitations due to the NCS-R Adol Supplement evolving as a supplement to an ongoing survey of mental disorders of U.S. adults include restricted age range of youths, cross-sectional assessment, and lack of full parental/surrogate informant reports on youth mental disorders and correlates. Despite these limitations, the NCS-R Adol Supplement contains unparalleled information that can be used to generate national estimates of prevalence and correlates of adolescent mental disorders, risk and protective factors, patterns of service use, and barriers to receiving treatment for these disorders. The retrospective NCS-R Adol Supplement data on the development of psychopathology can additionally complement data from longitudinal studies based on more geographically restricted samples and serve as a useful baseline for future prospective studies of the onset and progression of mental disorders in adulthood. Merikangas KR, Avenevoli S, Costello EJ, Koretz D, Kessler RC. Journal of the American Academy of Child and Adolescent Psychiatry. 2009; Feb 25. [Epub ahead of print].

National Comorbidity Survey Replication Adolescent Supplement:

II. Overview and Design

This article presents an overview of the design and field procedures of the National Comorbidity Survey Replication Adolescent Supplement (NCS-R Adol Supplement). The NCS-R Adol Supplement is a nationally representative face-to-face household survey of the prevalence and correlates of DSM-IV mental disorders among U.S. adolescents (aged 13-17 years) that was performed between February 2001 and January 2004 by the Survey Research Center of the Institute for Social Research at the University of Michigan. The sample was based on a dual-frame design that included 904 adolescent residents of the households that participated in the National Comorbidity Survey Replication (response rate 85.9%) and 9,244 adolescent students selected from a representative sample of 320 schools in the same nationally representative sample of counties as the National Comorbidity Survey Replication (response rate 74.7%). Comparisons of sample and population distributions on census sociodemographic variables and, in the school sample, school characteristics documented only minor differences that were corrected with poststratification weighting. Comparisons of DSM-IV disorder prevalence estimates among household versus school sample respondents in counties that differed in the use of replacement schools for originally selected schools that refused to participate showed that the use of replacement schools did not introduce bias into prevalence estimates. In brief, the NCS-R Adol Supplement is a rich nationally representative dataset that will substantially increase understanding of the mental health and well-being of adolescents in the United States. Kessler RC, Avenevoli S, Costello EJ, Green JG, Gruber MJ, Heeringa S, Merikangas KR, Pennell BE, Sampson NA, Zaslavsky AM. Journal of the American Academy of Child and Adolescent Psychiatry. 2009; Feb 25. [Epub ahead of print].

National Comorbidity Survey Replication Adolescent Supplement: III. Concordance of DSM-IV/CIDI Diagnoses With Clinical Reassessments

This article reports results of the clinical reappraisal study of lifetime DSM-IV diagnoses based on the fully structured lay-administered World Health Organization Composite International Diagnostic Interview (CIDI) Version 3.0 in the U.S. National Comorbidity Survey Replication Adolescent Supplement (NCS-R Adol Supplement). Blinded clinical reappraisal interviews with a probability subsample of 347 NCS-R Adol Supplement respondents were administered using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) as the gold standard. The DSM-IV/CIDI cases were oversampled, and the clinical reappraisal sample was weighted to adjust for this oversampling. The results show good aggregate consistency was found between CIDI and K-SADS prevalence estimates, although CIDI estimates were meaningfully higher than K-SADS estimates for specific phobia (51.2%) and oppositional defiant disorder (38.7%). Estimated prevalence of any disorder, in comparison, was only slightly higher in the CIDI than K-SADS (8.3%). Strong individual-level CIDI versus K-SADS concordance was found for most diagnoses. Area under the receiver operating characteristic curve, a measure of classification accuracy not influenced by prevalence, was 0.88 for any anxiety disorder, 0.89 for any mood disorder, 0.84 for any disruptive behavior disorder, 0.94 for any substance disorder, and 0.87 for any disorder. Although area under the receiver operating characteristic curve was unacceptably low for alcohol dependence and bipolar I and II disorders, these problems were resolved by aggregation with alcohol abuse and bipolar I disorder, respectively. Logistic regression analysis documented that consideration of CIDI symptom-level data significantly improved prediction of some K-SADS diagnoses. In conclusion, these results document that the diagnoses made in the NCS-R Adol Supplement based on the CIDI have generally good concordance with blinded clinical diagnoses. Kessler RC, Avenevoli S, Green J, Gruber MJ, Guyer M, He Y, Jin R, Kaufman J, Sampson NA, Zaslavsky AM, Merikangas KR. Journal of the

American Academy of Child and Adolescent Psychiatry. 2009;48(4):386-39.

Validity of Self-Reported Adherence among Injection Drug Users

In Vancouver, the availability of prescription refill data for all HIV-infected individuals plus a prospective cohort of injection drug users (IDUs participating in the Vancouver Injection Drug Use Study or VIDUS) permitted an examination of the validity of self-reported HAART adherence among IDUs. Self-reported HAART adherence among VIDUS participants was compared with pharmacy refill rates from the British Columbia Drug Treatment Program database. Pearson's correlation coefficient and Pearson's chi(2) test were used to assess associations between adherence as measured by self-report and pharmacy refill data. Among 88 HIV-infected IDUs, 48 (55%) had an adherence rate of >/=75% as measured by pharmacy refill adherence, whereas 81 (92%) had an adherence rate of >/=75% as measured by self-report. Self-reported adherence was not statistically associated with pharmacy refill adherence (P >.1). These findings suggest that the validity of self-report HAART adherence measures may be limited when applied to community-recruited IDUs. Kerr T, Hogg R, Yip B, Tyndall M, Montaner J, Wood E. Validity of Self-Reported Adherence among Injection Drug Users. J Int Assoc Physicians AIDS Care (Chic Ill). 2008;7(4):157-9.

Hallucinogen Use Disorders among Adult Users of MDMA and Other Hallucinogens

The authors investigated the prevalence, patterns, and correlates of past-year DSM-IV hallucinogen use disorders (HUDs) among past-year users of MDMA and other hallucinogens utilizing data from 37,227 subjects age 18 and older who participated in the 2005 National Survey on Drug Use and Health. Users were categorized as MDMA users and other hallucinogen users. Overall, one in five (20%) MDMA users and about one in six (16%) other hallucinogen users reported at least one clinical feature of HUDs. Among MDMA users, prevalence of hallucinogen abuse, subthreshold dependence, and dependence was 4.9%, 11.9%, and 3.6%, respectively. The majority with hallucinogen abuse displayed subthreshold dependence. Most with hallucinogen dependence exhibited abuse. These findings suggest that subthreshold hallucinogen dependence is relatively prevalent and represents a clinically important subgroup that warrants future research and consideration in a major diagnostic classification system. Wu L, Ringwalt C, Mannelli P, Patkar A. Hallucinogen Use Disorders among adult users of MDMA and other hallucinogens. Am J Addict. 2008;17(5):354-63.

Group Sex Events and HIV/STI Risk in an Urban Network

This study sought to describe: (a) the prevalence and individual and network characteristics of "group sex events" (GSEs) and GSE attendees; and (b) HIV/sexually transmitted infection (STI) discordance among respondents who report they went to a GSE together. In a sociometric network study of risk partners (defined as sexual partners, persons with whom respondents attended a GSE, or drug injection partners) in Brooklyn, NY, researchers recruited a high-risk sample of 465 adults. Respondents reported on GSE attendance, the characteristics of GSEs, and their own and others' behaviors at GSEs. Sera and urines were collected, and STI prevalence was assayed. Of the 465 participants, 36% had attended a GSE in the last year, 26% had sex during the most recent of these GSEs, and 13% had unprotected sex there. Certain subgroups (hard drug users, MSM, women who have sex with women, and sex workers) were more likely to attend and more likely to engage in risk behaviors at these events. Among 90 GSE dyads in which at least 1 partner named the other as someone with whom they attended a GSE in the previous 3 months,

STI/HIV discordance was common [herpes simplex virus (HSV-2): 45% of dyads, HIV: 12% of dyads, and chlamydia: 21% of dyads]. Many GSEs had 10 or more participants, and multiple partnerships at GSEs were common. High attendance rates at GSEs among members of large networks may increase community vulnerability to STI/HIV, particularly because network data show that almost all members of a large sociometric risk network either had sex with a GSE attendee or had sex with someone who had sex with a GSE attendee. Self-reported GSE attendance and participation were common among this high-risk sample. STI/HIV discordance among GSE attendees was also high, underscoring the potential transmission risk associated with GSEs. Research on sexual behaviors should routinely incorporate measures of GSE behaviors to improve the standard research protocol. Effective interventions are needed to reduce risks and avert transmission of STI/HIV at GSEs. Friedman S, Bolyard M, Khan M, Maslow C, Sandoval M, Mateu-Gelabert P, Krauss B, Aral S. Group Events and HIV/STI Risk in an Urban Network. J Acquir Immune Defic Syndr. 2008;49(4):440-6.

Long-term Effectiveness of Diagnosing and Treating Latent Tuberculosis Infection in a Cohort of HIV-infected and At-Risk Injection Drug Users

Between 1990 and 1998, tuberculin skin tests (TST) and isoniazid preventive therapy (IPT) were provided to injection drug users participating in the AIDS Linked to the Intravenous Experiences (ALIVE) cohort. A registry match was conducted with the ALIVE cohort database and the Maryland State Department of Health and Mental Hygiene tuberculosis registry. Of 2010 participants, 1753 (74%) had a TST placed and read; 536 (31%) were positive. TST positivity was 16% in HIV positives; 39% in HIV negatives ($P<0.01$). Overall, 299 (56%) TST reactors started IPT; 165 (55%) completed 6 months. Three tuberculosis (TB) cases were diagnosed among HIV negatives (incidence rate=0.16/1000 person-years); 19 among HIV positives (1.94/1000 person-years; incidence rate ratio=12.3 (3.61-64.70). Within the entire cohort, TB rates were 0.81 per 1000 person-years for those not receiving IPT, 0.48 per 1000 person-years for those receiving any IPT, 0.29 per 1000 person-years for those completing at least 30 days, and 0 per 1000 person-years for completers. Ten cases of TB occurred in HIV-infected individuals with negative TSTs. IPT was associated with protection against TB, but uptake was modest. Although it is likely that TB incidence would have increased, especially in HIV-positive subjects, if the IPT program had not occurred, more significant declines in TB incidence in this population will require improved methods for ensuring uptake and completion of IPT and preventing disease in TST-negative individuals. Golub J, Astemborski J, Ahmed M, Cronin W, Mehta S, Kirk G, Vlahov D, Chaisson R. Long-term effectiveness of diagnosing and treating latent tuberculosis infection in a cohort of HIV-infected and at-risk injection drug users. J Acquir Immune Defic Syndr. 2008;49(5):532-7.

Heavy Drinking and Polydrug Use among College Students

Excessive alcohol consumption is a serious problem on college campuses but may not be adequately captured by traditional methods of defining binge drinking. This study examined a new approach to categorizing alcohol use and its relationship with illicit drug use. A survey was administered to 484 college students ages 18 to 25. Drinkers were divided into three groups based on the number of typical drinks consumed per day: "light"-1 to 4 (n=182); "moderate"-5 to 9 (n=173); and "heavy"-10+ (n=56). Heavy drinkers could be differentiated from moderate and light drinkers on age of onset of alcohol use, illicit drug use, and frequency of illicit drug use. A binary categorization of "binge" vs. "nonbinge" drinking may obscure important differences within binge drinkers. These findings have implications for prevention, as well as clinical risk assessment of college student drinkers for adverse consequences of

concomitant alcohol and illicit drug consumption. O'Grady KE, Arria AM, Fitzelle DM, Wish ED. Heavy drinking and polydrug use among college students. J Drug Issues. 2008;38(2):445-66.

Disorders Among Inhalant Users

This study examined the prevalence, correlates, and age of onset of DSM-IV substance use disorders (SUDs) among adult inhalant users. Analyses were based on structured psychiatric interviews of a nationally representative sample of 43,093 US adults. The lifetime prevalence of SUDs among adult inhalant users was 96%. Alcohol (87%), marijuana (68%), nicotine (58%), cocaine (35%), hallucinogen (31%), and stimulant (28%) use disorders were more prevalent than inhalant use disorders (19%). An estimated 62% of inhalant users met criteria for a past-year SUD. Less education, residence in non-metropolitan areas, early onset of inhalant use, and a history of substance abuse treatment were associated with increased odds of having an inhalant use disorder. Inhalant users who were under age 30 or who were members of families with low incomes had increased odds of having nicotine dependence and an alcohol or drug use disorder in the past year. Compared with substance users without a history of inhalant use, inhalant users, on average, initiated use of cigarettes, alcohol, and almost all other drugs at younger ages, and had a higher lifetime prevalence of nicotine, alcohol, and any drug use disorder. These findings demonstrate that lifetime and past-year SUDs are prevalent among adults with a history of inhalant use. Wu L, Howard M, Pilowsky D. Substance use disorders among inhalant users: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Addict Behav. 2008;33(7):968-73.

Childhood Maltreatment and the Development of Relational and Physical Aggression: The Importance of a Gender-informed Approach

The researchers examined the associations between maltreatment and aggression using a gender-informed approach among a cohort of inner-city youth attending a summer day camp. Peer ratings, peer nominations, and counselor reports of aggression were collected on 211 maltreated and 199 nonmaltreated youth (median age = 9.9 years). Maltreatment was associated with aggressive conduct; however, these effects were qualified by gender, maltreatment subtype, and the form of aggression under investigation. Findings revealed that maltreatment was associated with physical aggression for boys and relational aggression for girls. Physical abuse was associated with physically aggressive behaviors, but sexual abuse predicted relational aggression for girls only. These findings suggest that investigating the interaction between familial risk and gender is important in understanding aggressive behaviors of boys and girls. Cullerton-Sen C, Cassidy A, Murray-Close D, Cicchetti D, Crick N, Rogosch F. Childhood maltreatment and the development of relational and physical aggression: the importance of a gender-informed approach. Child Dev. 2008;79(6):1736-51.

A Meta-Analysis of the Hepatitis C Virus Distribution in Diverse Racial/Ethnic Drug Injector Groups

Hepatitis C virus (HCV) is mostly transmitted through blood-to-blood contact during injection drug use via shared contaminated syringes/needles or injection paraphernalia. This paper used meta-analytic methods to assess whether HCV prevalence and incidence varied across different racial/ethnic groups of injection drug users (IDUs) sampled internationally. The 29 prevalence and 11 incidence studies identified as part of the HCV Synthesis Project were categorized into subgroups based on similar racial/ethnic comparisons. The

effect estimate used was the odds or risk ratio comparing HCV prevalence or incidence rates in racial/ethnic minority groups versus those of majority status. For prevalence studies, the clearest disparity in HCV status was observed in the Canadian and Australian Aboriginal versus White comparison, followed by the US non-White versus White categories. Overall, Hispanic IDUs had greater HCV prevalence, and HCV prevalence in African-Americans was not significantly greater than that of Whites in the US. Aboriginal groups showed higher HCV seroconversion rates when compared to others, and African-Americans had lower seroconversion rates compared to other IDUs in the US. The findings suggest that certain minority groups have elevated HCV rates in comparison to other IDUs, which may be a consequence of stigma, discrimination, different risk behaviors or decreased access to health care, services and preventive education. Future research should seek to explicitly explore and explain racial/ethnic variations in HCV prevalence and incidence, and define the groups more precisely to allow for more accurate detection of possible racial/ethnic differences in HCV rates. Lelutiu-Weinberger C, Pouget E, Des Jarlais D, Cooper H, Scheinmann R, Stern R, Strauss S, Hagan H. A meta-analysis of the hepatitis C virus distribution in diverse racial/ethnic drug injector groups. Soc Sci Med. 2009;68(3):579-90.

Nonadherence Increases the Risk of Hospitalization among HIV-infected Antiretroviral Naive Patients Started on HAART

Since the advent of highly active antiretroviral therapy (HAART), AIDS-related hospitalizations have decreased. The objective of this study was to assess the impact of adherence on hospitalization among antiretroviral-na•ve HIV-infected persons initiating HAART. Analysis was based on a cohort of individuals initiating HAART between 1996 and 2001. The primary outcome was hospitalization for one or more days. Survival methods were used to assess the impact of adherence on hospitalization. Of 1605 eligible participants, 672 (42%) were hospitalized for one or more days after initiating HAART. Median adherence levels were 92 (IQR: 58, 100) and 100 (IQR: 83, 100) among those ever and never hospitalized, respectively. After controlling for confounders, those with <95% adherence had 1.88 times (95% CI: 1.60, 2.21) higher risk for hospitalization. These findings indicate that suboptimal adherence among HIV-infected patients taking HAART predicts hospitalization. Identifying and addressing the factors that contribute to poor adherence early in treatment could improve patient care and lower hospitalization costs. Fielden S, Rusch M, Yip B, Wood E, Shannon K, Levy A, Montaner J, Hogg R. Nonadherence increases the risk of hospitalization among HIV-infected antiretroviral naive patients started on HAART. J Int Assoc Physicians AIDS Care (Chic Ill). 2009;7(5):238-44.

Incidence and Determinants of Initiation into Cocaine Injection and Correlates of Frequent Cocaine Injectors

Researchers investigated the incidence and correlates of cocaine injection initiation and the impacts of daily cocaine injection among a cohort of injection drug users. Among 1603 participants, from May 1996 to December 2005, risk factors for initiation of cocaine injection among baseline heroin users were determined by Cox proportional hazards regression and correlates of daily cocaine injection by generalized estimating equations. Of the 238 individuals who had never injected cocaine, 200 (84%) had at least one follow-up visit and 121 (61%) consequently initiated into cocaine injection, yielding an incidence density of initiation into cocaine injection of 21.9% (95% confidence interval (CI): 17.9-25.8) per 100 person-years. In a multivariate model, Downtown Eastside (DTES) residence (adjusted hazard ratio (AHR)=2.46, 95% CI: 1.68-3.60), incarceration (AHR=1.50, 95% CI: 1.01-2.24), requiring help injecting (AHR=1.57, 95% CI: 0.99-2.49), and binge drug use (AHR=1.82, 95% CI: 1.22-2.73) remained associated with initiation into cocaine injection. DTES

residence (adjusted odds ratio (AOR)=1.99, 95% CI: 1.62-2.46), unstable housing (AOR=1.28, 95% CI: 1.04-1.53), incarceration (AOR=1.29, 95% CI: 1.04-1.60), sex trade involvement (AOR=1.46, 95% CI: 1.15-1.85), requiring help injecting (AOR=2.11, 95% CI: 1.73-2.58)), borrowing syringes (AOR=1.81, 95% CI: 1.35-2.43) and binge drug use (AOR=2.16, 95% CI: 1.81-2.58) were independently associated with daily cocaine injection. These findings show that the baseline prevalence and subsequent incidence of initiation into cocaine injection was high in this population. Daily cocaine injection was independently associated with a number of health and social harms, including elevated HIV risk behavior. Lloyd-Smith E, Wood E, Li K, Montaner J, Kerr T. Incidence and determinants of initiation into cocaine injection and correlates of frequent cocaine injectors. Drug Alcohol Depend. 2009;99(1-3):176-82.

Tri-city Study of Ecstasy Use Problems: a Latent Class Analysis

This study used latent class analysis to examine distinctive subtypes of Ecstasy users based on 24 abuse and dependence symptoms underlying standard DSM-IV criteria. Data came from a three site epidemiological study to examine diagnostic nosology for Ecstasy use. Subject inclusion criteria included lifetime Ecstasy use exceeding five times and once in the past year, with participants ranging in age between 16 and 47 years of age from St. Louis (N=297), Miami (N=186) and Sydney, Australia (N=156). A satisfactory model typified four latent classes representing clearly differentiated diagnostic clusters including: (1) a group of sub-threshold users endorsing few abuse and dependence symptoms (negatives), (2) a group of ''diagnostic orphans '' who had characteristic features of dependence for a select group of symptoms (mild dependent), (3) a ''transitional group '' mimicking the orphans with regard to their profile of dependence also but reporting some abuse symptoms (moderate dependent), and (4) a ''severe dependent '' group with a distinct profile of abuse and dependence symptoms. A multinomial logistic regression model indicated that certain latent classes showed unique associations with external non-diagnostic markers. Controlling for demographic characteristics and lifetime quantity of Ecstasy pill use, criminal behavior and motivational cues for Ecstasy use were the most efficient predictors of cluster membership. This study reinforces the heuristic utility of DSM-IV criteria applied to Ecstasy but with a different collage of symptoms that produced four distinct classes of Ecstasy users. Scheier L, Ben Abdallah A, Inciardi J, Copeland J, Cottler L. Tri-city study of ecstasy use problems: a latent class analysis. Drug Alcohol Depend. 2008;98(3):249-63.

High Dead-Space Syringes and the Risk of HIV and HCV Infection among Injecting Drug Users

This study examines the association between using and sharing high dead-space syringes (HDSSs)-which retain over 1000 times more blood after rinsing than low dead-space syringes (LDSSs)-and prevalent HIV and hepatitis C virus (HCV) infections among injecting drug users (IDUs). A sample of 851 out-of-treatment IDUs was recruited in Raleigh-Durham, North Carolina, between 2003 and 2005. Participants were tested for HIV and HCV antibodies. Demographic, drug use, and injection practice data were collected via interviews. Data were analyzed using multiple logistic regression analysis. Participants had a mean age of 40 years and 74% are male, 63% are African American, 29% are non-Hispanic white, and 8% are of other race/ethnicity. Overall, 42% of participants had ever used an HDSS and 12% had shared one. HIV prevalence was 5% among IDUs who had never used an HDSS compared with 16% among IDUs who had shared one. The HIV model used a propensity score approach to adjust for differences between IDUs who had used an HDSS and those who had never used one. The HCV models included all potential confounders as covariates. A history of sharing HDSSs was associated with

prevalent HIV (odds ratio=2.50; 95% confidence interval=1.01, 6.15). Use and sharing of HDSSs were also associated with increased odds of HCV infection. However, prospective studies are needed to determine the extent to which sharing HDSSs is associated with increased HIV and HCV incidence among IDUs. Zule W, Bobashev G. High Dead-Space Syringes and the risk of HIV and HCV infection among injecting drug users. Drug Alcohol Depend. 2009;100(3):204-13.

Incarceration and Drug Use Patterns among a Cohort of Injection Drug Users

Drug law enforcement remains the dominant response to drug-related harm. However, the impact of incarceration on deterring drug use remains under-evaluated. Researchers explored the relationship between incarceration and patterns of drug use among people who inject drugs (IDU). Using generalized estimating equations (GEE), they examined the prevalence and correlates of injection cessation among participants in the Vancouver Injection Drug User Study followed over 9 years. In subanalyses, they used McNemar's tests and linear growth curve analyses to assess changes in drug use patterns before and after a period of incarceration among participants reporting incarceration and those not incarcerated. Among 1603 IDU, 842 (53%) reported injection cessation for at least 6 months at some point during follow-up. In multivariate GEE analyses, recent incarceration was associated negatively with injection cessation [adjusted odds ratio (AOR) = 0.43, 95% confidence interval (CI) 0.37-0.50], whereas the use of methadone was associated positively with cessation (AOR = 1.38, 95% CI 1.22-1.56). In subanalyses assessing longitudinal patterns of drug use among incarcerated individuals and those not incarcerated over the study period, linear growth curve analyses indicated that there were no statistically significant differences in patterns of drug use between the two groups (all $P > 0.05$). These observational data suggest that incarceration does not reduce drug use among IDU, and in fact incarceration may inhibit access to mechanisms that promote injection cessation among IDU. By contrast, the results indicate that methadone use is associated positively with injection cessation, independent of previous frequency of drug use. DeBeck K, Kerr T, Li K, Milloy M, Montaner J, Wood E. Incarceration and drug use patterns among a cohort of injection drug users. Addiction. 2009;104(1):69-76.

Predictors and Comparisons of Polydrug and Non-polydrug Cocaine Use in Club Subcultures

Club drug users have been shown to tend towards patterns of polydrug use, which has been linked to adverse health outcomes, such as impaired mental health, overdose, dependence, infectious disease exposure, and decreased cognitive functioning. This study analyzed data from the Club Drugs and Health Project, a study designed to examine the patterns and contexts of club drug use among young adults. Four-hundred recent club drug users were recruited through time-space sampling. Among recent cocaine users (n = 361), 61.2% were polydrug users. Male gender was predictive of polydrug cocaine use (OR = 1.66). Gay, lesbian, and bisexual (GLB) sexual orientation, White race, and Non-Latino ethnicity were not. No differences in mental health factors were found between cocaine polydrug users and users of only cocaine. However, polydrug users were significantly more likely to score high on drug-related sensation seeking as well as to use drugs to deal with unpleasant emotions and to have pleasant times with others. In light of these findings, the authors stress that prevention and intervention efforts should consider contextual and motivational factors in attempting to reduce polydrug use and its negative effects. Kelly B, Parsons J. Predictors and comparisons of polydrug and non-polydrug cocaine use in club subcultures. Am J Drug Alcohol Abuse. 2008;34(6):774-81.

Pathways from Adolescent Marijuana Use in the Familial and Non-Familial Environments to Marijuana Use in the Fourth Decade of Life

This research examined the extent to which marijuana use by parents, siblings, peers, and others from adolescence (mean age 14) through early adulthood (mean age 27), predicts one's own marijuana use in the fourth decade of life (assessed at mean ages of 32 and 37). Understanding the longitudinal interpersonal influences on, and stability of, marijuana use is an important part of expanding efforts to prevent marijuana use by adolescents. 586 participants from a longitudinal sample interviewed since 1983 and who completed marijuana study measures in the two most recent study waves (2002, 2007) participated. Participants were predominantly White (92%) and female (57%). The research team analyzed the data using the LISREL VIII structural equation program. Maximum likelihood methods were used to estimate the models and the LISREL goodness of fit index (GFI) and the root mean square error of approximation (RMSEA) were used to assess the fit of the models. The research team obtained the following indices of fit: GFI=.99 and RMSEA=.03, indicating a satisfactory model of fit. Findings indicated the influence of earlier parental marijuana use on their offspring's later marijuana use as an adult was mediated through sibling marijuana use, which in turn was related to peer and significant other marijuana use. In addition, aspects of the familial environment (sibling marijuana use) and the non-familial environment (peer and significant other marijuana use) had direct effects on the participants' marijuana use in the fourth decade of life. Results emphasize the importance of the impact of the peer network in young adulthood on the individual''s marijuana use over time and support prevention efforts that target social networks of young adults as a locus through which long-lasting marijuana habits are formed. Brook JS, Zhang C, Koppel J, Brook DW. Pathways from earlier marijuana use in the familial and non-familial environments to self-marijuana use in the fourth decade of life. Am J Addict. 2008:497-503.

Poverty, Bridging between Injecting Drug Users and the General Population, and "Interiorization" may Explain the Spread of HIV in Southern Brazil

This analysis examined structural determinants and the role of injecting drug use as bridges to the general population affected the AIDS subepidemic in southern Brazil during 1986-2000. Data from 288 southernmost Brazilian municipalities were analyzed. Using hierarchical modeling and inputs from a Geographic Information System, a multilevel model was constructed. The dependent variable was the logged AIDS standardized incidence rate (among the heterosexual population aged 15-69-years-old); independent variables included indicators for education, water provision, sewage, and garbage collection, per capita income, Gini coefficient (on income), Human Development Index, indicators of accessibility, and AIDS rate among IDUs. Significant predictors included AIDS rate among IDUs, distance from/to highways/railways, the Human Development Index and the ratio of residents who have access to sanitary installations. Poverty (as measured by socioeconomic indicators) and bridging from IDUs were found to contribute to the spread of HIV/AIDS in Brazilian southern municipalities. Hacker M, Leite I, Friedman S, Carrijo R, Bastos F. Poverty, bridging between injecting drug users and the general population, and "interiorization" may explain the spread of HIV in southern Brazil. Health Place. 2009;15(2):514-9.

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

Research Findings - Prevention Research

Changes in Marijuana Outcome Expectancies Over Time Translate to Changes in Use Intentions

An evaluation of the National Youth Anti-Drug Media Campaign revealed that greater Campaign exposure was associated with weaker anti-drug norms and higher rates of marijuana initiation. There are many possible reasons for these effects, including the possibility that the typical campaign often is designed to develop expectancies regarding marijuana use outcomes that may not be experienced by the initiate. Indeed drug prevention media campaigns commonly seek to change outcome expectancies associated with substance use, but the effects of violating such expectancies are rarely considered. This study details an application of the expectancy violation framework in this real world context by investigating whether changes in marijuana expectations were associated with subsequent future marijuana intentions. Using data from a cohort of adolescents (N = 1,344; age range = 12-18 years) collected as part of the National Survey of Parents and Youth, nonusers at baseline were assessed 1 year later. Changes in expectancies were significantly associated with changes in intentions ($p < .001$). Moreover, in most cases, changes in expectancies and intentions had the strongest relationship among those who became users. The final model accounted for 31% of the variance ($p < .001$). Consistent with laboratory studies, changes in marijuana expectancies were predictive of changes in marijuana intentions. These results counsel caution when describing negative outcomes of marijuana initiation. If adolescents conclude that the harms of marijuana use are not as grave as they had been led to expect, intentions to use may intensify. Skenderian J, Siegel J, Crano W, Alvaro E, Lac A. Expectancy change and adolescents' intentions to use marijuana. Psychol Addict Behav. 2008;22(4):563-9.

Infrequent Use of Evidence-based Prevention Programs in America's High Schools

Despite a substantial proportion of high school students who initiate substance use following middle school, the implementation of universal evidence-based prevention curricula appears to be scant. This study on school-based substance use prevention practices reports on data collected in 2005 from a nationally representative sample of 1,392 school district-based drug prevention coordinators. Overall, only 10.3% of districts with high schools reported administering one of six prevention programs rated as effective by the Substance Abuse and Mental Health Services Administration's National Registry of Effective Programs and Practices or Blueprints for Violence Prevention, and only 5.7% reported that they used one of these effective programs most. Strikingly only 56.5% of the nation's high school districts administered any substance use prevention programming at all in at least one of their

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constituent high schools. This study highlights the very infrequent use of evidence-based prevention programs in America's high schools, despite increasing requirements for use of evidence based practices and the increasing availability of efficacious and effective prevention programs. Ringwalt C, Hanley S, Vincus A, Ennett S, Rohrbach L, Bowling J. The prevalence of effective substance use prevention curricula in the nation's high schools. J Prim Prev. 2008;29(6):479-88.

Majority of America's Middle Schools Administer Drug Prevention Programs with Limited Evidence of Effectiveness

Since the dissemination of its Principles of Effectiveness in 1998, the Office of Safe and Drug-Free Schools of the U.S. Department of Education has promoted the use of evidence-based drug prevention programs in the nation's schools. This paper reports on a 2005 survey of a nationally representative sample of 1,721 schools with middle school grades. Respondents included the middle school staff identified as most knowledgeable about each school's drug prevention programs. The survey asked questions concerning which drug use prevention curricula the schools used, and if they used more than one, which program they used most frequently. Three federally-sponsored registries were used to characterize which curricula were considered evidence-based programs (EBP): "model" or "effective" programs from the Substance Abuse and Mental Health Services Administration (SAMHSA) NREPP (National Registry of Evidence-based Programs and Practices), "model" or "promising" programs listed by "Blueprints for Violence Prevention" (Center for the Study and Prevention of Violence), or "exemplary" programs identified by the Office of Safe and Drug-Free Schools (Safe, Disciplined, and Drug-Free Schools Expert Panel). Findings from this 2005 survey were then compared to earlier estimates based on a similar 1999 survey. Results showed that 42.6% of the nation's schools with middle school grades were using an evidence-based curriculum, an increase of 8% from the 1999 estimate. The two most prevalent programs in use, at 19% each, were Life Skills Training and Project ALERT. However, only 8% of Life Skills Training users and 9% of Project ALERT users reported using these programs the most, and only 23% of schools reported that they used an EBP the most. This study points to the need for more information on why over three-quarters of the nation's middle schools continue to administer programs that may have limited evidence of effectiveness. Ringwalt C, Vincus A, Hanley S, Ennett S, Bowling J, Rohrbach L. The prevalence of evidence-based drug use prevention curricula in U.S. middle schools in 2005. Prev Sci. 2009;10(1):33-40.

College Substance Use: Being Caught and Reprimanded Leads to Behavior Change

Studies evaluating the efficacy of brief interventions with mandated college students have reported declines in drinking from baseline to short-term follow-up regardless of intervention condition. A key question is whether these observed changes are due to the intervention or to the incident and/or reprimand. This study evaluates a brief personalized feedback intervention (PFI) for students (N = 230) who were referred to a student assistance program because of infractions of university rules regarding substance use to determine whether observed changes in substance use are attributable to the intervention. Half the students received immediate feedback (at baseline and after the 2-month follow-up), and half received delayed feedback (only after the 2-month follow-up). Students in both conditions generally reduced their drinking and alcohol-related problems from baseline to the 2-month follow-up and from the 2-month to the 7-month follow-up; however, there were no significant between-group differences at either follow-up. Therefore, it appears that the incident and/or reprimand are important instigators of mandated student change and that written PFIs do not enhance these effects on a short-

Planned Meetings

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term basis but may on a longer term basis. White H, Mun E, Morgan T. Do brief personalized feedback interventions work for mandated students or is it just getting caught that works? Psychol Addict Behav. 2008;22(1):107-16.

Morning Cortisol Levels in Preschool-Aged Foster Children

Maltreated foster children are subjected to a range of early adverse experiences, including neglect, abuse, and multiple caregiver disruptions. Research suggests that such disturbances alter the development and subsequent functioning of the hypothalamic-pituitary-adrenocortical system. The current study was designed to investigate morning cortisol levels in 117 foster children and 60 low-income, nonmaltreated children. Maltreatment and foster care placement experiences were coded from official records. Analyses revealed that the foster children were significantly more likely than the nonmaltreated children to have low morning cortisol levels. Additionally, specific maltreatment experiences were significantly associated with foster children's morning cortisol levels. Foster children with low morning cortisol levels experienced more severe physical neglect than the other foster children. In contrast, foster children with high morning cortisol levels experienced more severe emotional maltreatment. These results suggest that specific early adverse experiences have differential effects on the functioning of the hypothalamic-pituitary-adrenocortical system. Bruce J, Fisher P, Pears K, Levine S. Morning cortisol levels in preschool-aged foster children: differential effects of maltreatment type. Dev Psychobiol. 2009;51(1):14-23.

Risk Factors Stronger Predictors of Adolescent Substance Use Than Protective Factors

To compare the relative influence of risk and protective factors across several domains on adolescent substance use in a large sample of youth cross-sectional survey, data were collected from students in grades 6, 8, 10, and 12 in Pennsylvania (N = 91,778). Generalized linear mixed models were estimated for each grade level to examine associations among indices of three risk factors (individual, peer, and family) and three protective factors (family, school, and community) and both recent and lifetime substance use. The risk factors were stronger predictors of substance use outcomes compared with the protective factors, regardless of grade level or substance use type. In particular, the individual and peer risk factors were strongly related to lifetime and recent use of cigarettes, alcohol, and marijuana. Among the protective factors, the strongest associations with substance use were found in the community domain. Several age-related differences in the associations were also found, suggesting that family and community factors were more salient among younger adolescents whereas peer and school factors were stronger among older adolescents. These findings provide support for the social development model (SDM), which proposes that adolescent substance use is associated with factors across multiple spheres of influence. Age-related differences in these associations suggest that effective interventions to reduce adolescent substance use may need to emphasize different domains of risk and protective factors at different stages of adolescent development. Cleveland M, Feinberg M, Bontempo D, Greenberg M. The role of risk and protective factors in substance use across adolescence. J Adolesc Health. 2008;43(2):157-64.

HealthWise Intervention Shows Promise for Reducing Sexual and Drug Risks Among South African Youth

Sexual behavior and substance use represent major threats to the health and well-being of South African adolescents, especially in light of the high prevalence of HIV infection in this population. However, there is currently a lack of evidence-based school programs designed to address health risk

behaviors. The current study details the evaluation of HealthWise South Africa, a leisure, life skills, and sexuality education intervention for eighth and ninth grade students currently being evaluated in South Africa. The investigators hypothesized that, compared to controls, HealthWise participants would have delayed sexual initiation, reduced rates of current sexual activity, increased use of and perceived access to condoms, and lower rates of lifetime and past use of drugs. Longitudinal data were analyzed using logistic regression of multiply imputed data. Results indicate that HealthWise was effective in increasing the perception of condom availability for both genders. Compared to HealthWise participants, control participants had steeper increases in recent and heavy use of alcohol, and recent and heavy cigarette use. Significant gender by intervention interactions were identified indicating that the program may have differentially affected girls and boys. Specifically, the program produced reduced sexual initiation favoring boys, and reductions in past month drinking, past month cigarette use, and smoking initiation favoring girls. These results suggest that HealthWise had a moderate, positive effect on multiple health risk behaviors among the population of school-going South African adolescents. Smith E, Palen L, Caldwell L, Flisher A, Graham J, Mathews C, Wegner L, Vergnani T. Substance use and sexual risk prevention in Cape Town, South Africa: an evaluation of the HealthWise Program. Prev Sci. 2008; 9(4):311-21.

Brief Family Intervention for High Risk Toddlers Improves School Readiness

This study examined the longitudinal effects of the Family Check-Up (FCU) on parents' positive behavior support and children's school readiness competencies in early childhood. It was hypothesized that the FCU would promote language skills and inhibitory control in children at risk for behavior problems as an indirect outcome associated with targeted improvements in parents' positive behavior support. High-risk families in the Women, Infants, and Children (WIC) federal nutrition program participated in a multisite preventive intervention study (N = 731) with 3 yearly assessments beginning at child age 2 years. Positive behavior support was measured using 4 indicators derived from at-home observations of parent-child interaction during semi structured tasks. Longitudinal structural equation models revealed that parents in families randomly assigned to the FCU showed improvements in positive behavior support from child age 2 to 3, which in turn promoted children's inhibitory control and language development from age 3 to 4, controlling for child gender, ethnicity, and parental education. These findings suggest that a brief, ecological preventive intervention supporting positive parenting practices can indirectly foster key facets of school readiness in children at risk. Lunkenheimer E, Dishion T, Shaw D, Connell A, Gardner F, Wilson M, Skuban E. Collateral benefits of the family check-up on early childhood school readiness: indirect effects of parents' positive behavior support. Dev Psychol. 2008;44(6):1737-52.

Peer Health Advocates Reduce HIV Risk in Injection Drug and Crack Users

The Risk Avoidance Partnership (RAP) Project tested 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 an urban area. 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. They 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 (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 the engagement of active drug users 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, Martinez M, Radda K. The risk avoidance partnership. Subst Use Misuse. 2009;44(2):253-81.

Mandated Interventions Contribute to Reductions in College Alcohol Use

Little is known about the effects of alcohol-related infractions and resulting reprimands for invoking behavioral change among mandated college students. The primary aim of this study was to assess the extent to which students significantly reduce their drinking between the time of an alcohol-related violation and the sanctioned intervention. Data came from 175 (70% male) students mandated to the Rutgers University Alcohol and Other Drug Assistance Program for Students because of infractions of university rules about alcohol and drug use. At intake, students reported on their alcohol consumption for the 30 days before the violation and the 30 days before the intake assessment. Mandated students significantly reduced peak blood alcohol concentration (BAC) levels, total weekly drinks, and frequency of alcohol use after the violation and before any intervention was delivered. Those students who had received a legal or medical referral (i.e., a serious infraction) reduced their alcohol consumption (BAC and total drinks) significantly more than those referred by residence hall advisors. The alcohol-related violation (including the event itself, getting caught, and/or getting mandated to an intervention) contributed to reductions in alcohol use for mandated college students. The finding that the seriousness of the infraction resulted in greater reductions in alcohol use suggests that the students' cognitive self-appraisal and affective response to the incident may be underlying mechanisms for their changes. Knowing if mandated students have already made significant changes in their drinking before intake would provide counselors with a valuable opportunity to identify and reinforce successful harm reduction strategies and could inform the type or intensity of intervention needed. Morgan T, White H, Mun E. Changes in drinking before a mandated brief intervention with college students. J Stud Alcohol Drugs. 2008;69(2):286-90.

Brief Interventions for Adolescents May Impact Multiple Health Behaviors

This study examined whether brief intervention strategies founded on the Behavior-Image Model that addresses positive images of college and career success have an impact on multiple health behavior habits of high-risk adolescents transitioning into adulthood. Participants included 375 11th and 12th grade students from a large, relatively diverse suburban school in northeast Florida. Students were stratified by grade level and drug use and individually randomized to one of the three "Plan for Success" interventions: (1) Goal Survey, (2) Goal Survey plus Contract, or (3) Goal Survey plus Consult. Data on multiple health risk, health promotion, and personal development behaviors, as well as image and beliefs measures were collected at baseline and 1 month post intervention. Findings from MANOVAs tests were significant for alcohol use, marijuana use, exercise, college preparation, and career preparation, with most behaviors improving over time. Group-by-time interaction effects were found for nutrition habits and career preparation, favoring the consultation. These results suggest that brief interventions founded on the Behavior-Image Model may have potential to improve selected health and personal development habits among older adolescents. Werch C, Bian H, Ames S, DiClemente, C, Thombs D, Pokorny S. Brief multiple behavior

health interventions for older adolescents. Am J Health Promot. 2008;23(2):92-6.

Two-month Follow-up Outcomes for a Mother-Daughter Computer-Mediated Drug Prevention Program

This study evaluated a computer-mediated intervention program to prevent underage drinking among early adolescent girls. Study participants were 202 pairs of adolescent girls (mean age = 12.2 years; ethnicity: 68% white, 14% Latina, 9% black, 1% Asian, 8% other) and their mothers (mean age = 41.1 years). Participants completed pretests online, were randomly divided between intervention and control arms, and completed posttest measures two months following the intervention. Program girls and their mothers interacted with a computer program aimed to enhance mother-daughter relationships and to teach girls skills for managing conflict, resisting media influences, refusing alcohol and drugs, and correcting peer norms about underage drinking, smoking, and drug use. Two months following program delivery and relative to control, girls and mothers in the program had improved their mother-daughter communication skills and their perceptions and applications of parental monitoring and rule-setting relative to girls' alcohol use. Also at follow-up, intervention-arm girls had improved their conflict management and alcohol use-refusal skills; reported healthier normative beliefs about underage drinking; demonstrated greater self-efficacy about their ability to avoid underage drinking; reported less alcohol consumption in the past 7 days, 30 days, and year; and expressed lower intentions to drink as adults. Study findings modestly support the viability of a mother-daughter, computer-mediated program to prevent underage drinking among adolescent girls. Schinke S, Cole K, Fang L. Gender-specific intervention to reduce underage drinking among early adolescent girls: a test of a computer-mediated, mother-daughter program. J Stud Alcohol Drugs. 2009;70(1):70-7.

Outcomes of the 5th Grade Version of the Keepin' It REAL Prevention Intervention

This study examined the immediate and short-term outcomes of adapting the culturally-grounded middle school program, keepin' it REAL, for elementary school students. Ten schools were randomly assigned to the intervention in 5th grade with follow-up boosters in 6th grade; 13 schools were randomly assigned to the control condition, implementing the school's pre-existing substance use prevention programming. Students (n = 1,566) completed a questionnaire prior to curriculum implementation and follow-up questionnaires toward the end of 5th and 6th grade. The 5th grade kiR curriculum generally appeared no more effective than the control schools' programming in changing students' resistance or decision-making skills, substance use intentions, expectancies, normative beliefs, or lifetime and recent substance use. Hecht ML, Elek E, Wagstaff DA, Kam JA, Marsiglia F, Dustman P, Reeves L, Harthun M. Immediate and short-term effects of the 5th grade version of The Keepin' It REAL substance use prevention intervention. J Drug Educ. 2008;38(3):225-51.

Measuring Quality of Delivery of Evidence-Based Drug Abuse Prevention

The purpose of this study was to develop and validate an observational measure designed to capture teachers' use of interactive teaching skills within the delivery of the All Stars substance use prevention program. This work was conducted within a larger study testing the relative effects of two training conditions to support implementation of the All Start program by teachers. Teachers in the standard condition received initial training, technical assistance on request, online video instruction on the program, and Internet-based

support. Teachers in the enhanced condition received onsite coaching, proactive technical assistance and assessments of fidelity. In this study on the development of a measure of quality of delivery, coders counted the number of times teachers praised and encouraged students, accepted and used students' ideas, asked questions, self-disclosed personal anecdotes, and corrected student misbehavior. In a factor analysis teacher behaviors loaded onto three factors: classroom management, acknowledgment, and student-centered methods. Classroom management was negatively related to student engagement. Acknowledgment was negatively related to students' normative beliefs. Student-centered methods were positively related to student idealism and normative beliefs, and marginally predicted decreases in student marijuana use. This study provides a promising approach to studying pedagogical prevention approaches that also link teaching processes to student outcomes. Giles S, Jackson-Newsom J, Pankratz M, Hansen W, Ringwalt C, Dusenbury L. Measuring Quality of Delivery in a Substance Use Prevention Program. J Prim Prev. 2008;29(6):489-501.

Factors Associated with Prevention Program Implementation

Teacher- and school-level factors influence the fidelity of implementation of school-based prevention and social character and development (SACD) programs. Using a diffusion of innovations framework, the relationships among teacher beliefs and attitudes towards a prevention/SACD program and the influence of a school's administrative support and perceptions of school connectedness, characteristics of a school's climate, were specified in two cross-sectional mediation models of program implementation. Implementation was defined as the amount of the programs' curriculum delivered (e.g., lessons taught), and use of program-specific materials in the classroom and in relation to school-wide activities. Teachers from 10 elementary schools completed year-end process evaluation reports for year 2 (N = 171) and 3 (N = 191) of a multi-year trial. Classroom and school-wide material usage were each favorably associated with the amount of the curriculum delivered, which were associated with teachers' attitudes toward the program which, in turn, were related to teachers' beliefs about SACD. These, in turn, were associated with teachers' perceptions of school climate. Perceptions of school climate were indirectly related to classroom material usage and both indirectly and directly related to the use of school-wide activities. Program developers need to consider the importance of a supportive environment on program implementation and attempt to incorporate models of successful school leadership and collaboration among teachers that foster a climate promoting cohesiveness, shared visions, and support. Beets M, Flay B, Vuchinich S, Acock A, Li K, Allred, C. School climate and teachers' beliefs and attitudes associated with implementation of the positive action program: a diffusion of innovations model. Prev Sci. 2008;9(4):264-75.

Child Maltreatment Profiles Predict Psychosocial and Cognitive Functioning

Up to 90% of child welfare system cases involve multiple types of maltreatment; however, studies have rarely incorporated multiple dimensions of maltreatment. The present study employed a latent profile analysis to identify naturally occurring subgroups of children who had experienced maltreatment. Reports of maltreatment incidents for 117 preschool-aged foster children were classified along two dimensions: type (e.g., physical abuse, sexual abuse, physical neglect, supervisory neglect, or emotional maltreatment) and severity within type. The analyses revealed four distinct profiles showing moderate to high levels of maltreatment: (a) supervisory neglect/emotional maltreatment; (b) sexual abuse/emotional maltreatment/neglect (when not otherwise specified neglect refers to both supervisory and physical neglect); (c) physical abuse/emotional

maltreatment/neglect; and (d) sexual abuse/physical abuse/emotional maltreatment/neglect. Profile membership was examined with respect to children's' cognitive functioning and externalizing and internalizing problems: lower cognitive functioning was related to profiles with neglect or physical abuse (or both), externalizing was highest in the sexual abuse/physical abuse/emotional maltreatment/neglect profile, and internalizing was highest in the profiles with physical or sexual abuse (or both). There appear to be distinct profiles of maltreatment among preschoolers that have differential associations to measures of adjustment. Using different profiles of maltreatment to understand specific vulnerabilities may guide in tailoring interventions to the needs of maltreated children. Pears K, Kim H, Fisher P. Psychosocial and cognitive functioning of children with specific profiles of maltreatment. Child Abuse Negl. 2008;32(10):958-71.

Maternal Depression as a Mediator of Parenting Efficacy

Parenting self-efficacy (PSE) has been positively linked to children's adjustment and negatively associated with maternal depression. The present study investigated: (1) how PSE changes over time, (2) the relationship between PSE when the child is age 2 and children's behavior problems 2 years later, and (3) the potential mediating role of maternal depression in relation to the association between PSE and child problem behavior. Participants were 652 ethnically and geographically diverse mothers and their children, at high risk for conduct problems. PSE increased while children were between ages 2 and 4 and higher initial levels predicted lower caregiver-reported conduct problems at age 4 after controlling for problem behavior at age 2. The relationship between PSE and later conduct problems was mediated, however, by maternal depression. These results point to the role of maternal depression as a potential disruptor of caregiver confidence in early childhood, and as a possible target for intervention. Weaver C, Shaw D, Dishion T, Wilson M. Parenting self-efficacy and problem behavior in children at high risk for early conduct problems: the mediating role of maternal depression. Infant Behav Dev. 2008;31(4):594-605.

Factors Associated with Methamphetamine Injection

In addition to the ill health effects of drug use, methamphetamine users are at risk for HIV and Hepatitis C (HCV) through drug injection and unsafe sex. The potential risks of injecting methamphetamine versus injecting other drugs are similar, that is, through shared needles and shared injecting equipment, as well as the possibility of unsafe sex while under the influence. This empirically based study compared injectors of methamphetamine with non-methamphetamine injectors to determine if these two groups differ in ways that put them at risk. From 2004-2006, 439 injection drug users were recruited in Denver, Colorado, to participate in a study of drug use and HCV risk. Over two-thirds were male, more than half were white, and 28% were methamphetamine injectors. Demographics, drug use, and HIV risk behaviors were assessed via the Risk Behavior Assessment. A logistic regression model was built using forward stepwise method to determine independent associations between variables of interest and methamphetamine injection. In comparing methamphetamine injectors to non-methamphetamine injectors, this study found injectors to be younger, more likely to be white and to have more education than non-injectors. This demographic, as well as the finding that methamphetamine injectors were more likely to report being gay/lesbian or bisexual than non-MA IDUs, mirrors the national profile of methamphetamine users. Having this information may allow for targeting intervention and prevention efforts to the most vulnerable segments of the population before they contract HIV or HCV. Corsi K, Kwiatkowski C, Booth R. Predictors of methamphetamine injection in out-of-treatment IDUs. Subst Use Misuse. 2009;44(3):332-42.

Substance Use Involvement Among Youth in Child Welfare

This study examined risk factors for substance use involvement for adolescents involved with the child welfare system. Participants included 214 adolescents 13 to 18, randomly sampled from active child welfare rolls in San Diego County, California. Severity of substance use involvement was assessed via structured diagnostic interviews determining lifetime substance use, abuse, and dependence. Hierarchical regression analyses revealed that both common and child welfare-specific risk factors were associated with severity of youth substance involvement. Multiple-placement changes, later entry into the child welfare system, and multiple-placement changes at an older age were associated with higher risk for more serious substance involvement for youths in child welfare. Aarons G, Monn A, Hazen A, Connelly C, Leslie L, Landsverk J, Hough R, Brown S. Substance involvement among youths in child welfare: the role of common and unique risk factors. Am J Orthopsychiatry;78(3):340-9.

Case Study of Process in a Brief Family Intervention for Toddlers

This article describes a case study in the use of the Family Check-Up (FCU), a family-based and ecological preventive intervention for children at risk for problem behavior. The FCU is an assessment-driven intervention that utilizes a health maintenance model; emphasizes motivation for change; and offers an adaptive, tailored approach to intervention. The FCU is currently under study in a randomized control trial (RCT) in 3 geographically diverse communities where 731 families with children at high risk for conduct problems were identified through local Women Infants and Children (WIC, federal food and nutrition) programs. This case study follows one Caucasian family through their initial assessment and subsequent intervention for their toddler daughter's conduct problems over a 2-year period. Clinically meaningful improvements in child and family functioning were found despite the presence of child, parent, and neighborhood risk factors. Gill A, Hyde L, Shaw D, Dishion T, Wilson M. The family check-up in early childhood: a case study of intervention process and change. J Clin Child Adolesc Psychol. 2008;37(4):893-904.

Needs Assessment of a Social Service Referral Telephone Program for High Risk Youth

This paper reports on a needs assessment study of a social service resource telephone program component among high risk youth who participated in Project Towards No Drug Abuse (TND), a classroom-based program, approximately 1 year earlier. Results supported youths' overwhelming receptiveness of a social service referral program. The vast majority of respondents indicated a strong desire for resource and referral information on vocational, educational, recreational, transportation, and mental health and drug counseling. Further research is needed to investigate the effectiveness of the provision of social service resource information on drug use among emerging adults. Sussman S, Skara S, Pumpuang P. Project Towards No Drug Abuse (TND): needs assessment of a social service referral telephone program for high risk youth. Subst Use Misuse. 2008;43(14):2066-73.

A Practical Guide for Estimating Causal Effects in Nonrandomized Intervention Trials

In a well-designed experiment, random assignment of participants to interventions makes causal inference straightforward. However, if participants are not randomized (as in observational study, quasi-experiment, or nonequivalent control-group designs), group comparisons may be biased by confounders that influence both the outcome and the alleged cause. Traditional

analysis of covariance, which includes confounders as predictors in a regression model, often fails to eliminate this bias. In this article, the authors review Rubin's definition of an average causal effect (ACE) as the average difference between potential outcomes under different treatments. The authors distinguish an ACE and a regression coefficient. The authors review 9 strategies for estimating ACEs on the basis of regression, propensity scores, and doubly robust methods, providing formulas for standard errors not given elsewhere. To illustrate the methods, the authors simulate an observational study to assess the effects of dieting on emotional distress. Drawing repeated samples from a simulated population of adolescent girls, the authors assess each method in terms of bias, efficiency, and interval coverage. Throughout the article, the authors offer insights and practical guidance for researchers who attempt causal inference with observational data. Schafer J, Kang, J. A practical guide on computing average causal effects from nonrandomized intervention studies. Psychol Methods. 2008;13(4):279-313.

STIs More Related to Sexual Risk than Substance Use Among Meth Using Thai Youth

Cross-sectional data were collected in Chiang Mai, Thailand in 2005--2006 among 658 sexually active participants aged 18 to 25 years, the majority having a history of recent methamphetamine use. Data were collected by interview and sexually transmitted infections (STI) were detected using standard laboratory assays. At least one laboratory confirmed STI was found in 38% of participants. Herpes simplex virus and Chlamydia were significantly more common among women, whereas hepatitis B virus was significantly more common among men. Men reported a greater number of sexual partners than women, and condom use at last sex was infrequent. Most participants reported using methamphetamine at least weekly, with men more frequent users than women, and more often giving reports of frequent drunkenness and lifetime arrests. Behavioral correlates of prevalent STI were similar to the published literature. In multivariate analysis, women > or =20 years of age, with > or =2 heterosexual partners in the past year and a younger age at sexual debut were significantly more likely to have a prevalent STI. Men > or =20 years of age, with > or =2 heterosexual partners in the past year and who enrolled both sex and drug network members were significantly more likely to have a prevalent STI, whereas men who used a condom at last sex were significantly less likely to have a prevalent STI. Substance abuse was associated with behavioral risks but not with prevalent STI. Sexual risks and substance abuse are substantially elevated among young Thai methamphetamine users, but only sexual risks are associated with prevalent STI. Celentano D, Sirirojn B, Sutcliffe C, Quan V, Thomson N, Keawvichit R, Wongworapat K, Latkin C, Taechareonkul S, Sherman S, Aramrattana A. Sexually transmitted infections and sexual and substance use correlates among young adults in Chiang Mai, Thailand. Sex Transm Dis. 2008;35(4):400-5.

Factors Associated with Methamphetamine Use Initiation in Thailand

Methamphetamine has become the leading drug of abuse in northern Thailand over the past several years, particularly among youth. The current qualitative study examines factors associated with initiation of methamphetamine use. Between March 2002 and January 2003, 48 in-depth interviews with young methamphetamine users were conducted in advance of a randomized, methamphetamine harm reduction, peer outreach intervention trial. The interviews were conducted in the city of Chiang Mai and the surrounding district. Participants were 57% male and had a median age of 20 years (range 15-31 years). A culture of methamphetamine ubiquity characterized participants' initiation stories. Drug ubiquity encompassed three elements: the extent of methamphetamine use within peer networks; the availability of

methamphetamine; and exposure to methamphetamine before initiation. All participants were introduced to methamphetamine by people close to them, most often by their friends. Internal reasons for trying methamphetamine were curiosity, a way to lose weight or to enhance hard work, and a way to "forget life's problems." With the prevalence of methamphetamine use among participants' peers, initiation seemed inevitable. Initiation was characterized as ubiquitous in terms of peer networks' use and availability. Because of the prevalent norm of methamphetamine use, these data indicate that interventions targeting social networks and young Thais before methamphetamine initiation are needed. Sherman S, German D, Sirirojn B, Thompson N, Aramrattana A, Celentano D. Initiation of methamphetamine use among young Thai drug users: a qualitative study. J Adolesc Health. 2008;42(1):36-42.

Meth Using Young Women in Thailand Have Varied Level of HIV Sexual Risk

Given high rates of methamphetamine use among young people in Thailand and evidence of an association between methamphetamine and increased sexual risk behavior, the associations among women's recent sexual partnerships, social network characteristics and drug and alcohol use were examined. Female participants (n=320) in an HIV behavioral trial among young (18-25 years) methamphetamine users in Chiang Mai completed a drug and sexual behavior survey and social network inventory. Multinomial regression analyses accounting for clustered data examined individual and network characteristics associated with recent sexual partnership category. Women with only one male partner in the past year (39%) were compared to those with multiple male partners (37%) and those with only female partners (24%). Differences in levels of drug and alcohol use and social and sexual network characteristics were dependent on recent sexual partnership profiles. The multiple partner group reported an average of five male partners in the past year; 12% reported consistent condom use in the past 30 days. Compared to both groups, women with multiple male partners used methamphetamine more frequently, had larger non-sex networks with more methamphetamine users, were more likely to have a methamphetamine-using sex partner, and received less emotional support from their partners. Women with multiple male partners and only female partners reported more frequent alcohol use. These data point to the need for targeted prevention approaches that take into account the varying characteristics and social influences of these different groups of women. German D, Sherman S, Latkin C, Sirirojn B, Thomson N, Sutcliffe C, Aramrattana A, Celentano D. Young Thai women who use methamphetamine: intersection of sexual partnerships, drug use, and social networks. Int J Drug Policy. 2008;19(2);122-9.

Daily Context Analysis of Methamphetamine Use in Thailand

Methamphetamine is the leading illicit drug in Thailand among youth and young adults. Sexual risk behaviors are associated with methamphetamine use, but few data are available on the daily context of methamphetamine use. The authors developed an inductive behavioral typology that young Thais engage in while using methamphetamine. A cross-sectional study in Chiang Mai, Thailand was conducted in 2005-2006 among 1,162 street-recruited methamphetamine smokers 18-25 years of age. Data collected included sociodemographic characteristics, sexual behaviors, and drug use patterns. Latent class analysis was used to describe patterns of activities in which participants reported engaging directly after using methamphetamine. Logistic regression was used to examine univariate correlates of class membership, separately by gender. Participants were 75% male with a median age of 19 years. More than half of participants reported frequent alcohol use (>or=4 days/week) and half of the sample reported smoking methamphetamine >or=2 days/ week. Three classes

of activities emerged for male participants (n = 863): "work" (job related); "high-risk behaviors" (motorcycle riding, fighting, sex); and "combined" (all activities). Two classes emerged for the women (n = 299): "work" (housework) and "high-risk behaviors." "High-risk behaviors" and "combined" (men only) classes were associated with more frequent alcohol and methamphetamine use compared with the "work" class. This study found a distinct typology of behaviors associated with substance abuse among young adults in Thailand. Sherman S, Sutcliffe C, German D, Sirirojn B, Aramrattana A, Celentano D. Patterns of risky behaviors associated with methamphetamine use among young Thai adults: a latent class analysis. J Adolesc Health. 2009;44(2):169-75.

Processes of Substance Use Among Youth of Mexican Heritage

This study examined the theory of planned behavior to explain normative processes in substance use among Mexican-heritage youth. The theory identifies norms, attitudes, and perceived behavioral control as predictors of intentions, which in turn, predict behaviors. It was hypothesized that norms are multidimensional, consisting of parental approval/disapproval, peer approval/disapproval, descriptive, and personal substance use norms. Second, it was hypothesized that parental approval/disapproval, peer approval/disapproval, and descriptive norms indirectly affect substance use intentions through attitudes, personal norms, and perceived behavioral control. Third, it was hypothesized that the model would operate differently based on Mexican-heritage youths' country of origin. Mexican-heritage youth (N = 1,499) from 30 elementary schools in Phoenix, AZ completed questionnaires in three waves over 18 months as part of a larger study. The findings supported the first hypothesis, showing the multidimensionality of norms. The second hypothesis was partially supported by findings from a multi-group multilevel path analysis using Mplus. Descriptive norms' association with intentions was partially mediated by attitudes, personal norms, and perceived behavioral control, while parental and peer approval/disapproval norms were fully mediated, partially supporting the second hypothesis. Contrary to the third hypothesis, the mediation model did not differ based on Mexican-heritage youths' country of origin. Kam JA, Matsunaga M, Hecht ML, Ndiaye K. Extending the theory of planned behavior to predict alcohol, tobacco, and marijuana use among youth of Mexican heritage. Prev Sci. 2009;10(1):41-53.

Ego Development and Parenting: Potential Application to Substance Abusing Mothers

This study examined maternal ego development in relation to psychopathology and parenting problems in a sample of substance abusing mothers. Given the tendency for introspection and guilt at higher levels of ego development, the authors expected mothers at higher levels to report more psychopathology. Given the tendency for dichotomous perceptions and limited conceptions of causation at lower levels of ego development, the authors expected mothers at low levels to report more problematic parenting behaviors. Intelligence was expected to correlate but not overlap with ego development. Participants were 182 mothers who expressed interest in a randomized clinical trial for a new parenting intervention. Measures included the Washington University Sentence Completion Task--Short Form, the Parental Acceptance-Rejection Questionnaire, the Brief Symptom Inventory and the Kaufman Brief Intelligence Test. Results of correlation and multivariate analyses of variance confirmed predictions. Suchman N, McMahon T, Decoste C, Castiglioni N, Luthar S. Ego Development, psychopathology, and parenting problems in substance-abusing mothers. Am J Orthopsychiatry. 2008;78(1):20-8.

Correlates of Early Alcohol and Drug Use Among Hispanic

Adolescents

This study examined associations of multiple contexts (e.g., family, school, and peers) and of attention deficit hyperactivity disorder (ADHD) and conduct disorder (CD) to adolescent alcohol and drug use in a sample of 217 eighth-grade adolescents with behavior problems from Hispanic/Latino immigrant families. Data for this study come from baseline assessments (collected prior to randomization) of adolescents and families participating in a randomized clinical trial testing the efficacy of an HIV and substance use prevention intervention. Adolescents and their families were recruited from three large predominantly Hispanic middle schools located in a single urban low-income school district in Miami-Dade County, Florida. The results from structural equation modeling analyses suggest that conduct disorder in youth with high levels of hyperactivity symptoms, poor school functioning, and peer alcohol and drug use was directly related to early adolescent alcohol and drug use. Attention deficit/hyperactivity disorder with comorbid conduct disorder and family functioning was indirectly related to early alcohol and drug use through poor school functioning and through peer alcohol and drug use. Lopez B, Schwartz SJ, Prado G, Huang S, Rothe EM, Wang W, Pantin H. Correlates of early alcohol and drug use in Hispanic adolescents: examining the role of ADHD with comorbid conduct disorder, family, school, and peers. J Clin Child Adolesc Psychol. 2008;37(4):820-32.

Longitudinal Effects of Student Mobility on Elementary School Engagement

This study examined the effects of student mobility during the elementary school years on longitudinal school engagement. Also of focus was how school engagement outcomes are influenced by school and home environmental factors. Data collected from second through fifth grades were drawn from the Raising Healthy Children (RHC) project, an ongoing longitudinal intervention study, which retained a high percentage of study participants despite a high degree of mobility. Data were collected annually from district records and from parent-child and teacher surveys. The sample was predominantly Caucasian, contained roughly equal numbers of boys and girls, and approximately one third low income. The students came from 10 public elementary schools in the Pacific Northwest suburban school district, which had high aggregate measures of risk relative to other schools in the district. Growth curve analyses were used to examine mobility effects within the context of other factors (e.g., behavior problems, school relationships, and family circumstances). Growth curve models showed that school changes predicted declines in academic performance and classroom participation but not positive attitude toward school. Time-varying factors such as peer acceptance and teacher support had a positive influence on the trajectories of child outcomes. Additionally, teacher support had a particularly strong influence on positive attitudes toward school among children who had more school changes. Gruman DH, Harachi TW, Abbott RD, Catalano RF, Fleming, CB. Longitudinal effects of student mobility on three dimensions of elementary school engagement. Child Dev. 2008;79(6):1833-52.

Tobacco Industry Targeting Youth in Argentina

This study examined whether and how the tobacco industry promotes cigarettes to adolescents in Argentina by conducting a systematic search of tobacco industry documents available through the internet dated between 1995 and 2004 using standard search terms to identify marketing strategies in Argentina. A selected review of the four leading newspapers and nine magazines with reported high readership among adolescents was completed. The selected print media were searched for tobacco images and these were

classified as advertisements if associated with a commercial product or as a story if not. For example, British American Tobacco (BAT) undertook a young adult psychographic study and classified them as "progressives," "Jurassics" or "conservatives" and "crudos" or "spoiled brats." Philip Morris promoted Marlboro by sponsoring activities directed at young people and they launched the 10 cigarettes packet as a starter vehicle. The tobacco industry used psychographic segmentation of the population and developed advertising strategies focused on youth. Tobacco control researchers and advocates must be able to address these strategies in counter-marketing interventions. Braun S, Mejia R, Ling P, PŽrez-Stable E. Tobacco industry targeting youth in Argentina. Tob Conrol. 2008;17(2):111-7.

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

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

Self-Efficacy and Depression as Mediators of the Relationship between Pain and Antiretroviral Adherence

The goals of this study were to examine the association between pain and antiretroviral adherence and to estimate the mediating effect of adherence self-efficacy and depression symptom severity. Surveys using audio computer-assisted self-interview were conducted among 70 HIV-infected current and former drug users enrolled in a methadone program. Researchers assessed antiretroviral adherence, adherence self-efficacy, depression symptoms, and pain. Participants reporting pain were 87% less likely to be classified as adherent compared to those without pain. Results indicated that neither adherence self-efficacy nor depression symptom severity fully mediated the relationship between pain and adherence. HIV providers should recognize the potential impact of pain on antiretroviral adherence among current and former drug users. Berg KM, Cooperman NA, Newville H, Arnsten JH. Self-efficacy and depression as mediators of the relationship between pain and antiretroviral adherence. AIDS Care. 2009;21(2):244-8.

A Deposit Contract Method to Deliver Abstinence Reinforcement for Cigarette Smoking

Dr. Jesse Dallery and colleagues from the University of Florida conducted this pilot study to test the feasibility and effects of a potentially cost-effective method to deliver an abstinence-reinforcement intervention for smoking cessation. Eight smokers were randomly assigned to a deposit contact of $50.00 or to a no-deposit group. Using a reversal design, participants could recoup their deposit (deposit group) or earn vouchers (no-deposit group) for smoking reductions and abstinence during treatment phases. Treatment was delivered via a novel Internet-based method to monitor smoking status. There were no clear differences in rates of abstinence between the deposit and no-deposit groups. In the deposit group, 65% of the samples were negative, and in the no-deposit group, 63% of the samples were negative. Although equivalent decreases in breath CO and abstinence were observed during treatment in both groups, $178.50 in vouchers were distributed to participants in the no-deposit group, whereas a small surplus remained in the deposit group. The authors conclude that a deposit contract method may represent a cost-effective model to deliver abstinence reinforcement for cigarette smoking, however, this method should be tested with a larger sample. Dallery J, Meredith S, Glenn IM. A deposit contract method to deliver abstinence reinforcement for cigarette smoking. Journal of Applied Behavior Analysis, 2008;41(4):609-15.

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Lack of an Inverse Relationship between Duration of Untreated Psychosis and Cognitive Function in First Episode Schizophrenia

This study assessed the relationship between duration of untreated psychosis (DUP) and cognitive measures in order to assess if longer DUP was associated with worse performance. One hundred two patients with first episode schizophrenia or schizoaffective disorder were assessed on cognitive measures of speed of processing, episodic memory, executive function, and visual spatial processing at baseline (when patients were drug naive and after 16 weeks of olanzapine or risperidone treatment), so that a change score could be derived. Researchers discovered that DUP for psychotic symptoms in this group of patients was long, with a median of 46 weeks. Neither correlational, parametric analyses in which DUP served as a class variable, nor multiple regression indicated that longer DUP was associated with worse cognition at baseline or smaller magnitude of improvement in cognition. The results suggest that while early intervention may be critical for symptom amelioration by shortening DUP, early intervention for treatment of psychiatric symptoms may have little or no impact on cognitive function. Furthermore, assuming that cognition is a core symptom of schizophrenia, the notion that ongoing psychosis is somehow toxic for a variety of information processing domains appears questionable. Goldberg TE, Burdick KE, McCormack J, Napolitano B, Patel RC, Sevy SM, Goldman R, Lencz T, Malhotra AK, Kane JM, Robinson DG. Lack of an inverse relationship between duration of untreated psychosis and cognitive function in first episode schizophrenia. Schizophr Res. 2009;107(2-3):262-6. Epub 2008 Nov 29.

Persistence of Virological Benefits Following Directly Administered Antiretroviral Therapy among Drug Users: Results from a Randomized Controlled Trial

Although directly administered antiretroviral therapy (DAART) has demonstrated impressive biological benefits compared with self-administered therapy (SAT) among drug users, the persistence of DAART after transition to SAT has not been examined. The authors conducted a community-based, prospective, randomized controlled trial of 6 months of DAART compared with SAT. The primary outcome was the proportion of subjects who achieved virological success at 6 months post-intervention (defined as either a 1.0 log10 reduction from baseline or HIV-1 RNA <400 copies per milliliter). Secondary outcomes included the change from baseline in HIV-1 RNA and CD4 lymphocyte count. Results suggest that the DAART (n = 88) and SAT (n = 53) arms did not differ on virological success (DAART 58.0% vs. SAT 56.6%, P = 0.64), mean reduction in log10 HIV-1 RNA (-0.79 vs. -0.31 log10 copies/mL, P = 0.53), or mean change in CD4 lymphocyte count (+60.2 vs. -15.4 cells/mL, P = 0.12). In the multivariate analysis, only high levels of social support significantly predicted virological success. These data, the first emerging from a randomized controlled trial of DAART among active drug users, are interesting in that they fail to show the persistence of the DAART intervention at improving virological outcomes. Additional strategies are needed to ensure that treatment benefits persist following the cessation of DAART. Maru DS, Bruce RD, Walton M, Springer SA, Altice FL. Persistence of virological benefits following directly administered antiretroviral therapy among drug users: results from a randomized controlled trial. J Acquir Immune Defic Syndr. 2009;50(2):176-81.

The Role of Anxiety Sensitivity and Difficulties in Emotion Regulation in Posttraumatic Stress Disorder among Crack/Cocaine Dependent Patients in Residential Substance Abuse Treatment

Current research suggests the importance of anxiety sensitivity (AS) in the risk for posttraumatic stress disorder (PTSD), and a growing body of research has

demonstrated that difficulties in emotion regulation may also play a role. This study examined the unique relationships between AS dimensions, difficulties in emotion regulation, and a probable PTSD diagnosis among a sample of inner-city crack/cocaine dependent patients in residential substance abuse treatment. Probable PTSD participants exhibited higher levels of the AS dimension of social concerns and emotion regulation difficulties. In addition, difficulties in emotion regulation reliably distinguished probable PTSD participants from non-PTSD participants above and beyond both anxiety symptom severity and the AS dimension of social concerns. Further, social concerns did not account for unique variance when difficulties in emotion regulation were entered into the model. Results provide support for the central role of difficulties in emotion regulation relative to AS dimensions in the prediction of PTSD within a crack/cocaine dependent population. McDermott MJ, Tull MT, Gratz KL, Daughters SB, Lejuez CW. The role of anxiety sensitivity and difficulties in emotion regulation in posttraumatic stress disorder among crack/cocaine dependent patients in residential substance abuse treatment. J Anxiety Disord. 2009; Jan 20; [Epub ahead of print].

Adolescent Change Language Within a Brief Motivational Intervention and Substance Use Outcomes

Homeless adolescents who used alcohol or illicit substances but were not seeking treatment (n = 54) were recorded during brief motivational interventions. Adolescent language during sessions was coded on the basis of motivational interviewing concepts (global ratings of engagement and affect, counts of commitment to change, statements about reasons for change, and statements about desire or ability to change), and ratings were tested as predictors of rates of substance use over time. Results indicate that statements about desire or ability against change were strongly and negatively predictive of changes in substance use rates (days of abstinence over the prior month) at both 1- and 3-month post-baseline assessment. Statements about reasons for change were associated with greater reductions in days of substance use at 1-month assessment. Commitment to change language was not associated with outcomes. The investigators conclude that specific aspects of adolescent speech in brief interventions may be important in the prediction of change in substance use behaviors, and that these relationships should be examined within larger samples and other clinical contexts. Baer JS, Beadnell B, Garrett SB, Hartzler B, Wells EA, Peterson PL. Adolescent change language within a brief motivational intervention and substance se outcomes. Psychology Addict Behav. 2008; 22(4):570-5.

A Randomized Controlled Trial of Multidimensional Family Therapy for Young Adolescent Substance Abuse: Twelve-Month Outcomes

Research has established the dangers of early onset substance use for young adolescents and its links to a host of developmental problems. Specialized interventions that target known risk and protective factors during this critical developmental period are needed. This controlled trial (n = 83) provided an experimental test comparing multidimensional family therapy (MDFT) and a peer group intervention with young teens. Participants were clinically referred, of low income, and mostly ethnic minority adolescents (average age = 13.73 years). Treatments were manual guided, lasted 4 months, and were delivered by community agency therapists. Adolescents and parent assessments took place at intake, 6-weeks post-intake, discharge, and 6 and 12 months following treatment intake. Latent growth curve modeling analyses demonstrated the superior effectiveness of MDFT over the 12-month follow-up in reducing substance use (effect size: substance use frequency, d = 0.77; substance use problems, d = 0.74), delinquency (d = 0.31), and internalized distress (d = 0.54), and in reducing risk in family, peer, and school domains (d = 0.27, 0.67, and 0.35, respectively) among young adolescents. Liddle HA, Rowe CL,

Henderson CE, Dakof GA, Greenbaum PE. Multidimensional family therapy for young adolescent substance abuse: twelve-month outcomes of a randomized controlled trial. J Consult Clin Psychol. 2009;77(1):12-25.

Computer-Assisted Delivery of Cognitive-Behavioral Therapy for Addiction Has Enduring Effects

A unique feature of Cognitive Behavioral Therapy (CBT) for drug addiction developed by Dr. Kathleen Carroll and colleagues at Yale University is the fact that effects of treatment appear to endure long after treatment ends. Research has suggested that this may be a result of patients practicing and improving at implementing CBT skills over time. During a recent randomized clinical trial in an outpatient community treatment setting patients were randomly assigned to either standard treatment or standard treatment with biweekly access to computer-based training in CBT (CBT4CBT) skills. For those assigned to CBT4CBT the number of CBT modules initiated had a significant relationships to abstinence during follow-up ($r=49$, $p=.02$). Additionally results show that during the follow-up period CBT patients tended to demonstrate increases in abstinence while usual care patients increased drug use. Effects were evident up to the six month follow-up point. These data suggest that CBT4CBT is an effective adjunct to standard outpatient treatment for substance dependence. The computerized version appears similar to the in-person version in that it effects endure after therapy ends. This is significant because the disseminability of CBT via this platform holds potential for making this empirically validated treatment more broadly available than in-person treatment which requires skilled highly trained therapists for in person implementation. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Rounsaville BJ. Enduring effects of a computer-assisted training program for cognitive behavioral therapy: a 6-month follow-up of CBT4CBT. Drug Alcohol Depend. 2009; 100(1-2):178-81.

Group Contingency Management Is Feasible and Improves Attendance Rates

Dr. Kirby and colleagues at the Treatment Research Institute implemented a novel contingency management treatment program in which the behavior of a single, randomly selected, anonymous individual determined reinforcement delivery for the entire group. In traditional contingency management, rewards or sanctions are typically given following the behavior of an individual. This approach has shown to be efficacious for improving abstinence rates in drug treatment settings. However, this approach is not necessarily compatible with methadone treatment which tends to be conducted in a group treatment format. In this study contingencies placed only on cocaine abstinence (CA) were compared to contingencies on one of four behaviors (CA, treatment attendance, group CM attendance, and methadone compliance) selected randomly at each drawing. A goal of this research was to leverage the power of the group to assist group members who might initially struggle with achieving treatment goals. A second goal was to incorporate contingencies on behaviors other than abstinence which methadone counselors felt would be helpful for producing long term treatment success. Two groups of 22 cocaine-dependent community-based methadone patients were exposed to both CA and multiple behavior (MB) conditions in a reversal design counterbalanced across groups. The group CM intervention was feasible and appeared safe such that participants did not report experiencing coercion from other group members. Additionally, the MB condition improved group CM meeting attendance relative to the CA condition. This is significant because it demonstrates implementation of CM in a group format is possible in community treatment programs and shows that Multiple Behavior targeting approach has an advantage over a traditional abstinence based CM with respect to treatment attendance outcomes. Kirby KC, Kerwin ME, Carpenedo CM, Rosenwasser BJ, Gardner RS.

Interdependent group contingency management for cocaine-dependent methadone maintenance patients. J Appl Behav Anal. 2008; 41(4):579-95.

Regular Exercise as a Protective Factor in Relapse following Smoking Cessation Treatment

Dr. Abrantes and colleagues at Butler Hospital and The Miriam Hospital conducted this study to determine if smokers who regularly exercised varied from those who did not on a number of baseline characteristics prior to initiating a smoking cessation intervention, as well as smoking cessation outcomes during the year after treatment. Baseline characteristics were examined for a sample of 524 smokers who participated in 12-week 2 x 2 clinical trial comparing standard smoking cessation treatment (ST) plus bupropion (BUP); ST plus placebo; ST plus cognitive behavioral therapy CBT for depression plus BUP; and ST plus CBT for depression plus placebo. Participants identified themselves as regular exercisers versus those who reported not exercising regularly. At baseline, exercisers were more likely to be female, have lower body mass index, report smoking fewer cigarettes per day, report lower smoking urges and have lower levels of depressive symptoms. At the end of treatment, abstinence rates were significantly higher for participants who took bupropion (42.7%) compared to placebo (27.1%), but these rates converged by the 12-month follow-up. Similarly, at the end of treatment, those who exercised regularly, independent of treatment condition, had significantly higher abstinence rates (40.1%) compared to non-exercisers (32.9%) but again abstinence rates converge at follow-up. Lastly, although rates of abstinence at the end of treatment were similar for exercisers (43.1%) and non-exercisers (42.4%) receiving bupropion, among smokers receiving placebo, abstinence rates were significantly higher for participants who exercised (36.9%) versus those who did not (24.1%). The authors suggest that regular exercise may be an important protective factor in smoking relapse and should continue to be explored as an adjunct to smoking cessation interventions. Abrantes AM, Strong, DR, Lloyd-Richardson, EE, Niaura, R, Kahler, CW, Brown, RA. Regular exercise as a protective factor in relapse following smoking cessation treatment. American Journal on Addictions. 2009;18(1):100-1.

Pain and Substance-Related Pain-Reduction Behaviors among Opioid Dependent Individuals Seeking Methadone Maintenance Treatment

Pain management in methadone maintenance treatment (MMT) represents an important clinical challenge. Prevalence estimates for chronic pain in MMT range from 37% with chronic severe pain to more than 60% with chronic pain of any intensity. Dr. Barry and colleagues from Yale University surveyed 293 opioid dependent individuals seeking MMT about their pain experiences and substance-related pain reduction behaviors. Among the 213 respondents reporting recent pain of at least moderate typical pain intensity, two-thirds had a lifetime history of chronic pain. In comparison to those without a lifetime history of chronic pain, those with a lifetime history were older, reported higher pain frequency, were more likely to endorse accident or surgery and less likely to endorse "don't know" as the genesis of their recent pain reduction behaviors. These findings may have implications for resources and program planning in MMT programs. Barry DT, Beitel M, Joshi D, Schottenfeld RS, Fiellin DA. Pain and substance-related pain-reduction behaviors among opioid dependent individuals seeking methadone maintenance treatment. Am J Addict. 2009;18(2):117-21.

Betting on Change: Modeling Transitional Probabilities to Guide Therapy Development for Opioid Dependence

What does change look like during treatment? Who is more likely to demonstrate it? And how can the process of change guide clinical decisions? The answers to these questions are relevant for understanding the effects of specific treatment procedures, identifying factors that can moderate specific intervening efforts, and developing therapy programs that are responsive to the ongoing process of change. Carpenter and others at Columbia University investigated the process of change by modeling transitions among four clinical states encountered in 64 detoxified opiate-dependent individuals treated with daily oral naltrexone: no opiate use, blocked opiate use (i.e., opiate use while adhering to oral naltrexone), unblocked opiate use (i.e., opiate use after having discontinued oral naltrexone), and treatment dropout. The effects of baseline characteristics and two psychosocial interventions of differing intensity, behavioral naltrexone therapy (BNT) and compliance enhancement (CE), on these transitions were studied. Participants using greater quantities of opiates were more likely than other participants to be retained in BNT relative to CE. Markov modeling indicated a transition from abstinence to treatment dropout was approximately 3.56 times greater among participants in CE relative to participants in BNT, indicating the more comprehensive psychosocial intervention kept participants engaged in treatment longer. Transitions to stopping treatment were more likely to occur after unblocked opiate use in both treatments. Continued opiate use while being blocked accounted for a relatively low proportion of transitions to abstinence and may have more deleterious effects later in a treatment episode. Carpenter KM, Jiang H, Sullivan MA, Bisaga A, Comer SD, Raby WN, Brooks AC, Nunes EV. Betting on change: modeling transitional probabilities to guide therapy development for opioid dependence. Psychol Addict Behav. 2009;23(1):47-55.

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

The cost of providing and receiving treatment for opioid dependence can determine its adoption. Dr. Jones and others at Yale University School of Medicine sought to compare the cost of clinic-based methadone (MC, n=23), office-based methadone (MO, n=21), and office-based buprenorphine (BO, n=34) treatment and patient costs over 6 months of maintenance in patients who had previously been stabilized for at least 1 year. Results suggest the cost of providing 1 month of treatment per patient was $147 (MC), $220 (MO) and $336 (BO) ($p<0.001$). Mean monthly medication cost was $93 (MC), $86 (MO) and $257 (BO) ($p<0.001$). The cost to patients was $92 (MC), $63 (MO) and $38 (BO) ($p=0.102$). Sensitivity analyses, varying cost estimates and clinical contact, result in total monthly costs of $117 to $183 (MC), $149 to $279 (MO), $292 to $499 (BO). Monthly patient costs were $84 to $133 (MC), $55 to $105 (MO) and $34 to $65 (BO). The findings suggest that providing clinic-based methadone is least expensive, and the price of buprenorphine accounts for a major portion of the difference in costs. For patients, however, office-based treatment may be less expensive. Jones ES, Moore BA, Sindelar JL, O'Connor PG, Schottenfeld RS, Fiellin DA. Cost analysis of clinic and office-based treatment of opioid dependence: Results with methadone and buprenorphine in clinically stable patients. Drug Alcohol Depend. 2009;99(1-3):132-40.

Effects of Parent Skills Training with Behavioral Couples Therapy for Alcoholism on Children: A Randomized Clinical Pilot Trial

It has been widely documented that children living with an alcohol-abusing parent are more likely than their peers to exhibit behavioral problems that encompass both internalizing and externalizing symptoms. Although many factors contribute to these problems, inadequate parenting has been strongly

linked to increased risks for children living with an alcohol-abusing parent. Drs. Lam, Fals-Stewart, and Kelley conducted this pilot study to examine preliminary effects of Parent Skills Training with Behavioral Couples Therapy on Children's behavioral functioning. Participants were men (N = 30) entering outpatient alcohol treatment, their female partners, and a custodial child between 8 and 12 years of age. Couples were randomly assigned to one of three equally intensive conditions: (1) Parent Skills with Behavioral Couples Therapy (PSBCT), (2) BCT (without parent training), or (3) Individual-Based Treatment (IBT; without couples-based or parent skills interventions). Parents completed measures of child externalizing and internalizing behaviors at pre-treatment, post-treatment, 6- and 12-month follow up; children completed self-reports of internalizing symptoms at each assessment. Only PSBCT participants reported significant effects on all child measures throughout the 12-month follow up. PSBCT showed medium to large effects in child functioning relative to IBT, and small to medium effects relative to BCT from baseline through follow up. Effect sizes suggest clinically meaningful differences between PSBCT and both BCT and IBT that warrant further empirical evaluation of BCT with parent training for alcohol-abusing men and their partners. Lam WK, Fals-Stewart, Kelly ML. Effects of parent skills training with behavioral couples therapy for alcoholism on children: a randomized clinical pilot trial. Addict Behav. 2008;33(8):1076-80.

Changing Network Support for Drinking: Network Support Project 2-Year Follow-Up

It has often been noted that the most significant problem related to treatment of alcohol dependence is not the attainment of initial abstinence but relapse following treatment. Given that an estimated one third of treated individuals relapse in the first 90 days after completion of treatment, Dr. Litt and colleagues at the University of Connecticut examined the role of changing network support in treatment. In this study, the Network Support Project was designed to determine whether a treatment could lead patients to change their social network from one that supports drinking to one that supports sobriety, with a focus on 2-years post-treatment. Alcohol-dependent men and women (N = 210) were randomly assigned to 1 of 3 outpatient treatment conditions: network support (NS), network support + contingency management (NS + CM), or case management (CaseM, a control condition). Analysis of drinking rates indicated that the NS condition yielded up to 20% more days abstinent than the other conditions at 2 years post-treatment. NS treatment also resulted in greater increases at 15 months in social network support for abstinence, as well as in Alcoholics Anonymous (AA) attendance and AA involvement than did the other conditions. Findings also suggested that social network changes were accompanied by increases in self-efficacy and coping that were strongly predictive of long-term drinking outcomes. These data indicate that a network support treatment can effect long-term adaptive changes in drinkers' social networks and that these changes contribute to improved drinking outcomes in the long term. Litt MD, Kadden RM, Kabela-Corimer E, Petry NM. Changing network support for drinking: network support project 2-year follow-up. J Consult Clin Psychol. 2009;77(2):229-42.

Coping Skills Training and Contingency Management Treatments for Marijuana Dependence: Exploring Mechanisms of Behavior Change

Achieving abstinence in the treatment of marijuana dependence has been difficult. To date the most successful treatments have included combinations of motivation enhancement treatment (MET) plus cognitive-behavioral coping skills training (CBT) and/or contingency management (ContM) approaches. Although these treatment approaches are theoretically based, their mechanisms of action have not been explored fully. Drs. Litt, Kadden, Kabela-

Corimer, and Petry used a dismantling study design to investigate the mechanisms of behavior change from a marijuana treatment trial in which CBT and ContM were evaluated separately and in combination. Participants were 240 adult marijuana smokers, meeting criteria for cannabis dependence in an outpatient treatment research facility located in a university medical center. Participants were assigned to one of four 9-week treatment conditions: a case management control condition, MET/CBT coping skills training, ContM and MET/CBT + ContM. Outcome measures were total 90-day abstinence, recorded every 90 days for 12 months post-treatment. Regardless of treatment condition, abstinence in near-term follow-ups was predicted most clearly by abstinence during treatment, but long-term abstinence was predicted by use of coping skills and especially by post-treatment self-efficacy for abstinence. These findings suggest that the most efficacious treatments for marijuana dependence are likely to be those that increase self-efficacy. Litt MD, Kadden RM, Kabela-Corimer E, Petry NM. Coping skills training and contingency management treatment for marijuana dependence: exploring mechanisms of behavior change. Addiction. 2008;103(4):638-48.

Maintenance Treatment with Buprenorphine and Naltrexone for Heroin Dependence in Malaysia: A Randomized, Double-Blind, Placebo-Controlled Trial

Expansion of access to effective treatments for heroin dependence is a worldwide health priority that has the potential to reduce HIV transmission. Drs. Schottenfeld, Chawarski, and Mazlan compared the efficacy of naltrexone, buprenorphine, and no additional treatment in patients receiving detoxification and subsequent drug counseling for maintenance of heroin abstinence, prevention of relapse, and reduction of HIV risk behaviors. Specifically, 126 detoxified heroin-dependent patients, from an outpatient research clinic and detoxification program in Malaysia, were randomly assigned to 24 weeks of manual-guided drug counseling and maintenance with naltrexone (n=43), buprenorphine (n=44), or placebo (n=39). Primary outcomes, assessed by urine testing three times per week, were days to first heroin use, days to heroin relapse (three consecutive opioid-positive urine tests), maximum consecutive days of heroin abstinence, and reductions in HIV risk behaviors over 6 months. The study was terminated after 22 months of enrollment because buprenorphine was shown to have greater efficacy in an interim safety analysis. The findings highlight the importance of the widespread dissemination of maintenance treatment with buprenorphine as an effective public-health approach to reduce problems associated with heroin dependence. Schottenfeld RS, Chawarski MC, Mazlan M. Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomized, double-blind, placebo-controlled trial. Lancet. 2008;28;371(9631):2192-2200.

Gender Differences in Predictors of Treatment Attrition with High Dose Naltrexone in Cocaine and Alcohol Dependence

Despite the promising results of large clinical trials of high-dose naltrexone treatment for cocaine- and alcohol-dependent (CAD) patients, the gender disparity in response to high-dose naltrexone raises important clinical issues, including potential gender differences in naltrexone-associated adverse events and treatment non-adherence. In line with this central question, Dr. Suh and colleagues examined whether there are gender-specific differences in predictors of treatment attrition between CAD men and women who received a high-dose of naltrexone versus placebo, with one of two types of psychosocial therapies. Variables affecting differential outcome or attrition for men and women, including experience of nausea, substance use and severity of psychiatric problems were considered. Additionally, six variables to predict treatment attrition for men and women were: 1) randomized medication treatment condition (high-dose naltrexone or placebo); 2) randomized

psychosocial treatment condition (cognitive behavioral therapy) or a medical management treatment model; 3) psychiatric severity prior to treatment, as women present with more severe psychiatric problems than men prior to substance use treatment, leading to treatment attrition; 4) experience of nausea, which is the most common adverse effect associated with the standard dose and high-dosage naltrexone, and a more frequently reported adverse event in women than men in naltrexone treatment; 5) alcohol use during treatment; and 6) cocaine use during treatment. No significant predictors were associated with treatment discontinuation in men. Women, however, were more likely to discontinue treatment when reporting severe pre-treatment psychiatric problems or nausea while in treatment. These findings suggest the need for research delineating how outcomes may be affected by gender differences in pre-treatment characteristics as well as potential pharmacokinetic-differential effects of high-dose naltrexone. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. Gender differences in predictors of treatment attrition with high dose naltrexone in cocaine and alcohol dependence. Am J Addict. 2008;17(6):463-8.

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

Research Findings - Research on Pharmacotherapies for Drug Abuse

Predictors of Treatment Outcome in Outpatient Cocaine and Alcohol Dependence Treatment

The investigators examined the ability of several baseline variables to predict treatment outcome in a pharmacotherapy trial that included 164 participants who were both cocaine- and alcohol-dependent and were selected for a randomized, double-blind, placebo-controlled study. Predictor variables included results from the baseline Addiction Severity Index (ASI), initial Urine Drug Screen results, cocaine and alcohol craving and cocaine and alcohol withdrawal symptoms at the start of treatment. Successful treatment was defined as four continuous weeks of self-reported cocaine abstinence verified by urine drug screens. In respect to demographic characteristics, there were no significant differences between patients who achieved four weeks of abstinence from cocaine and those who did not. Baseline variables that most consistently predicted cocaine abstinence included initial urine drug screen (UDS) results, the initial Cocaine Selective Severity Assessment (CSSA) scores, and initial self-reported cocaine use in past 30 days, whereas cocaine craving, cocaine composite scores, alcohol craving, alcohol withdrawal symptoms, and alcohol composite scores did not. The results of this study suggest that cocaine dependence severity in general, and initial UDS results, the CSSA scores and frequency of recent cocaine use in particular, have a significant impact on treatment outcome in the treatment of cocaine-dependent patients with comorbid alcoholism. Initial UDS results and CSSA scores are very useful predictors of treatment outcome and could be used as stratifying variables in outpatient cocaine and alcohol medication trials. Ahmadi J, Kampman KM, Oslin DM, Pettinati HM, Dackis C, Sparkman T. Predictors of treatment outcome in outpatient cocaine and alcohol dependence treatment. Am J Addict. 2009;18(1):81-6.

Influence of Phase-related Variability in Premenstrual Symptomatology, Mood, Smoking Withdrawal, and Smoking Behavior during Ad Libitum Smoking, on Smoking Cessation Outcome

Emerging evidence suggests that women have a more difficult time quitting smoking than men-possibly due, in part, to sex hormones. The present study characterized mood, premenstrual symptomatology, and smoking withdrawal, as well as smoking behavior, in the follicular and luteal phases during ad libitum smoking in 25 women intending to quit. The investigators also investigated the possible influence of phase-related variability in these measures on likelihood of study adherence and smoking cessation. The investigators found that premenstrual symptomatology, as well as some

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measures of mood and smoking withdrawal, were significantly higher during the luteal phase than in the follicular phase. Cigarettes/day did not vary by menstrual cycle phase. Phase-related variability in premenstrual symptomatology [F(3, 20)=2.82, p=0.0650)] and urge to smoke [F(2, 21)=4.85, p=0.0186)] were associated with relapse. These data support the inference that sex hormones influence smoking cessation outcome. This knowledge may contribute to the development of more rational and effective smoking cessation interventions for women. Allen SS, Allen AM, Pomerleau CS. Influence of phase-related variability in premenstrual symptomatology, mood, smoking withdrawal, and smoking behavior during ad libitum smoking, on smoking cessation outcome. Addict Behav. 2009;34(1):107-11.

A Prospectively Measured Serum Biomarker for a Tobacco-Specific Carcinogen and Lung Cancer in Smokers

No prior studies have related a tobacco-specific carcinogen to the risk of lung cancer in smokers. Of the over 60 known carcinogens in cigarette smoke, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is specific to tobacco and causes lung cancer in laboratory animals. Its metabolites, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), have been studied as biomarkers of exposure to NNK. The investigators studied the relation of prospectively measured NNK biomarkers to lung cancer risk. In a case-control study nested in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, the investigators randomly selected 100 lung cancer cases and 100 controls who smoked at baseline and analyzed their baseline serum for total NNAL, cotinine, and r-1,t-2,3,c-4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT), a biomarker of polycyclic aromatic hydrocarbon exposure and metabolic activation. To examine the association of the biomarkers with all lung cancers and for histologic subtypes, computed odds ratios for total NNAL, PheT, and cotinine using logistic regression to adjust for potential confounders. Findings: Individual associations of age, smoking duration, and total NNAL with lung cancer risk were statistically significant. After adjustment, total NNAL was the only biomarker significantly associated with risk (odds ratio, 1.57 per unit SD increase; 95% confidence interval, 1.08-2.28). A similar statistically significant result was obtained for adenocarcinoma risk, but not for nonadenocarcinoma. This first reporting of the effect of the prospectively measured tobacco-specific biomarker total NNAL, on risk of lung cancer in smokers provides insight into the etiology of smoking-related lung cancer and reinforces targeting NNK for cancer prevention. Church TR, Anderson KE, Caporaso NE, Geisser MS, Le CT, Zhang Y, Benoit AR, Carmella SG, Hecht SS. A prospectively measured serum biomarker for a tobacco-specific carcinogen and lung cancer in smokers. Cancer Epidemiol Biomarkers Prev. 2009;18(1):260-6.

Self-Administration of Cocaine, Cannabis and Heroin in the Human Laboratory: Benefits and Pitfalls

The objective of this review is to describe self-administration procedures for modeling addiction to cocaine, cannabis and heroin in the human laboratory, the benefits and pitfalls of the approach, and the methodological issues unique to each drug. In addition, the predictive validity of the model for testing treatment medications will be addressed. The results show that all three drugs of abuse are reliably and robustly self-administered by non-treatment-seeking research volunteers. In terms of pharmacotherapies, cocaine use is extraordinarily difficult to disrupt either in the laboratory or in the clinic. A range of medications has been shown to significantly decrease cocaine's subjective effects and craving without decreasing either cocaine self-administration or cocaine abuse by patients. These negative data combined with recent positive findings with modafinil suggest that self-administration procedures are an important intermediary step between pre-clinical and clinical

studies. In terms of cannabis, a recent study suggests that medications that improve sleep and mood during cannabis withdrawal decrease the resumption of marijuana self-administration in abstinent volunteers. Clinical data on patients seeking treatment for their marijuana use are needed to validate these laboratory findings. Finally, in contrast to cannabis or cocaine dependence, there are three efficacious Food and Drug Administration-approved medications to treat opioid dependence, all of which decrease both heroin self-administration and subjective effects in the human laboratory. In summary, self-administration procedures provide meaningful behavioral data in a small number of individuals. These studies contribute to our understanding of the variables maintaining cocaine, marijuana and heroin intake, and are important in guiding the development of more effective drug treatment programs. Haney M. Self-administration of cocaine, cannabis and heroin in the human laboratory: benefits and pitfalls. Addict Biol 2009;14(1):9-21.

Comorbidity in Pediatric Bipolar Disorder

The growing literature shows the pervasiveness and importance of comorbidity in youth with bipolar disorder (BPD). For instance, up to 90% of youth with BPD have been described to manifest comorbidity with attention-deficit hyperactivity disorder. Multiple anxiety, substance use, and disruptive behavior disorders are the other most commonly reported comorbidities with BPD. Moreover, important recent data highlight the importance of obsessive-compulsive and pervasive developmental illness in the context of BPD. Data suggest that not only special developmental relationships are operant in the context of comorbidity but also that the presence of comorbid disorders with BPD results in a more severe clinical condition. Moreover, the presence of comorbidity has therapeutic implications for the treatment response for both BPD and the associated comorbid disorder. Future longitudinal studies to address the relationship and the impact of comorbid disorders on course and therapeutic response over time are required in youth with BPD. Joshi G, Wilens T. Comorbidity in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am. 2009;18(2):291-viii.

Perspective: Translational Studies on Glutamate and Dopamine Neurocircuitry in Addictions: Implications for Addiction Treatment

New research suggests that the modulation of dopamine neurocircuitry by glutamate plays a key role in the development of nicotine and other addictions. For example, manipulation of glutamatergic pathways can alter the mood-enhancing and reinforcing properties of nicotine. These glutamatergic pathways are also sensitive to manipulation by other drugs of abuse. The studies described in this special issue of Neuropsychopharmacology bring together rodent studies with translational work in humans to enhance our understanding of the cellular mechanisms underlying the subjective and objective effects of drugs of abuse. These studies suggest new therapeutic targets based on central glutamate systems that may lead to the development of novel and more effective treatments for addictive disorders. Lambe EK, George TP. Perspective: Translational studies on glutamate and dopamine neurocircuitry in addictions: implications for addiction treatment. Neuropsychopharmacology. 2009;34(2):255-6.

Provigil (Modafinil) Plus Cognitive Behavioral Therapy for Methamphetamine Use in HIV+ Gay Men: A Pilot Study

The objective of this study was to evaluate the efficacy of modafinil combined with cognitive behavioral therapy (CBT) for treatment of methamphetamine (MA) dependence among HIV+ gay men. In a single blind trial, modafinil was administered for 12 weeks, followed by a 4-week placebo phase. CBT was

conducted for 18 sessions over the 16-week study. Primary outcome measures were self-reported use of days per week plus urine toxicology assays. Additional measures included the Beck Depression Inventory, Cravings Scale, and O/C Crystal Use Scale. Response was defined as > 50% decline in days used per week. Thirteen patients were enrolled over an 18-month period. Ten patients (77%) completed the trial, although two discontinued modafinil due to side effects. Six of the ten study completers reduced their MA use by > 50%. These preliminary results suggest good retention using combined medication and psychotherapy, and support further examination of modafinil and CBT in double-blind placebo controlled trials. McElhiney MC, Rabkin JG, Rabkin R, Nunes EV. Provigil (modafinil) plus cognitive behavioral therapy for methamphetamine use in HIV+ gay men: a pilot study. Am J Drug Alcohol Abuse. 2009;35(1):34-7.

Effects of Oral Methamphetamine on Cocaine Use: A Randomized, Double-Blind, Placebo-Controlled Trial

No medication is currently approved for the treatment of cocaine dependence, but several preclinical and clinical reports suggest agonist-like medications, e.g., amphetamine analogues, may be a productive strategy for medication development. This current proof-of-concept study sought to evaluate the safety, tolerability, and effectiveness of methamphetamine as a candidate treatment for cocaine dependence. A randomized, double-blind, placebo-controlled study served to evaluate three treatment conditions in 82 cocaine-dependent individuals: (1) placebo (0mg, 6x/day; n=27), (2) immediate release (IR) methamphetamine (5mg, 6x/day; n=30), (3) sustained release (SR) methamphetamine (30 mg first pill, 1x/day; 0mg 5x/day; n=25). The study employed a sequential, two-phase design (i.e., 4 weeks of medication and counseling followed by 4 weeks of medication/counseling plus a contingency management procedure). Both preparation forms of methamphetamine were well-tolerated, with similar retention to placebo (0mg, 33%; 30 mg IR, 30%, 30 mg SR, 32%). Methamphetamine SR was associated with decreased sleep and increased weight loss. Medication adherence rates were high for the first dose of the day (95%), while adherence for subsequent capsules was lower. Those in the SR condition exhibited consistently lower rates of cocaine-positive urine samples (0mg, 60%; 30 mg IR, 66%; 30 mg SR, 29%), $p<0.0001$, and reported the greatest reduction in craving for cocaine, $p<0.05$. SR methamphetamine significantly reduced cocaine use and craving. Additional research is warranted to develop and evaluate agonist-like medications that may effectively treat cocaine dependence. Mooney ME, Herin DV, Schmitz JM, Moukaddam N, Green CE, Grabowski J. Effects of oral methamphetamine on cocaine use: a randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend. 2009;101(1-2):34-41.

Mechanisms Underlying the Comorbidity Between Depressive and Addictive Disorders in Adolescents: Interactions Between Stress and HPA Activity

Depression may be a precursor to substance use disorder in some youngsters, and substance abuse might complicate the subsequent course of depression. This study examined whether hypothalamic-pituitary-adrenal (HPA) activity and stressful life experiences are related to the development of substance use disorder in depressed and nondepressed adolescents, and whether substance use disorder predicts a worsening course of depression. Urinary-free cortisol was measured for 3 nights in 151 adolescents with no prior history of substance use disorder (55 depressed, 48 at high risk for depression, and 48 normal subjects). Information was obtained on recent stressful life experiences. The participants were followed for up to 5 years to assess the onset of substance use disorder, course of depression, and stressful experiences. The relationships among depression, cortisol as a measure of HPA

activity, stressful experiences, and substance use disorder were examined. Elevated cortisol was associated with onset of substance use disorder. Stressful life experiences moderated this relationship. Cortisol and stress accounted for the effects of a history or risk of depression on the development of substance use disorder. Substance use disorder was associated with higher frequency of subsequent depressive episodes. Higher cortisol prior to the onset of substance use disorder may indicate vulnerability to substance use disorder. Stressful experiences increase the risk for substance use disorder in such vulnerable youth. The high prevalence of substance use disorders in depressed individuals may be explained, in part, by high levels of stress and increased HPA activity. Rao U, Hammen CL, Poland RE. Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: interactions between stress and HPA activity. Am J Psychiatry. 2009;166(3):361-9.

Caffeinated Energy Drinks--A Growing Problem

Since the introduction of Red Bull in Austria in 1987 and in the United States in 1997, the energy drink market has grown exponentially. Hundreds of different brands are now marketed, with caffeine content ranging from a modest 50 mg to an alarming 505 mg per can or bottle. Regulation of energy drinks, including content labeling and health warnings differs across countries, with some of the most lax regulatory requirements in the U.S. The absence of regulatory oversight has resulted in aggressive marketing of energy drinks, targeted primarily toward young males, for psychoactive, performance-enhancing and stimulant drug effects. There are increasing reports of caffeine intoxication from energy drinks, and it seems likely that problems with caffeine dependence and withdrawal will also increase. In children and adolescents who are not habitual caffeine users, vulnerability to caffeine intoxication may be markedly increased due to an absence of pharmacological tolerance. Genetic factors may also contribute to an individual's vulnerability to caffeine-related disorders including caffeine intoxication, dependence, and withdrawal. The combined use of caffeine and alcohol is increasing sharply, and studies suggest that such combined use may increase the rate of alcohol-related injury. Several studies suggest that energy drinks may serve as a gateway to other forms of drug dependence. Regulatory implications concerning labeling and advertising, and the clinical implications for children and adolescents are discussed. Reissig CJ, Strain EC, Griffiths RR. Caffeinated energy drinks--a growing problem. Drug Alcohol Depend. 2009;99(1-3):1-10.

Diurnal Variation in Cue-Induced Responses Among Protracted Abstinent Heroin Users

The physiological and psychological responses to drug cue exposure have been assessed in substance abusers. However, there is no study to demonstrate whether the responses to drug cue exposure are diurnal dependence. The present study was to examine whether there was a variation in drug-related cue reactivity across the diurnal cycle among recently abstinent opiate addicts. Four groups of 20 abstinent heroin dependent patients (n=80) were exposed to both neutral and drug-related videos at four separate times during the day: 8:00, 12:00, 16:00, and 20:00 h. Physiological and psychological responses, including heart rate, blood pressure, heroin craving, and subjective anxiety were assessed before and after each cue exposure. Drug cue significantly increased craving ratings compared to neutral cues across all the four separate times of day. Drug cue-induced craving was greater in the morning (8:00 am) than noon (12:00 pm), but was similar to evening assessments (8:00 pm). Drug cues also significantly increased anxiety, which positively correlated with cue-induced craving. Drug cues increased heart rate, systolic and diastolic blood pressures, which were not correlated with cue-induced craving or anxiety. However, no time effects were found on the three physiological measures. Cue-induced craving could be profoundly affected by the time points

of cue exposure, using cue-reactivity paradigm. The relative sensitivity of morning and evening assessments of drug craving suggests a need for replication and further research on mechanisms contributing to these diurnal variations. Ren ZY, Zhang XL, Liu Y, Zhao LY, Shi J, Bao Y, Zhang XY, Kosten TR, Lu L. Diurnal variation in cue-induced responses among protracted abstinent heroin users. Pharmacol Biochem Behav. 2009; 91(3):468-72.

Cocaine Effects During D-amphetamine Maintenance: A Human Laboratory Analysis of Safety, Tolerability and Efficacy

Agonist replacement therapies are effective for managing substance abuse disorders including nicotine and opioid dependence. The results of preclinical laboratory studies and clinical trials indicate that agonist replacements like D-amphetamine may be a viable option for managing cocaine dependence. This experiment determined the physiological and behavioral effects of cocaine during D-amphetamine maintenance in seven cocaine-dependent participants. The investigators predicted cocaine would be well tolerated during D-amphetamine maintenance. The investigators also predicted D-amphetamine would attenuate the behavioral effects of cocaine. After 3-5 days of D-amphetamine maintenance (0, 15, and 30 mg/day), volunteers were administered ascending doses of cocaine (4, 30, 60 mg, i.n.) within a single session. Cocaine doses were separated by 90 min. Cocaine produced prototypical physiological (e.g., increased heart rate, blood pressure, and body temperature) and subject-rated (e.g., increased ratings of Good Effects) effects. During maintenance on the highest D-amphetamine dose, the heart rate increasing effects of cocaine were larger than observed during placebo maintenance. These effects were not clinically significant and no unexpected or serious adverse events were observed. D-amphetamine attenuated some of the subject-rated effects of cocaine. These results are concordant with those of previous preclinical studies, human laboratory experiments and clinical trials, further suggesting that agonist replacement therapy may be a viable strategy for managing cocaine abuse. Additional research in humans is needed to determine whether D-amphetamine attenuates the effects of cocaine under different experimental conditions (e.g., higher cocaine doses) and behavioral arrangements (e.g., drug self-administration or discrimination). Rush CR, Stoops WW, Hays LR. Cocaine effects during D-amphetamine maintenance: a human laboratory analysis of safety, tolerability and efficacy. Drug Alcohol Depend. 2009;99(1-3):261-71.

Discriminative Stimulus and Subject-Rated Effects of Methamphetamine, D-amphetamine, Methylphenidate, and Triazolam in Methamphetamine-Trained Humans

Methamphetamine abuse is a significant public health concern. Although widely studied in laboratory animals, little is known about the abuse-related behavioral effects of methamphetamine relative to other abused stimulants in controlled laboratory settings in humans. The aim of this study was to examine the discriminative stimulus, subject-rated, performance, and cardiovascular effects of methamphetamine in humans. In the present study, subjects first learned to discriminate 10 mg of oral methamphetamine from placebo. After acquiring the discrimination (> or = 80% drug-appropriate responding on four consecutive sessions), a range of oral doses of methamphetamine (2.5-15 mg), d-amphetamine (2.5-15 mg), methylphenidate (5-30 mg), and triazolam (0.0625-0.375 mg) was tested. Methamphetamine functioned as a discriminative stimulus and produced prototypical stimulant-like subject-rated effects. D-amphetamine and methylphenidate produced dose-related increases in methamphetamine-appropriate responding, whereas triazolam did not. D-amphetamine and methylphenidate produced stimulant-like behavioral effects, whereas triazolam produced sedative-like effects. Methamphetamine, but no other drug, increased heart rate, systolic pressure, and diastolic pressure

significantly above placebo levels. Performance in the Digit-Symbol Substitution Test was not affected by any of the drugs tested. Overall, these results demonstrate that the acute behavioral effects of methamphetamine, d-amphetamine, and methylphenidate overlap extensively in humans, which is concordant with findings from preclinical studies. Future studies should assess whether the similarity in the behavioral effects of methamphetamine and related stimulants can be extended to other behavioral assays, such as measures of reinforcement, in humans. Sevak RJ, Stoops WW, Hays LR, Rush CR. Discriminative stimulus and subject-rated effects of methamphetamine, d-amphetamine, methylphenidate, and triazolam in methamphetamine-trained humans. J Pharmacol Exp Ther. 2009;328(3):1007-18.

Modeling Stress and Drug Craving in the Laboratory: Implications for Addiction Treatment Development

Addition is a chronic relapsing illness affected by multiple social, individual and biological factors that significantly impact course and recovery of the illness. Stress interacts with these factors and increases addiction vulnerability and relapse risk, thereby playing a significant role in the course of the illness. This paper reviews the authors' efforts in developing and validating laboratory models of stress and drug cue-related provocation to assess stress responses and stress-related adaptation in addicted individuals compared with healthy controls. Empirical findings from human laboratory and brain imaging studies are presented to show the specific stress-related dysregulation that accompanies the drug-craving state in addicted individuals. In order to adequately validate the laboratory model, the investigators have also carefully examined relapse susceptibility in the addicted individuals and these data are reviewed. The overarching goal of these efforts is to develop a valid laboratory model to identify the stress-related pathophysiology in addiction with specific regard to persistent craving and compulsive seeking. Finally, the significant implications of these findings for the development of novel treatment interventions that target stress processes and drug craving to improve addiction relapse outcomes are discussed. Sinha R. Modeling stress and drug craving in the laboratory: implications for addiction treatment development. Addict Biol. 2009;14(1):84-98.

Posttraumatic Stress Disorder and Substance Use Disorder in Adolescent Bipolar Disorder

Anxiety disorders such as posttraumatic stress disorder (PTSD) and substance use disorders (SUD) are increasingly recognized as comorbid disorders in children with bipolar disorder (BPD). This study explores the relationship between BPD, PTSD, and SUD in a cohort of BPD and non-BPD adolescents. The investigators studied 105 adolescents with BPD and 98 non-mood-disordered adolescent controls. Psychiatric assessments were made using the Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiologic Version (KSADS-E), or Structured Clinical Interview for DSM-IV (SCID) if 18 years or older. SUD was assessed by KSADS Substance Use module for subjects under 18 years, or SCID module for SUD if age 18 or older. Nine (8%) BPD subjects endorsed PTSD and nine (8%) BPD subjects endorsed subthreshold PTSD compared to one (1%) control subject endorsing full PTSD and two (2%) controls endorsing subthreshold PTSD. Within BPD subjects endorsing PTSD, seven (39%) met criteria for SUD. Significantly more SUD was reported with full PTSD than with subthreshold PTSD ($chi(2) = 5.58$, $p = 0.02$) or no PTSD ($chi(2) = 6.45$, $p = 0.01$). Within SUD, the order of onset was BPD, PTSD, and SUD in three cases, while in two cases the order was PTSD, BPD, SUD. The remaining two cases experienced coincident onset of BPD and SUD, which then led to trauma, after which they developed PTSD and worsening SUD. An increased rate of PTSD was found in adolescents with BPD. Subjects with both PTSD and BPD developed significantly more subsequent SUD, with

BPD, PTSD, then SUD being the most common order of onset. Follow-up studies need to be conducted to elucidate the course and causal relationship of BPD, PTSD and SUD. Steinbuchel PH, Wilens TE, Adamson JJ, Sgambati S: Posttraumatic stress disorder and substance use disorder in adolescent bipolar disorder. Bipolar Disord. 2009;11(2):198-204.

Clinical Characteristics of Treatment-Seeking Prescription Opioid vs. Heroin-Using Adolescents with Opioid Use Disorder

The objectives of this study were to compare the clinical characteristics of treatment-seeking prescription opioid-using adolescents with DSM-IV opioid use disorder (OUD) to those with heroin-using OUD adolescents. The investigators analyzed the data on OUD adolescents (94, ages 14-18 years) extracted from the parent study dataset comparing clinical characteristics of treatment-seeking OUD to non-OUD adolescents from a adolescent substance abuse treatment program in Baltimore, MD. The sample consisted of 41 non-heroin prescription opioid-using and 53 heroin-using OUD adolescents who were assessed cross-sectionally using standardized interviews and self-reports. Chi-square and t-tests were performed to determine group differences on demographic, substance use, psychiatric and HIV-risk behaviors. Both groups were older (mean 17 years), predominantly Caucasian, and had a suburban residence; they had high rates of co-occurring psychiatric disorders (83%) and they reported moderately high depression symptoms. The heroin-using sample was more likely to have dropped out of school, be dependent on opioids and inject drugs using needles. The prescription opioid-using OUD youth were more likely to meet criteria for multiple SUDs (including prescription sedatives and psychostimulants), current ADHD and report selling drugs; and more likely to be court ordered to current treatment and report prior psychiatric treatment. Both groups of treatment-seeking OUD adolescents had multiple comorbidities but there were substantial differences between prescription opioid-users and heroin-users. These differences may suggest different prognoses and treatment implications. Future research may shed light on the factors leading to differences in choice of opioids and their impact on treatment outcomes; and assess the role of agonist assisted treatments and integrated psychiatric care. Subramaniam GA, Stitzer MA. Clinical characteristics of treatment-seeking prescription opioid vs. heroin-using adolescents with opioid use disorder. Drug Alcohol Depend. 2009;101(1-2):13-19.

Clinical Characteristics of Treatment-Seeking Adolescents with Opioid Versus Cannabis/Alcohol Use Disorders

The objectives of this study were to assess the clinical characteristics of adolescents with DSM-IV opioid use disorder (OUD) and compare them to adolescents with cannabis/alcohol use disorders. Ninety-four adolescents (ages 14-18 years) with a current OUD and 74 adolescents with a current non-OUD cannabis/alcohol use disorder were recruited from admissions, predominantly residential, to a substance abuse treatment program in Baltimore, ML. Participants were assessed cross-sectionally using standardized interviews and self-reports. Chi-square, t-tests and ANCOVA (adjusting for age, gender and treatment setting, race and residence) were performed to determine group differences on demographic, substance use, psychiatric and HIV-risk behaviors; logistic regression analyses, both unadjusted and adjusted for the above five factors were conducted to assess the strength of associations. The OUD group was more likely to be Caucasian, to have dropped out of school and to live in the suburbs (trend). They also had greater substance use severity with higher proportion of current sedative and multiple substance use disorders (SUD). There were generally no differences in rates of criminal behaviors. Both groups had high rates of current psychiatric disorders (83% vs. 78%, n.s.) but the OUD adolescents reported higher depressive symptoms, mostly in the moderate range. Injection drug use (IDU) and needle sharing was almost

exclusive to the OUD group, while both groups reported similar high rates of risky sexual behaviors. While there were similarities between the two groups, OUD adolescents evidenced greater impairment in academic, substance use, depressive symptom and IDU-related HIV-risk areas. Findings suggest poorer long-term prognosis and highlight the need for specialized interventions for treatment-seeking OUD adolescents. Subramaniam GA, Stitzer ML, Woody G, Fishman MJ, Kolodner K. Clinical characteristics of treatment-seeking adolescents with opioid versus cannabis/alcohol use disorders. Drug Alcohol Depend. 2009;99(1-3):141-149.

Low Prefrontal Perfusion Linked to Depression Symptoms in Methadone-Maintained Opiate-Dependent Patients

Clinically depressed patients without substance use disorders, compared to controls, exhibit significantly lower resting regional cerebral blood flow (rCBF) in the prefrontal cortex (PFC). In this study, the investigators examined the link between resting rCBF in the PFC and current depressive symptoms in methadone-maintained opiate-dependent (MM) patients with or without major depression. Arterial spin labeled perfusion fMRI at 3 Tesla was used to measure resting rCBF in 21 MM patients. Perfusion data were analyzed using SPM2. The relationship between Beck Depression Inventory (BDI) score and resting rCBF was examined in a single regression analysis. The BDI scores ranged between 0 and 18 (m=7.0, S.D.=4.8), and 30% of the sample had mild to moderate depression symptoms according to BDI scores. A negative correlation was observed between BDI scores and relative rCBF in the bilateral ventrolateral prefrontal cortex, and middle frontal gyri. The inverse relationship between prefrontal paralimbic rCBF and depression scores suggests a link between reduced fronto-limbic activity and depressive symptoms in MM patients. A significant subgroup of opiate-dependent patients has clinical or sub-clinical depression that is often undetected; our data identify brain substrates of depression symptoms that may also be a potential marker of relapse in this population. Treatment strategies targeting these brain regions may improve outcomes in depressed substance abusers. Suh JJ, Langleben DD, Ehrman RN, Hakun JG, Wang Z, Li Y, Busch SI, O'Brien CP, Childress AR. Low prefrontal perfusion linked to depression symptoms in methadone-maintained opiate-dependent patients. Drug Alcohol Depend. 2009;99(1-3):11-17.

Dramatically Decreased Cocaine Self-Administration in Dopamine But Not Serotonin Transporter Knock-Out Mice

There has been much interest in the relative importance of dopamine and serotonin transporters in the abuse-related-effects of cocaine. The investigators tested the hypotheses that mice lacking the dopamine transporter (DAT(-/-)), the serotonin transporter (SERT(-/-)), or both (DAT(-/-)SERT(-/-)) exhibit decreased reinforcing effects of cocaine. The investigators also assessed whether observed effects on self-administration are specific to cocaine or if operant behavior maintained by food or a direct dopamine agonist are similarly affected. The investigators used a broad range of experimental conditions that included acquisition without previous training, behavior established with food training and subsequent testing with food, cocaine or a direct dopamine agonist as reinforcers, fixed ratio and progressive ratio schedules of reinforcement, and a reversal procedure. Wild-type mice readily acquired cocaine self-administration and showed dose-response curves characteristic of the schedule of reinforcement that was used. While some DAT(-/-) mice appeared to acquire cocaine self-administration transiently, almost all DAT(-/-) mice failed to self-administer cocaine reliably. Food-maintained behaviors were not decreased by the DAT mutation, and IV self-administration of a direct dopamine agonist was robust in the DAT(-/-) mice. In contrast to those mice, cocaine's reinforcing effects were not diminished in SERT(-/-) mice under any of the conditions tested, except for impaired initial acquisition of both food- and cocaine-

maintained behavior. These findings support the notion that the DAT, but not the SERT, is critical in mediating the reinforcing effects of cocaine. Thomsen M, Hall FS, Uhl GR, Caine SB. Dramatically decreased cocaine self-administration in dopamine but not serotonin transporter knock-out mice. J Neurosci. 2009;29(4):1087-92.

Does Conduct Disorder Mediate the Development of Substance Use Disorders in Adolescents With Bipolar Disorder?

Recent work has highlighted important relationships among conduct disorder (CD), substance use disorders (SUD), and bipolar disorder in youth. However, because bipolar disorder and CD are frequently comorbid in the young, the impact of CD in mediating SUD in bipolar disorder youth remains unclear. One hundred and five adolescents with DSM-IV bipolar disorder (mean +/- SD age = 13.6 +/- 2.50 years) and 98 controls (mean +/- SD age = 13.7 +/- 2.10 years) were comprehensively assessed with a structured psychiatric diagnostic interview for psychopathology and SUD. The study was conducted from January 2000 through December 2004. Among bipolar disorder youth, those with CD were more likely to report cigarette smoking and/or SUD than youth without CD. However, CD preceding SUD or cigarette smoking did not significantly increase the subsequent risk of SUD or cigarette smoking. Adolescents with bipolar disorder and CD were significantly more likely to manifest a combined alcohol plus drug use disorder compared to subjects with bipolar disorder without CD ($chi(2) = 11.99$, $p < .001$). While bipolar disorder is a risk factor for SUD and cigarette smoking in a sample of adolescents, comorbidity with preexisting CD does not increase the risk for SUD. Further follow-up of this sample through the full risk of SUD into adulthood is necessary to confirm these findings. Wilens TE, Martelon M, Kruesi MJ, Parcell T, Westerberg D, Schillinger M, Gignac M, Biederman J. Does conduct disorder mediate the development of substance use disorders in adolescents with bipolar disorder? A case-control family study. J Clin Psychiatry. 2009;70(2):259-65.

Opioid Detoxification Enhanced by Use of Low Dose Naltrexone

Although withdrawal severity and treatment completion are the initial focus of opioid detoxification, post-detoxification outcome better defines effective interventions. Very low dose naltrexone (VLNTX) in addition to methadone taper was recently associated with attenuated withdrawal intensity during detoxification. This article describes the results of a seven-day follow-up evaluation of 96 subjects who completed inpatient detoxification consisting of the addition of VLNTX (0.125 or 0.250 mg per day) or placebo to methadone taper in a double blind, randomized investigation. Individuals receiving VLNTX during detoxification reported reduced withdrawal and drug use during the first 24 hours after discharge. VLNTX addition was also associated with higher rates of negative drug tests for opioids and cannabis and increased engagement in outpatient treatment after one week. Further studies are needed to test the utility of this approach in easing the transition from detoxification to various follow-up treatment modalities designed to address opioid dependence. Mannelli P, Patkar AA, Peindl K, Gottheil, E, Wu LT, Gorelick, DA. Early outcomes following low dose naltrexone enhancement of opioid detoxification. Am J Addict. 2009;18(2):109-16.

Psychopharmacologic Management of Opioid-dependent Women During Pregnancy

Illicit drug use during pregnancy presents complex clinical challenges, including reducing drug use and treating psychiatric disorders. Pharmacologic treatment of psychiatric disorders in a pregnant woman requires an evaluation of the

balance between potential clinical benefit and the risk of potential neonatal consequences. This study describes psychiatric symptoms in 111 opioid-dependent pregnant women and their prescribed psychotropic medications. Hypomania, generalized anxiety disorder and depression were the most common disorders for which psychiatric symptoms were endorsed. Over half of women studied were prescribed some form of psychoactive medication during pregnancy. Pharmacologic vs. non-pharmacologic treatment approaches in this patient population are discussed. Martin PR, Arria AM, Fischer G, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Selby P, Jones HE. Psychopharmacologic management of opioid-dependent women during pregnancy. Am J Addict. 2009;18(2):148-56.

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

Laboratory animals allowed to self-administer stimulants for extended periods of time escalate drug intake compared to animals that self-administer under temporally limited conditions. Prior to this study, this phenomenon had not been systematically investigated in humans. Researchers interviewed 106 (77 male, 29 female) methamphetamine (Meth) and 96 (81 male, 15 female) cocaine (Coc) users to determine if they had experienced discrete period(s) of unrestricted access to unlimited quantities of Meth or Coc in the past. Fifty-eight Meth users and 53 Coc users reported having a discrete period of unrestricted access in the past, but not in the present. Meth-using participants with a prior history of unrestricted access reported significantly more current Meth use, compared to Meth users with no prior history of unrestricted access. Specifically, these participants reported more days used in the past 30 d, more days of use per week, greater use per day and greater total use per week ($p<0.05$ for each). Coc-using participants with a prior history of unrestricted access also reported significantly more current Coc use, compared to Coc users with no prior history of unrestricted access. This was true across all measures of current use for these participants, including more days used in the past 30 d, more days of use per week, greater use per day, and higher total use per week ($p<0.02$ for each). Taken together, these results suggest that a history of unrestricted access to stimulants is associated with long-lasting increases in stimulant use. Culbertson C, De La Garza R, Costello M, Newton TF. Unrestricted access to methamphetamine or cocaine in the past is associated with increased current use. Int J Neuropsychopharmacol. 2009;Feb 16:1-9.

Cocaine Dependence May Not be Associated With a Reduction in D1 Receptor Availability

The goal of this study was to determine D1 receptor availability in human cocaine dependent subjects and matched healthy controls. In addition, cocaine dependent subjects performed cocaine self-administration sessions to explore the association between D1 receptor availability and cocaine-seeking behavior. In this study, 25 cocaine dependent subjects and 23 matched healthy controls were scanned with PET and the radiotracer [11C]NNC 112. During the cocaine self-administration sessions, cocaine dependent volunteers were given the choice to self-administer cocaine (0, 6 and 12 mg) or to receive a monetary voucher worth $5. D1 receptor availability was measured in the limbic, associative, and sensori-motor striatum in addition to cortical brain regions. No difference in D1 receptor availability was seen between the two groups. A negative association was seen between D1 receptor BPND in the limbic striatum and the choice for the 6 mg dose of cocaine. These results do not support the hypothesis that cocaine dependence is associated with a reduction in D1 receptor availability in the striatum. However, within the cocaine dependent subjects group, low D1 receptor availability in the ventral striatum was associated with the choice to self-administer cocaine, suggesting that low D1 receptor availability may be associated with an increased risk of relapse in

cocaine dependence. Martinez D, Slifstein M, Narendran R, Foltin RW, Broft A, Hwang DR, Perez A, Abi-Dargham A, Fischman MW, Kleber HD, Laruelle M. Dopamine D1 receptors in cocaine dependence measured with PET and the choice to self-administer cocaine. Neuropsychopharm. 2009;Jan 1-9, (Epub ahead of print).

D-Amphetamine Attenuated Some of the Subject-rated Effects of Cocaine

Agonist replacement therapies are effective for managing substance abuse disorders including nicotine and opioid dependence. The results of preclinical laboratory studies and clinical trials indicate that agonist replacements like D-amphetamine may be a viable option for managing cocaine dependence. This experiment determined the physiological and behavioral effects of cocaine during D-amphetamine maintenance in seven cocaine-dependent participants. Researchers predicted cocaine would be well tolerated during D-amphetamine maintenance. They also predicted D-amphetamine would attenuate the behavioral effects of cocaine. After 3-5 days of D-amphetamine maintenance (0, 15, and 30 mg/day), volunteers were administered ascending doses of cocaine (4, 30, 60 mg, i.n.) within a single session. Cocaine doses were separated by 90 min. Cocaine produced prototypical physiological (e.g., increased heart rate, blood pressure, and body temperature) and subject-rated (e.g., increased ratings of Good Effects) effects. During maintenance on the highest D-amphetamine dose, the heart rate increasing effects of cocaine were larger than observed during placebo maintenance. These effects were not clinically significant and no unexpected or serious adverse events were observed. D-amphetamine attenuated some of the subject-rated effects of cocaine. These results are concordant with those of previous preclinical studies, human laboratory experiments and clinical trials, further suggesting that agonist replacement therapy may be a viable strategy for managing cocaine abuse. Additional research in humans is needed to determine whether D-amphetamine attenuates the effects of cocaine under different experimental conditions (e.g., higher cocaine doses) and behavioral arrangements (e.g., drug self-administration or discrimination). Rush CR, Stoops WW, Hays LR. Cocaine effects during D-amphetamine maintenance: a human laboratory analysis of safety, tolerability and efficacy. Drug Alcohol Depend. 2009;99(1-3):261-71.

Preclinical Data Support the Hypothesis that Chronic Cocaine Alters the Composition of White Matter in Corpus Callosum

Studies in cocaine-dependent human subjects have shown differences in white matter on diffusion tensor imaging (DTI) compared with non-drug-using controls. It is not known whether the differences in fractional anisotropy (FA) seen on DTI in white matter regions of cocaine-dependent humans result from a pre-existing predilection for drug use or purely from cocaine abuse. To study the effect of cocaine on brain white matter, DTI was performed on 24 rats after continuous infusion of cocaine or saline for 4 weeks, followed by brain histology. Voxel-based morphometry analysis showed an 18% FA decrease in the splenium of the corpus callosum (CC) in cocaine-treated animals relative to saline controls. On histology, significant increase in neurofilament expression (125%) and decrease in myelin basic protein (40%) were observed in the same region in cocaine-treated animals. This study supports the hypothesis that chronic cocaine use alters white matter integrity in human CC. Unlike humans, where the FA in the genu differed between cocaine users and non-users, the splenium was affected in rats. These differences between rodent and human findings could be due to several factors that include differences in the brain structure and function between species and/or the dose, timing, and duration of cocaine administration. Narayana PA, Ahobila-Vajjula P, Ramu J, Herrera J, Steinberg JL, Moeller FG. Diffusion tensor imaging of cocaine-treated rodents.

Psychiatry Res. 2009;171(3):242-51.

Tolerance, Rather Than Sensitization, Appears to Result from Repeated Exposure to Smoked Cocaine

Studies using rodents have shown that behavioral responses to a stimulant are enhanced when the stimulant is given within the same context as previous stimulant administrations; this increase in effect related to context is often referred to as sensitization. The investigators examined the role of environmental stimuli in modulating the subjective and cardiovascular effects of cocaine in humans (1) within a daily "binge" and (2) after cocaine abstinence. Ten non-treatment seeking users of smoked cocaine were admitted to the hospital for 17 consecutive days. Participants smoked cocaine (25mg/dose) under two counterbalanced conditions: paired stimuli (same stimuli presented each session) and unpaired stimuli (varied stimuli presented each session). Under each stimulus condition, participants had cocaine test sessions for three consecutive days, no sessions for the next 3 days, then another cocaine test session on the following day, for a total of eight test days. Stimulus condition had no effect on cardiovascular or subjective effects so data were analyzed as a function of repeated cocaine administration over 2 weeks. Maximal ratings on "good drug" and "drug rating" subjective effects clusters decreased over days of repeated cocaine exposure. In contrast, baseline and peak heart rate and systolic pressure increased over days of repeated cocaine administration. Thus, repeated administration of smoked cocaine to experienced cocaine users resulted in increases in baseline blood pressure and heart rate and modest decreases in positive subjective effects. These data indicate modest tolerance rather than sensitization to the positive subjective effects of cocaine with repeated exposure. Reed SC, Haney M, Evans SM, Vadhan NP, Rubin E, Roltin RW. Cardiovascular and subjective effects of repeated smoked cocaine administration in experienced cocaine users. Drug Alcohol Depend. 2009; Mar 19. (Epub ahead of print).

Reinforcing and Subjective Effects of Methylphenidate in Adults With and Without ADHD

There has been controversy over the abuse potential of methylphenidate (MPH) in the context of treatment for attention deficit hyperactivity disorder (ADHD). The objective of this study was to compare the reinforcing and subjective effects of oral MPH in adults with and without ADHD. Following screening, 33 adults (n = 16 with ADHD; n = 17 free from psychiatric diagnoses) completed four pairs of experimental sessions, each of which included a sampling session and a self-administration session. During sampling sessions, subjects received in randomized order 0 (placebo), 20, 40, and 60 mg MPH. During self-administration sessions, subjects completed a progressive ratio (PR) task to earn portions of the dose received on the corresponding sampling session. Subjective effects were recorded throughout all sessions. The main outcome measure for the study was the number of ratios completed on the PR task. Secondary measures included peak subjective effects and area-under-the-curve values for subjective effects. Compared to the control group, the ADHD group completed more ratios on the PR task. Both groups showed robust effects of methylphenidate on subjective endpoints. Main effects of group were noted on subjective effects involving concentration and arousal. Compared to placebo, MPH produced reinforcing effects only for the ADHD group and not for the control group. Increases in stimulant-related subjective effects in non-ADHD subjects were not associated with drug reinforcement. Kollins SH, English J, Robinson R, Hallyburton M, Chrisman AK. Reinforcing and subjective effects of methylphenidate in adults with and without attention deficit hyperactivity disorder (ADHD). Psychopharmacology (Berl). 2008; Dec 23. (Epub ahead of print).

Drug Self-Administration Using a Progressive-Ratio Schedule in Humans Better Predicts Stimulant Drug Abuse and Dependence

Drug self-administration methodologies have been developed for use in humans to model naturalistic stimulant drug-taking behaviors. These methodologies use a number of schedules of reinforcement, including progressive-ratio schedules. As the name implies, in a progressive-ratio schedule, the response requirement for each subsequent delivery of drug increases, and the primary outcome variable is often the break point (i.e., the last ratio completed to receive a drug delivery). These schedules have been used in a number of human laboratory studies evaluating the reinforcing effects of stimulants. The results of these studies have demonstrated that progressive-ratio schedules are sensitive to manipulation of a pharmacological variable, dose, and to non-pharmacological variables contributing to stimulant drug effects. In addition, findings with progressive-ratio schedules are largely concordant with clinical findings, suggesting that drug self-administration under these schedules has predictive validity in terms of drug abuse and dependence. Future research is necessary, however, to understand better how pharmacological factors like route of administration, onset of effects, and pretreatment influence the reinforcing effects of stimulants under progressive-ratio schedules. Stoops WW. Reinforcing effects of stimulants in humans: sensitivity of progressive-ratio schedules. Exp Clin Psychopharmacol. 2008;16(6):503-12.

Bayesian Statistical Analysis May be a Better Means for Evaluating Salient Interactions in Pharmacotherapy Trials

Difficulty identifying effective pharmacotherapies for cocaine dependence has led to suggestions that subgroup differences may account for some of the heterogeneity in treatment response. Well-attested methodological difficulties associated with these analyses recommend the use of Bayesian statistical reasoning for evaluation of salient interaction effects. A secondary data analysis of a previously published, double-blind, randomized controlled trial examines the interaction of decision-making, as measured by the Iowa Gambling Task, and citalopram in increasing longest sustained abstinence from cocaine use. Bayesian analysis indicated that there was a 99% chance that improved decision-making enhances response to citalopram. Given the strong positive nature of this finding, a formal, quantitative Bayesian approach to evaluate the result from the perspective of a skeptic was applied. Bayesian statistical reasoning provides a formal means of weighing evidence for the presence of an interaction in scenarios where conventional, Frequentist analyses may be less informative. Green CE, Moeller FG, Schmitz JM, Lucke JF, Lane SD, Swann AC, Lasky RE, Carbonari JP. Evaluation of heterogeneity in pharmacotherapy trials for drug dependence: a Bayesian approach. Am J Drug Alcohol Abuse. 2009;35(2):95-102.

A Preliminary Trial of Nefazodone and SR Bupropion on Cannabis Use and Cannabis Withdrawal Symptoms

This study investigated the efficacy of nefazodone and bupropion-sustained release for treating cannabis dependence in a double-blind, placebo-controlled, 13 week outpatient study in 106 subjects. Subjects were randomized to one of three medication conditions: nefazodone, bupropion-sustained release, or placebo with a weekly therapy program. Results indicated an increased probability of achieving abstinence over the course of treatment and a decrease in the severity of cannabis dependence and the withdrawal symptom of irritability. There were no significant effects demonstrated for nefazodone and bupropion-sustained release on cannabis use or cannabis withdrawal symptoms. The results indicate that nefazodone and bupropion-sustained

release may have limited efficacy in treating cannabis dependence. Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR. A preliminary trail: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. Am J Addictions. 2009;18:53-64.

Preliminary Data Suggests Inhibition of Nitric Oxide (NO) Synthesis Reduces Craving for Cigarettes

In recent preclinical studies, the role of nitric oxide (NO) in nicotine dependence has become increasingly evident. Inhibition of NO synthesis blocks acquisition of conditioned place preference, and attenuates the nicotine abstinence syndrome in rodents. These findings have not been followed up in human studies. In order to obtain preliminary data on NO inhibition in human smokers, the investigators conducted a randomized, double-blind, crossover study (N=12) of minocycline, a tetracycline derivative antibiotic, that inhibits the neuronal nitric oxide (NO) synthase enzyme with resultant inhibition of NO production. Medication effects were assessed through a smoking choice procedure as well as subjective and physiological responses to nicotine administered via the intravenous route (IV). Minocycline treatment did not affect smoking self-administration in this choice procedure and did not affect most of the subjective responses to IV nicotine or sample smoking. Following IV nicotine administration, there was a greater reduction in craving for cigarettes under minocycline, compared to placebo. Similarly, smokers had greater reduction in their craving for cigarettes following sample smoking under minocycline treatment. These findings provide limited support for the potential use of minocycline as a treatment of nicotine dependence. Sofuoglu M, Waters AJ, Mooney M, O'Malley SS. Minocycline reduced craving for cigarettes but did not affect smoking or intravenous nicotine responses in humans. Pharmacol Biochem Behav. 2009;92(1):135-40.

Early Exposure to Nicotine May Facilitate the Subsequent Development of Stimulant Abuse

Stimulant users smoke cigarettes at high rates; however, little is known about the relationship between tobacco and stimulants. The authors' goal in this article is to synthesize a growing literature on the role of cigarette smoking in stimulant addiction. Early nicotine exposure may influence the development of stimulant addiction. Preclinical and clinical studies suggest a facilitatory role of nicotinic agonists for stimulant addiction. Smoking appears to be associated with more severe stimulant use and poorer treatment outcomes. It is important to assess smoking and smoking-related variables within stimulant research studies to more fully understand the comorbidity. Integrating smoking cessation into stimulant treatment may improve nicotine and stimulant treatment outcomes. Weinberger AH, Sofuoglu M. The impact of cigarette smoking on stimulant addiction. Am J Drug Alcohol Abuse. 2009;35(1):12-17.

Smoking Abstinence Does Not Increase Short-Term Weight Gain by Menstrual Phase

Prevention of early weight gain may be critical to avoid relapse among women with a fear of weight gain. Menstrual phase has physiological fluctuation of fluid resulting in short-term weight gain, suggesting menstrual phase of smoking cessation may impact short-term weight gain. This study examined the effect of smoking abstinence and menstrual cycle on short-term weight gain. Women were randomized to quit smoking during the follicular or luteal phase of their cycle and followed for four weeks. Weight, among other measures, was recorded at five post-quit date visits (days 2, 5, 9, 12 and week 4). Participants (n=152) were grouped based on randomized quit phase and smoking status after assigned quit date: 1) follicular (F), quit < 24 h, 2) F, quit > or = five

days, 3) luteal (L), quit < 24 h, and 4) L, quit > or = five days. Participants who quit smoking experienced significantly more weight gain than those who quit for less than 24 h. There were no significant increases in short-term weight gain based on menstrual cycle phase during attempted smoking cessation. Allen SS, Allen AM, Mooney M, Bade T. Short-term weight gain by menstrual phase following smoking cessation in women. Eat Behav. 2009;10(1):52-5.

Cognitive Measures of Bitterness or Hostility, As Opposed to Aggressive Behaviors, Were Positively Correlated to Poor Smoking Cessation Outcomes and Greater Withdrawal Symptoms

Hostility is a multifaceted construct encompassing affective, behavioral, and cognitive aspects. There is preliminary evidence linking hostility to poorer outcomes in smoking cessation treatment; however, it is unclear which components of hostility are most important in cessation. In this study, the authors examined multiple aspects of trait hostility in 92 heavy social drinkers who were seeking smoking cessation treatment. Consistent with their hypothesis, the authors found that the cognitive component of hostility was most relevant to smoking cessation outcome. Specifically, those who expressed bitterness about their lives and tended to believe that they had poor luck and had gotten a raw deal out of life had poor smoking cessation outcomes. Cognitive measures of hostility also predicted greater nicotine withdrawal symptoms 1 week after quitting smoking. Other components of hostility including anger and both physical and verbal aggression did not significantly predict smoking outcome or nicotine withdrawal. Further examination of how a hostile worldview contributes to smoking cessation failure is warranted, as this facet of hostility may prove a valuable target for smoking cessation interventions. Kahler CW, Spillane NS, Leventhal AM, Strong DR, Brown RA, Monti PM. Hostility and smoking cessation treatment outcome in heavy social drinkers. Psychol Addict Behav. 2009;23(1):67-76.

Microneedles Permit Transdermal Delivery of a Skin-Impermeant Medication to Humans

Drugs with poor oral bioavailability usually are administered by hypodermic injection, which causes pain, poor patient compliance, the need for trained personnel, and risk of infectious disease transmission. Transdermal (TD) delivery provides an excellent alternative, but the barrier of skin's outer stratum corneum (SC) prevents delivery of most drugs. Micrometer-scale microneedles (MNs) have been used to pierce animal and human cadaver skin and thereby enable TD delivery of small molecules, proteins, DNA, and vaccines for systemic action. A clinical study of MN-enhanced drug delivery was carried out in humans. Naltrexone (NTX) is a potent mu-opioid receptor antagonist used to treat opiate and alcohol dependence. This hydrophilic and skin-impermeant molecule was delivered from a TD patch to healthy human subjects with and without pretreatment of the skin with MNs. Whereas delivery from a standard NTX TD patch over a 72-h period yielded undetectable drug plasma levels, pretreatment of skin with MNs achieved steady-state plasma concentrations within 2 h of patch application and were maintained for at least 48 h. The MNs and NTX patch were well tolerated with mild systemic and application site side effects. The MN arrays were painless upon administration and not damaged during skin insertion, and no MNs were broken off into the skin. This human proof-of-concept study demonstrates systemic administration of a hydrophilic medication by MN-enhanced TD delivery. These findings set the stage for future human studies of skin-impermeant medications and biopharmaceuticals for clinical applications. Wermeling DP, Banks SL, Hudson DA, Gill HS, Gupta J, Prausnitz MR, Stinchcomb AL. Proc Natl Acad Sci USA. 2008;105(6):2058-63.

Methadone Pharmacokinetics are Independent of Cytochrome P4503A (CYP3A) Activity and Gastrointestinal Drug Transport: Insights from Methadone Interactions with Ritonavir/Indinavir

This paper reports that inhibition of both hepatic and intestinal CYP3A activity is responsible for ritonavir/indinavir drug interactions. Methadone disposition was unchanged, despite profound inhibition of CYP3A activity, suggesting little or no role for CYP3A in clinical methadone metabolism and clearance. Methadone bioavailability was unchanged, despite inhibition of gastrointestinal P-glycoprotein activity, suggesting that this transporter does not limit methadone intestinal absorption. Kharasch ED, Hoffer C, Whittington D, Walker A, Bedynek PS. Anesthesiology. 2009;110(3):660-72.

Methadone Metabolism and Clearance are Induced by Nelfinavir Despite Inhibition of Cytochrome P4503A (CYP3A) Activity

This article reports that nelfinavir induces methadone clearance by increasing renal clearance, and more so by stereoselectively increasing hepatic metabolism, extraction and clearance. Induction occurred despite 50% inhibition of hepatic CYP3A4/5 activity and more than 75% inhibition of first-pass CYP3A4/5 activity, suggesting little or no role for CYP3A in clinical methadone disposition. Nelfinavir may alter methadone pharmacodynamics, increasing clinical effects. Kharasch ED, Walker A, Whittington D, Hoffer C, Bedynek PS. Drug Alcohol Depend. 2009;101(3):158-68.

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

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

Accessing Antiretroviral Therapy Following Release From Prison

Interruption of antiretroviral therapy (ART) during the first weeks after release from prison may increase risk for adverse clinical outcomes, transmission of human immunodeficiency virus (HIV), and drug-resistant HIV reservoirs in the community. The extent to which HIV-infected inmates experience ART interruption following release from prison is unknown. The objectives of this study were to determine the proportion of inmates who filled an ART prescription within 60 days after release from prison and to examine predictors of this outcome. This was a retrospective cohort study of all 2115 HIV-infected inmates released from the Texas Department of Criminal Justice prison system between January 2004 and December 2007 and who were receiving ART before release. The study's main outcome measure was the proportion of inmates who filled an ART prescript-tion within 10, 30, and 60 days of release from prison. Among the entire study cohort (N=2115), an initial prescription for ART was filled by 115 (5.4%) inmates within 10 days of release (95% confidence interval [CI], 4.5%-6.5%), by 375 (17.7%) within 30 days (95% CI, 16.2%-19.4%), and by 634 (30.0%) within 60 days (95% CI, 28.1%-32.0%). In a multivariate analysis of predictors (including sex, age, race/ethnicity, viral load, duration of ART, year of discharge, duration of incarceration, parole, and AIDS Drug Assistance Program application assistance), Hispanic and African American inmates were less likely to fill a prescription within 10 days (adjusted estimated risk ratio [RR], 0.4 [95% CI, 0.2-0.8] and 0.4 [95% CI, 0.3-0.7], respectively) and 30 days (adjusted estimated RR, 0.7 [95% CI, 0.5-0.9] and 0.7 [95% CI, 0.5-0.9]). Inmates with an undetectable viral load were more likely to fill a prescription within 10 days (adjusted estimated RR, 1.8 [95% CI, 1.2-2.7]), 30 days (1.5 [95% CI, 1.2-1.8]), and 60 days (1.3 [95% CI, 1.1-1.5]). Inmates released on parole were more likely to fill a prescription within 30 days (adjusted estimated RR, 1.3 [95% CI, 1.1-1.6]) and 60 days (1.5 [95% CI, 1.4-1.7]). Inmates who received assistance completing a Texas AIDS Drug Assistance Program application were more likely to fill a prescription within 10 days (adjusted estimated RR, 3.1 [95% CI, 2.0-4.9]), 30 days (1.8 [95% CI, 1.4-2.2]), and 60 days (1.3 [95% CI, 1.1-1.4]). The authors conclude that only a small percentage of Texas prison inmates receiving ART while incarcerated filled an initial ART prescription within 60 days of their release. Baillargeon J, Giordano TP, Rich JD, Wu ZH, Wells K, Pollock BH, Paar DP. Accessing antiretroviral therapy following release from prison. JAMA. 2009;301(8):848-57.

HIV-1 Harboring Renal Tubular Epithelial Cell Interaction with T Cells Results in T Cell Trans-Infection

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Renal biopsy data suggest that renal tubular cells may serve as a reservoir for HIV-1, however the mechanism underlying this finding has not been studied. Here the investigators show that primary human renal proximal tubular epithelial cells (HRPTECs) have the potential to harbor HIV-1 through the DEC-205 receptor. The interaction of HIV-1 with DEC-205 results in the rapid internalization of the virus for lysosomal degradation, without establishing a productive infection. However, a small fraction of incoming virus escapes degradation and can be rescued by T cells. Since pH-modulating agents and an inhibitor of endosomal transport increased HIV-1 accumulation and trans-infection to T cells, it appears that HRPTECs endocytic compartments may be the site of viral persistence and transmission to target cells. The ability of T cells to rescue the virus from HRPTECs further supports the hypothesis that these cells have the potential to serve as a reservoir for HIV-1. Mikulak J, Teichberg S, Faust T, Schmidtmayerova H, Singhal PC. Virology, 2009;Mar 1(385).

Recurrence of Primary Biliary Cirrhosis and Development of Autoimmune Hepatitis after Liver Transplant: A Blind Histologic Study

This long-term study aimed to evaluate recurrence and evolution of primary biliary cirrhosis (PBC) after orthotopic liver transplantation (OLT). The investigators reviewed "blindly" allograft biopsy specimens of women who underwent transplantation for PBC (n = 84), and women who received a transplant for chronic hepatitis C virus infection (CHCV) (n = 108). All needle liver biopsy specimens obtained more than 6 months post-OLT were examined, including 83 specimens from 44 PBC patients and 152 specimens from 58 CHCV patients. Granulomatous destructive cholangitis was found in five biopsies from four PBC patients (P = 0.0048). Non-necrotizing epithelioid cell granulomas were present in four biopsies from four PBC patients, and in two biopsies from one CHCV patient. Piecemeal necrosis (P = 0.0002), lobular necroinflammatory activity (P < 0.0001), steatosis (P < 0.0001) and fibrosis (P < 0.0001) were more prevalent in CHCV patients than PBC patients. Four PBC patients developed histologic evidence of autoimmune hepatitis (AIH), at a mean time of 3.66 years post-OLT. One of these patients had histologic features of AIH/PBC overlap syndrome. All four patients developed bridging fibrosis (n = 2) or cirrhosis (n = 2). No other PBC patient had evidence of cirrhosis after OLT. Histologic findings indicative of recurrent PBC were present in 15.9% of the PBC patients undergoing biopsy in this series. However, this group of patients did not suffer significant bile duct loss or fibrosis, as compared to the control group, suggesting that recurrent PBC is a mild or slowly progressive disease. Histologic evidence of AIH was observed in allograft biopsies of some PBC patients. Hytiroglou P, Gutierrez JA, Freni M, Odin JA, Stanca CM, Merati S, Thomas D, Branch AD, Thung SN. Hepatology Research. 2009;Jan 12. (Epub ahead of print).

Internal Initiation Stimulates Production of p8 Minicore, a Member of a Newly Discovered Family of Hepatitis C Virus Core Protein Isoforms

The hepatitis C virus (HCV) core gene is more conserved at the nucleic acid level than is necessary to preserve the sequence of the core protein, suggesting that it contains information for additional functions. The investigators used a battery of anticore antibodies to test the hypothesis that the core gene directs the synthesis of core protein isoforms. Infectious viruses, replicons, and RNA transcripts expressed a p8 minicore containing the C-terminal portion of the p21 core protein and lacking the N-terminal portion. An interferon resistance mutation, U271A, which creates an AUG at codon 91, upregulated p8 expression in Con1 replicons, suggesting that p8 is produced by

an internal initiation event and that 91-AUG is the preferred, but not the required, initiation codon. Synthesis of p8 was independent of p21, as shown by the abundant production of p8 from transcripts containing an UAG stop codon that blocked p21 production. Three infectious viruses, JFH-1 (2a core), J6/JFH (2a core), and H77/JFH (1a core), and a bicistronic construct, Bi-H77/JFH, all expressed both p8 and larger isoforms. The family of minicores ranges in size from 8 to 14 kDa. All lack the N-terminal portion of the p21 core. In conclusion, the core gene contains an internal signal that stimulates the initiation of protein synthesis at or near codon 91, leading to the production of p8. Infectious viruses of both genotype 1 and 2 HCV express a family of larger isoforms, in addition to p8. Minicores lack significant portions of the RNA binding domain of p21 core. Studies are under way to determine their functions. Eng FJ, Walewski JL, Klepper AL, Fishman SL, Desai SM, McMullan LK, Evans MJ, Rice CM, and Branch AD. J Virology. 2009; April 3104-14.

Rare Birds in North America: Acute Hepatitis C Cohorts

This dynamic cohort was established in 2006 in response to the current HCV outbreak in New York City. It includes 35 subjects with acute HCV infection. Most are HIV-infected men who have sex with men (median age, 41 years). Acute HCV infection was defined using 3 criteria in combination: seroconversion, marked increases in ALT levels, and >1 log10 fluctuations in HCV viral load. The majority of infections were likely sexually acquired, although percutaneous exposures were reported by some subjects. A detailed risk factor questionnaire is administered at the initial visit and blood samples are collected for peripheral blood mononuclear cell, plasma, and serum analyses every 2 weeks during the initial 12-week observation period. Liver biopsy and treatment are offered if spontaneous clearance is not apparent within this period. Histopathology studies on this cohort showed that fibrogenesis occurred early and was markedly accelerated in this group of subjects: 17 of the first 20 biopsies, performed at a median of 4.3 months after the first noted increase in ALT levels, revealed stage 2 (of 4, Scheuer scale) fibrosis, a much greater number than reported in patients who acquired HCV infection before HIV infection. Age and male gender may contribute to this rapid fibrosis progression, but no other known risk factors for fibrosis explain these findings. Treatment with pegylated interferon and weight-based ribavirin during the acute phase resulted in a 70% sustained viral response rate. Early spontaneous clearance occurred in approximately 15% of patients, but was not related to the occurrence of symptomatic hepatitis. Ongoing work centers on understanding factors contributing to the accelerated fibrosis progression, maximizing treatment response, and characterizing factors that are contributing to this ongoing outbreak of acute HCV infection among HIV-infected men who have sex with men in New York City. Investigators of the Philadelphia Cohort collaborate in this study to characterize early immunologic responses in HIV-infected patients. Fierer D, Branch AD. Gastroenterology. 2009;1(136):26-31.

Mutations in the Hepatitis C Virus Core Gene Are Associated with Advanced Liver Disease and Hepatocellular Carcinoma

Hepatitis C virus (HCV) infection can promote the development of hepatocellular carcinoma (HCC). Published data implicate the HCV core gene in oncogenesis. The authors tested the hypothesis that core gene sequences from HCC patients differ from those of patients without cirrhosis/HCC. Full-length HCV sequences from HCC patients and controls were obtained from the investigators and GenBank and compared with each other. A logistic regression model was developed to predict the HCC risk of individual point mutations and other sequence features. Mutations in partial sequences (bases 36-288) from HCC patients and controls were also analyzed. The first base of the AUG start codon was designated position1. A logistic regression model developed through

analysis of full-length core gene sequences identified seven polymorphisms significantly associated with increased HCC risk (36G/C, 209A, 271U/C, 309A/C, 435A/C, 481A, and 546A/C) and an interaction term (for 209A-271U/C) that had an odds ratio <1.0. Three of these polymorphisms could be analyzed in the partial sequences. Two of them, 36G/C and 209A, were again associated with increased HCC risk, but 271U/C was not. The odds ratio of 209A-271U/C was not significant. HCV core genes from patients with and without HCC differ at several positions. Of interest, 209A has been associated with IFN resistance and HCC in previous studies. These findings suggest that HCV core gene sequence data might provide useful information about HCC risk. Prospective investigation is needed to establish the temporal relationship between appearance of the viral mutations and development of HCC. Fishman SL, Factor SH, Balestrieri C, Fan X, DiBisceglie AM, Desai SM, Benson G, and Branch AD. Clin Cancer Res. 2009;15(9):3205-13.

Heroin in Brown, Black and White: Structural Factors and Medical Consequences in the US Heroin Market

Heroin coming into the United States historically comes from three widely dispersed geographical regions: Southwest Asia, Southeast Asia and Mexico. A fourth source of US-bound heroin, from Colombia, originated in the early 1990s. The fact that the four heroin sources produce differing morphologies and qualities of heroin has not been critically examined. In addition, it is not well established how the contemporary competing dynamics of interdiction, or restriction of heroin flows across international boundaries, and neoliberal, e.g., global expansion of free trade, policies are affecting heroin markets. This paper will highlight changes in the US heroin market, including source trends, the political economy of the now dominant source and the resultant effects on the heroin risk environment by US region. Using a structural and historical framework this paper examines two decades of secondary data sources, including government and drug control agency documents, on heroin flows together with published work on the political and economic dynamics in Latin America. Co-occurring neoliberal economic reforms may have contributed to paradoxical effects of US/Colombian interdiction efforts. Since entering the US market, heroin from Colombia has been distributed at a much higher quality and lower retail price. An increasingly exclusive market has developed with Mexican and Colombian heroin gaining market share and displacing Asian heroin. These trends have had dramatic effects on the risk environment for heroin consumers. An intriguing factor is that different global sources of heroin produce substantially different products. Plausible associations exist between heroin source/form and drug use behaviors and harms. For example, cold water-soluble powdered heroin (sources: Asia, Colombia) may be associated with higher HIV prevalence in the US, while low-solubility "black tar" heroin (BTH; source: Mexico) is historically used in areas with reduced HIV prevalence. BTH is associated with soft tissue infections caused by Clostridium bacteria. The authors conclude that the source and type of heroin are structural factors in the risk environment of heroin users: source dictates distribution and type predicts practice. How specific types of heroin are used and with what risk is therefore distributed geographically. Continued flux in the heroin market and its effects on the risk environment for drug users deserves further attention. Ciccarone D. International Journal of Drug Policy. 2009;3(20) 277-82.

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

Anti-platelet integrin GPIIIa49-66 Ab induces complement-independent platelet oxidative fragmentation and death by generation of platelet peroxide following NADPH oxidase activation. A C-terminal 385 amino acid fragment of ADAMTS-18 (A Disintegrin Metalloproteinase with Thrombospondin motifs produced in

endothelial cells) induces oxidative platelet fragmentation in an identical kinetic fashion as anti-GPIIIa49-66 Ab. Endothelial cell ADAMTS-18 secretion is enhanced by thrombin and activated by thrombin cleavage to fragment platelets. Platelet aggregates produced ex vivo with ADP or collagen and fibrinogen are destroyed by the C-terminal ADAMTS-18 fragment. Anti-ADAMTS-18 Ab shortens the tail vein bleeding time. The C-terminal fragment protects against FeCI3 induced carotid artery thrombosis as well as cerebral infarction in a post-ischemic stroke model. Thus, a new mechanism is proposed for platelet thrombus clearance, via platelet oxidative fragmentation induced by thrombin cleavage of ADAMTS-18. Li Z, Nardi MA, Li YS, Zhang W, Pan R, Dang S, Yee H, Quarterma D, Jonas S, Karpatkin S. Blood. 2009; Feb (Epub ahead of print).

Medical Comorbidity in Patients with Schizophrenia and Alcohol Dependence

Schizophrenia and alcohol dependence are major risk factors for a variety of medical problems, yet there has been little research on the medical status of patients in whom both conditions coexist. The investigators assessed the prevalence and severity of medical illness in 80 patients with schizophrenia or schizoaffective disorder and comorbid alcohol use disorders who entered a controlled trial of monitored naltrexone treatment, and analyzed the relationship between medical illness burden and demographic variables, alcohol and other substance use, and psychosis. Participants underwent physical examination, laboratory tests, medical record review and standardized assessments of medical illness burden, alcohol and other substance use, and psychosis. Nested block multiple regression analyses were used to assess the contribution to illness burden made by demographic variables, alcohol and substance use, and psychosis severity. Eighty-three percent of participants had at least one chronic medical illness, hypertension being the most common (43%). Medical comorbidity in this cohort was more severe than for schizophrenia patients in the CATIE trial (Chwastiak L, Rosenheck R, McEvoy JP, Keefe RS, Swartz MS, Lieberman JA. Interrelationships of psychiatric symptom severity, medical comorbidity, and functioning in schizophrenia. Psychiatr Serv. 2006;57(8):1102-9.); the prevalence of hypertension, chronic obstructive pulmonary disease, and coronary artery disease, was more than twice greater. Medical illness burden correlated with alcohol use severity, but appeared to be independent of other substance use or psychosis severity. Patients with co-occurring alcohol use disorder may have significantly more medical illness burden than patients with schizophrenia or schizoaffective disorder alone. Interventions to reduce alcohol use may be necessary to lessen medical morbidity. Batki SL, Meszaros ZS, Strutynski K, Dimmock JA, Leontieva L, Ploutz-Snyder R, Canfield K, Drayer RA. Schizophr Res. 2009; 107(2-3):139-46.

Selection Pressure from Neutralizing Antibodies Drives Sequence Evolution during Acute Infection with Hepatitis C Virus

Despite recent characterization of hepatitis C virus-specific neutralizing antibodies, it is not clear to what extent immune pressure from neutralizing antibodies drives viral sequence evolution in vivo. This lack of understanding is particularly evident in acute infection, the phase when elimination or persistence of viral replication is determined and during which the importance of the humoral immune response has been largely discounted. The investigators analyzed envelope glycoprotein sequence evolution, and neutralization of sequential autologous hepatitis C virus pseudoparticles in eight individuals throughout acute infection. Amino acid substitutions occurred throughout the envelope genes, primarily within the hypervariable region 1 of E2. When individualized pseudoparticles expressing sequential envelope sequences were used to measure neutralization by autologous sera, antibodies

neutralizing earlier sequence variants were detected at earlier time points than antibodies neutralizing later variants, indicating clearance and evolution of viral variants in response to pressure from neutralizing antibodies. To demonstrate the effects of amino acid substitution on neutralization, site-directed mutagenesis of a pseudoparticle envelope sequence revealed amino acid substitutions in hypervariable region 1 that were responsible for a dramatic decrease in neutralization sensitivity over time. In addition, high-titer neutralizing antibodies peaked at the time of viral clearance in all spontaneous resolvers, while chronically evolving subjects displayed low-titer or absent neutralizing antibodies throughout early acute infection. These findings indicate that during acute hepatitis C virus infection in vivo, virus-specific neutralizing antibodies drive sequence evolution and, in some individuals, play a role in determining the outcome of infection. Dowd KA, Netski DM, Wang XH, Cox AL, Ray SC. Gastroenterology. 2009; Mar. (Epub ahead of print).

Predictors of Insulin Resistance Among Hispanic Adults Infected with or At Risk of Infection with the Human Immunodeficiency Virus and Hepatitis C Virus

Both the human immunodeficiency (HIV) and hepatitis C (HCV) viruses have been associated with insulin resistance (IR). However, our understanding of the prevalence of IR, the underlying mechanisms and predisposing factors is limited, particularly among minority populations. The investigators conducted a study of 333 Hispanic adults including: 76 HIV mono-infected, 62 HCV mono-infected, 97 HIV/HCV co-infected and 98 uninfected controls with a specific focus on HCV infection and liver injury as possible predictors of IR. IR was measured using the Quantitative Insulin Sensitivity Check Index (QUICKI). The majority (55-69%) of participants in all groups had QUICKI values <0.350. Body mass index was associated with IR in all groups. Triglycerides were associated with IR in the uninfected control group only (-1.83, SE = 0.58, P = 0.0022). HCV was associated with IR in participants infected with HIV (-0.012, SE = 0.0046, P = 0.010). Liver injury, as measured by score to assess liver injury (FIB-4) score, was significantly associated with IR independently of HCV infection (-0.0035, SE = 0.0016, P = 0.027). In the HIV/HCV co-infected group, treatment with nucleoside reverse-transcriptase (RT) inhibitors plus non-nucleoside RT inhibitors (-0.021, SE = 0.080, P = 0.048), but not protease inhibitors (-0.000042, SE = 0.0082, P = 0.96) was associated with IR. HCV infection and antiretroviral agents, including nucleoside RT inhibitor plus non-nucleoside RT inhibitor treatment are contributors to IR in HIV infection. Liver injury, as measured by the FIB-4 score, is a predictor of IR independently of HCV infection. Castaneda-Sceppa C, Bermudez OI, Wanke C, Forrester JE. J Viral Hepat. 2008;15(12):878-87.

Short-Term Clarithromycin Administration Impairs Clearance and Enhances Pharmacodynamic Effects of Trazodone but Not of Zolpidem

The kinetic and dynamic interactions of 5 mg zolpidem and 50 mg trazodone with 500 mg clarithromycin (4 doses given over 32 h) were investigated in a 5-way double crossover study with 10 healthy volunteers. The five treatment conditions were: placebo + placebo; zolpidem + placebo; zolpidem + clarithromycin; trazodone+ placebo; and trazodone + clarithromycin. Coadministration of clarithromycin increased trazodone area under the curve, prolonged elimination half-life, increased peak plasma concentration (Cmax), and reduced oral clearance. In contrast, clarithromycin had no significant effect on any kinetic parameter for zolpidem. Clarithromycin did not potentiate sedation caused by zolpidem. However, clarithromycin coadministered with trazodone significantly increased self- and observer-rated sedation and ratings of feeling "spacey." Thus, short-term clarithromycin coadministration significantly impairs trazodone clearance, elevates plasma concentrations, and

enhances sedative effects. However, clarithromycin has no significant kinetic or dynamic interaction with zolpidem. Clin Pharmacol Ther. 2009; advance online publication 25 February 2009. doi:10.1038/clpt.2008.293. Farkas D, Volak L, Harmatz J, von Moltke L, Court M, Greenblatt D. Clin Pharmacol Ther. 2009; Feb (Epub ahead of print).

Ritonavir Greatly Impairs CYP3A Activity in HIV Infection with Chronic Viral Hepatitis

Ritonavir is a powerful inhibitor of cytochrome P450 3A (CYP3A) that metabolizes many antiretrovirals. The investigators examined the effect of ritonavir and of chronic viral hepatitis (CVH) status on CYP3A activity. Twenty-six HIV-positive men (13 with CVH, 16 on chronic ritonavir-based highly active antiretroviral therapy) received oral and intravenous midazolam, a probe for CYP3A phenotypic activity. CYP3A activity was expressed as oral clearance of the midazolam probe. In HIV-positive subjects not on ritonavir, CYP3A activity (mean +/- SD) did not differ between subjects by CVH (no CVH, controls: 28.5 +/- 9.0 vs. CVH+: 23.2 +/- 6.2 mL/min/kg, not significant). In those on ritonavir (R), CYP3A activity was 7% of controls (R: 2.1 +/- 0.8 vs. no R 28.5 +/- 9.0 mL/min/kg, $P < 0.0004$). CYP3A activity in subjects on ritonavir and with CVH was further reduced to 4% of controls (no CVH, R+ 2.1 +/- 0.8 vs. R+, CVH+ 1.0 +/- 0.4 mL/min/kg, $P < 0.006$). Ritonavir markedly decreases CYP3A activity. In the presence of CVH, ritonavir-based therapy further reduces CYP3A activity by half. Coinfection with CVH impairs CYP3A activity in the presence of the CYP3A inhibitor ritonavir. Knox TA, Oleson L, von Moltke LL, Kaufman RC, Wanke CA, Greenblatt DJ. J Acquir Immune Defic Syndr. 2008;49(4):358-68.

Methamphetamine Enhances HIV-1 Infectivity in Monocyte Derived Dendritic Cells

The US is currently experiencing an epidemic of methamphetamine (Meth) use as a recreational drug. Recent studies also show a high prevalence of HIV-1 infection among Meth users. The investigators report that Meth enhances HIV-1 infectivity of dendritic cells as measured by multinuclear activation of a galactosidase indicator (MAGI) cell assay, p24 assay, and LTR-RU5 amplification. Meth induces increased HIV-1 infection in association with an increase in the HIV-1 coreceptors, CXCR4 and CCR5, and infection is mediated by downregulation of extracellular-regulated kinase (ERK2) and the upregulation of p38 mitogen-activated protein kinase (MAPK). A p38 inhibitor (SB203580) specifically reversed the Meth-induced upregulation of the CCR5 HIV-1 coreceptor. The dopamine D2 receptor antagonist RS +/- sulpiride significantly reversed the Meth-induced upregulation of CCR5, demonstrating that the Meth-induced effect is mediated via the D2 receptor. These studies report for the first time that Meth fosters HIV-1 infection, potentially via upregulating coreceptor gene expression. Further, Meth mediates its regulatory effects via dopamine receptors and via downregulating ERK2 with a reciprocal upregulation of p38 MAPK. Elucidation of the role of Meth in HIV-1 disease susceptibility and the mechanism through which Meth mediates its effects on HIV-1 infection may help to devise novel therapeutic strategies against HIV-1 infection in high-risk Meth-using HIV-1-infected subjects. Nair MP, Saiyed ZM, Nair N, Gandhi NH, Rodriguez JW, Boukli N, Provencio-Vasquez E, Malow RM, Miguez-Burbano MJ. J Neuroimmune Pharmacol. 2009;4(1):129-39.

Characteristics and Treatment Outcomes Among HIV-infected Individuals in the Australian Trial in Acute Hepatitis C

The Australian Trial in Acute Hepatitis C (ATAHC) is a National Institutes of Health-funded prospective cohort study of the natural history and efficacy of

treatment in individuals with recently acquired hepatitis C. Enrollment is open to both human immunodeficiency virus (HIV)-infected and -uninfected individuals. The aim of this article was to evaluate characteristics and virological outcomes among HIV-infected individuals enrolled in ATAHC. Eligibility criteria included the first positive result of testing for anti-hepatitis C virus (HCV) antibody within 6 months and either clinical hepatitis diagnosed within the past 12 months or documented anti-HCV seroconversion within the past 24 months. Of the initial 103 patients enrolled, 27 (26%) were HIV infected. HIV-infected patients were more likely to be older, to have HCV genotype 1 infection and high levels of HCV RNA at baseline than were HCV-mono-infected patients. Sexual acquisition accounted for the majority (56%) of HCV infections among HIV-infected patients, compared with only 8% of HCV-mono-infected patients. The median duration from estimated HCV infection to treatment was 30 weeks. Treatment with 24 weeks of pegylated interferon and ribavirin resulted in rates of undetectability of HCV RNA of 95%, 90%, and 80% at weeks 12, 24, and 48, respectively. Undetectability at week 4 was achieved in 44% of patients and yielded positive and negative predictive values for sustained virological response of 100% and 33%, respectively. Significant differences were demonstrated between HIV-infected and HIV-uninfected individuals enrolled in ATAHC. Treatment responses among HIV-infected individuals with both acute and early chronic infection are encouraging and support regular HCV screening of high-risk individuals and early treatment for recently acquired HCV infection. Collaborators: Kaldor J, Dore G, Matthews G, Marks P, Lloyd A, Hellard M, Haber P, Ffrench R, White P, Rawlinson W, Day C, van Beek I, McCaughan G, Madden A, Dolan K, Farrell G, Crofts N, Sievert W, Baker D, Yeung B, Acraman B, Petoumenos K, Amin J, Doab A, Carroll T, Nguyen O, Teutsch S, Li H, Oon A, Cameron B, Jacka B, Pan Y, Flynn J, Goy K, Shaw D, Haber P, Sasadeusz J, Crawford D, Phung N, George J, Bloch M, Hughes B, Mollison L, Roberts S, Desmond P. Clin Infect Dis. 2009;48(5):650-8.

Exceeding the Limits of Liver Histology Markers

Alternatives to liver biopsy for staging liver disease caused by hepatitis C virus (HCV) have not appeared accurate enough for widespread clinical use. the investigators characterized the magnitude of the impact of error in the "gold standard" on the observed diagnostic accuracy of surrogate markers. The investigators calculated the area under the receiver operating characteristic curve (AUROC) for a surrogate marker against the gold standard (biopsy) for a range of possible performances of each test (biopsy and marker) against truth and a gradient of clinically significant disease prevalence. In the 'best' scenario where liver biopsy accuracy is highest (sensitivity and specificity of biopsy are 90%) and the prevalence of significant disease 40%, the calculated AUROC would be 0.90 for a perfect marker (99% actual accuracy) which is within the range of what has already been observed. With lower biopsy sensitivity and specificity, AUROC determinations >0.90 could not be achieved even for a marker that perfectly measured disease. The investigators demonstrate that error in the liver biopsy result itself makes it impossible to distinguish a perfect surrogate from ones that are now judged by some as clinically unacceptable. An alternative gold standard is needed to assess the accuracy of tests used to stage HCV-related liver disease. Mehta SH, Lau B, Afdhal NH, Thomas DL. J Hepat. 2009;50(1):36-41. Comment in J Hepatol. 2009;50(1):1-3.

Substance Use in Vulnerable Patients with Orofacial Injury: Prevalence, Correlates, and Unmet Service Needs

A large portion of injuries treated at urban trauma centers are preventable. Substance use presents as one of the most common antecedent risk factors. Substance use characteristics of vulnerable adults treated for intentional orofacial injury at a regional trauma center were investigated. Patients (N =

154) presenting with intentional facial injury were recruited. Patients were considered eligible for recruitment if they were adults, recently used alcohol or drugs, and had a fracture within the 30 days preceding recruitment that involved the jaw, orbit, nose, or cheekbone as determined by clinical history, examination, and radiographic findings and that injury was due to interpersonal violence. This patient cohort evidenced significant levels of alcohol use, with 58% of the patient cohort meeting the criteria for problem drinking. Although lower than alcohol use rates, the reported use of illicit drugs was substantial. Almost half of the sample reported other substance use in the previous month, with 24% meeting the criteria for problem drug use. Despite the very high percentage of individuals needing alcohol or drug treatment, only a small proportion of the patient sample reported having been seen by a professional for alcohol or drug treatment. Integrating substance use services into trauma care is warranted and is further discussed. Murphy DA, Shetty V, Resell J, Zigler C, Yamashita DD. J Trauma. 2009;66(2):477-84.

Naturally Occurring Dominant Resistance Mutations to Hepatitis C Virus Protease and Polymerase Inhibitors in Treatment-Na•ve Patients

Resistance mutations to hepatitis C virus (HCV) nonstructural protein 3 (NS3) protease inhibitors in <1% of the viral quasispecies may still allow >1000-fold viral load reductions upon treatment, consistent with their reported reduced replicative fitness in vitro. Recently, however, an R155K protease mutation was reported as the dominant quasispecies in a treatment-na•ve individual, raising concerns about possible full drug resistance. To investigate the prevalence of dominant resistance mutations against specifically targeted antiviral therapy for HCV (STAT-C) in the population, HCV genome sequences were analyzed from 507 treatment-na•ve patients infected with HCV genotype 1 from the United States, Germany, and Switzerland. Phylogenetic sequence analysis and viral load data were used to identify the possible spread of replication-competent, drug-resistant viral strains in the population and to infer the consequences of these mutations upon viral replication in vivo. Mutations described to confer resistance to the protease inhibitors Telaprevir, BILN2061, ITMN-191, SCH6 and Boceprevir; the NS5B polymerase inhibitor AG-021541; and to the NS4A antagonist ACH-806 were observed mostly as sporadic, unrelated cases, at frequencies between 0.3% and 2.8% in the population, including two patients with possible multidrug resistance. Collectively, however, 8.6% of the patients infected with genotype 1a and 1.4% of those infected with genotype 1b carried at least one dominant resistance mutation. Viral loads were high in the majority of these patients, suggesting that drug-resistant viral strains might achieve replication levels comparable to nonresistant viruses in vivo. The authors concluse that naturally occurring dominant STAT-C resistance mutations are common in treatment-na•ve patients infected with HCV genotype 1. Their influence on treatment outcome should further be characterized to evaluate possible benefits of drug resistance testing for individual tailoring of drug combinations when treatment options are limited due to previous nonresponse to peginterferon and ribavirin. Kuntzen T, Timm J, Berical A, Lennon N, Berlin AM, Young SK, Lee B, Heckerman D, Carlson J, Reyor LL, Kleyman M, McMahon CM, Birch C, Schulze Zur, Wiesch J, Ledlie T, Koehrsen M, Kodira C, Roberts AD, Lauer GM, Rosen HR, Bihl F, Cerny A, Spengler U, Liu Z, Kim AY, Xing Y, Schneidewind A, Madey MA, Fleckenstein JF, Park VM, Galagan JE, Nusbaum C, Walker BD, Lake-Bakaar GV, Daar ES, Jacobson IM, Gomperts ED, Edlin BR, Donfield SM, Chung RT, Talal AH, Marion T, Birren BW, Henn MR, Allen TM. Hepatology. 2008;48(6):1769-78.

The Risk of Emergency Room Treatment Due to Overdose in Injection Drug Users

This cohort study was conducted to identify risk factors for lifetime emergency

room treatment due to overdose in injection drug users. Data of 1049 patients on admission for opioid detoxification were analyzed. More than every third injection drug user (34.7%) experienced emergency room treatment due to an overdose. Using multiple logistic regression not living with a significant other drug user (odds ratio [OR] = 1.78, P = .002), history of suicide attempt (OR = 3.0, P = .000), daily use of barbiturates (OR = 2.17, P = .006) and cannabis (OR = 1.89, P = .001) were independently associated with emergency room treatment, whereas shorter duration of opioid use (OR = 0.23, P = .001) was independently associated with lack of emergency room treatment. Suicidal thoughts and multiple use of central nervous system depressants should be considered in injection drug users entering the emergency room due to an overdose. The authors conclude that emergency rooms should be seen as important places for offering further assistance (e.g., counseling) or referral to an addiction unit to drug users. Backmund M, Schuetz C, Meyer K, Edlin BR, Reimer J. J Addict Dis. 2009;28(1):68-73.

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. The investigators compared elastography with histologic methods among hepatitis C virus (HCV)-infected and human immunodeficiency virus (HIV)-HCV-coinfected participants in an urban, predominantly black study population. Participants recruited from the AIDS Linked to the Intravenous Experience and the Johns Hopkins HIV Clinical Cohort studies underwent elastography to determine liver stiffness measurements. Liver biopsy specimens were staged F0-F4 in accordance with the Metavir score. Diagnostic accuracy and determination of liver stiffness cutoff values, compared with histologic methods, were determined by receiver operating characteristic analysis. Logistic regression methods identified parameters associated with discordant classification status. Of 192 participants, 139 (72%) were coinfected with HIV and HCV, 121 (63%) had insignificant fibrosis, and 48 (25%) had cirrhosis. Overall, the area-under-the-curve receiver operating characteristic was 0.87 for detection of both significant fibrosis (95% confidence interval, 0.82-0.92) and cirrhosis (95% confidence interval, 0.81-0.93). With use of cutoff values of 9.3 kPa for fibrosis and 12.3 kPa for cirrhosis, 79%-83% of participants were correctly classified by liver stiffness measurement (compared with histologic methods); accuracy appeared to be higher among HIV-uninfected participants than among HIV-infected participants. Most discordance occurred when liver stiffness measurements indicated liver disease and histologic examination did not (in 16% of participants); the patients with these discordant results were more likely to have attributes that increased the odds of significant fibrosis, such as elevated serum fibrosis markers or HIV-related immunosuppression, compared with persons in whom low fibrosis was predicted by both examination of a biopsy specimen and elastography. The authors conclude 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 GD, Astemborski J, Mehta SH, Spoler C, Fisher C, Allen D, Higgins Y, Moore RD, Afdhal N, Torbenson M, Sulkowski M, Thomas DL. Clin. Infect. Dis. 2009;48(7):963-72.

Safety and Antiviral Activity of Albinterferon Alfa-2b in Prior Interferon Nonresponders with Chronic Hepatitis C

Pegylated interferon alfa-2a/2b is used in combination with ribavirin to treat patients with chronic hepatitis C (CHC), although many do not achieve a sustained virologic response (SVR). Albinterferon alfa-2b, a recombinant

protein consisting of interferon alfa-2b fused to human albumin, may increase drug exposure. This phase 2 study evaluated the safety/efficacy of albinterferon in CHC patients who had not responded to interferon-based regimens. A total of 115 patients were assigned to 5 groups given 1200 microg albinterferon every 4 weeks or 900, 1200, 1500, or 1800 microg every 2 weeks, plus oral ribavirin, for 48 weeks. The primary efficacy end point was achievement of an SVR after 24 weeks. Treatment was extended to 72 weeks for 6 slow responders who were negative for hepatitis C virus RNA after 24 weeks. The types of adverse events were similar across groups; the overall discontinuation rate as a result of adverse events was 10.4%. Reductions in absolute neutrophil counts were less frequent in the every 4 weeks group and comparable among the every 2 weeks groups. The overall SVR rate was 17% (11% for previous nonresponders to pegylated interferon-alfa/ribavirin with genotype 1 infection). An SVR occurred in 3 of 6 slow responders by 72 weeks. The greatest reductions in hepatitis C virus RNA in nonresponders to pegylated interferon-alfa/ribavirin with genotype 1 infection were observed in the 1800-microg group. In patients with CHC who did not respond to interferon-based regimens, higher doses of albinterferon had significant early antiviral activity and a low incidence of adverse events, with the types of adverse events similar to those observed with interferon. Nelson DR, Rustgi V, Balan V, Sulkowski MS, Davis GL, Muir AJ, Lambiase LR, Dickson RC, Weisner RH, Fiscella M, Cronin PW, Pulkstenis E, McHutchison JG, Subramanian GM. Clin. Gastroenterol. Hepatol. 2009;7(2):212-8.

Efficacy and Safety of Peginterferon Alfa-2a/Ribavirin in Methadone Maintenance Patients: Randomized Comparison of Direct Observed Therapy and Self-Administration

Adherence to chronic hepatitis C (CHC) treatment may be particularly challenging in methadone maintenance patients. The investigators assessed the safety, tolerability, and efficacy of peginterferon alfa-2a/ribavirin treatment in methadone maintenance patients previously untreated for CHC. Patients were randomized 1:1 to direct observed therapy (DOT) or self-administration (SA) of peginterferon alfa-2a. DOT patients were seen weekly at methadone clinics; SA patients were seen less frequently, only at investigative sites. Genotype 1-infected patients were treated for 48 wk with peginterferon alfa-2a (180 microg/wk)/ribavirin (1,000/1,200 mg/day); genotypes 2- and 3-infected patients were treated for 24 wk with peginterferon alfa-2a (180 microg/wk)/ribavirin (800 mg/day). Based on defined efficacy stopping rules, 77% (37/48) completed their targeted length of treatment, and 44% (21/48) achieved sustained virologic response (SVR). Two DOT and 3 SA patients were withdrawn for safety reasons and 6 and 9, respectively, for nonsafety reasons. Over 60% and 50% of each group were >80% compliant with the planned cumulative doses of peginterferon alfa-2a and ribavirin, respectively, and over 60% with overall treatment duration. SVR rates were 54% (13/24) for DOT and 33% (8/24) for SA; 23% (3/13) and 38% (6/16), respectively, for genotype 1 and 91% (10/11) and 25% (2/8), respectively, for genotypes 2 and 3. Stepwise logistic regression analysis, showed that DOT (vs SA; OR 3.27, 95% CI 0.90-11.91, P = 0.073) and Caucasian race (vs Other; OR 13.31, 95% CI 1.42-124.71, P = 0.023) were predictors of SVR. Peginterferon alfa-2a/ribavirin can be used safely and successfully in CHC patients receiving methadone maintenance. Bonkovsky HL, Tice AD, Yapp RG, Bodenheimer HC Jr, Monto A, Rossi SJ, Sulkowski MS. Am. J. Gastroenterol. 2008 Nov 103(11):2757-65.

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

Injection drug users constitute 60% of the more than 4 million people in the United States with hepatitis C virus (HCV), including many methadone maintenance patients. Few data exist describing clinical outcomes for patients receiving HCV treatment on-site in methadone maintenance settings. In this retrospective study, clinical outcomes for 73 patients receiving HCV treatment are described on-site in a methadone maintenance treatment program. Fifty-five percent of patients achieved end-of-treatment response, and 45% achieved sustained viral response. These treatment response rates are nearly equivalent to previously published HCV treatment response rates, despite high prevalences of ongoing drug use (49%), psychiatric comorbidity (67%), and HIV coinfection (32%). These data show that on-site HCV treatment with pegylated interferon and ribavirin is effective in methadone-maintained patients, many of whom are active drug users, psychiatrically ill, or HIV coinfected, and that methadone maintenance treatment programs represent an opportunity to safely treat chronic hepatitis C. Litwin AH, Harris KA Jr, Nahvi S, Zamor PJ, Soloway IJ, Tenore PL, Kaswan D, Gourevitch MN, Arnsten JH. J Subst Abuse Treat. 2008; Nov (Epub ahead of print).

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

Research Findings - Services Research

Buprenorphine and Methadone Maintenance in Jail and Post-Release: A Randomized Clinical Trial

Buprenorphine has rarely been administered as an opioid agonist maintenance therapy in a correctional setting. This study introduced buprenorphine maintenance in a large urban jail, Rikers Island in New York City. Heroin-dependent men not enrolled in community methadone treatment and sentenced to 10-90 days in jail (N= 116) were voluntarily randomly assigned either to buprenorphine or methadone maintenance, the latter being the standard of care for eligible inmates at Rikers. Buprenorphine and methadone maintenance completion rates in jail were equally high, but the buprenorphine group reported for their designated post-release treatment in the community significantly more often than did the methadone group (48% vs. 14%, $p < .001$). Consistent with this result, prior to release from Rikers, buprenorphine patients stated an intention to continue treatment after release more often than did methadone patients (93% vs. 44%, $p < .001$). Buprenorphine patients were also less likely than methadone patients to withdraw voluntarily from medication while in jail (3% vs. 16%, $p < .05$). There were no post-release differences between the buprenorphine and methadone groups in self-reported relapse to illicit opioid use, self-reported re-arrests, self-reported severity of crime or re-incarceration in jail. From this study, it appears that after initiating opioid agonist treatment in jail, continuing buprenorphine maintenance in the community appears to be more acceptable to offenders than continuing methadone maintenance. Magura S, Lee JD, Hershberger J, Joseph H, Marsh L, Shropshire C, Rosenblum A. Buprenorphine and methadone maintenance in jail and post-release: a randomized clinical trial. Drug Alcohol Depend. 2009;99:222-30.

Racial Disparities Persist in Low-Dose Methadone Maintenance

Previous research identified a persistent pattern of low-dosing among methadone maintenance programs. It is generally accepted that a therapeutic dose for patients in the maintenance phase of treatment is at or above 80mg/day. While there is likely variation around this target level, programs whose caseloads are receiving average doses below this threshold are described by the authors as "low dose" settings. This article adds additional waves of data to a longitudinal national survey to determine whether programs have made improvements in average dosage levels. Data were collected from a nationally representative sample of methadone treatment facilities in 1988 (n=172), 1990 (n=140), 1995 (n=116), 2000 (n=150), and 2005 (n=146). In 1988, fully 94.2% of patients in sampled programs were receiving doses under 80mg/day. By 2005, this number decreased to 56.3%. Random-effects regression models found that programs serving higher percentages of African-

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American and Hispanic clients were more likely to be characterized as low-dose settings, as were programs whose directors endorsed a 12-step approach to recovery. The proportion of programs with an average daily dose below recommended levels remains much higher than optimal. The stigma of methadone maintenance persists even within the opioid addiction treatment community, and impedes the delivery of evidence-based care. Racial minorities appear disproportionately affected by these patterns. Pollack HA, D'Aunno T. Dosage patterns in methadone treatment: results from a national survey, 1988-2005. Health Serv Res. 2008;43(6):2143-63.

Persistence of Virologic Benefits Following Directly Administered Antiretroviral Therapy (DAART) Among Drug Users: Results from a Randomized Controlled Trial

Although directly administered antiretroviral therapy (DAART) has demonstrated impressive biological benefits compared with self-administered therapy (SAT) among drug users, the persistence of DAART after transition to SAT has not been examined. A community-based, prospective, randomized controlled trial was conducted of 6 months of DAART compared with SAT. The primary outcome was the proportion of subjects who achieved virologic success at 6 months post-intervention, defined as either a 1.0 log10 reduction from baseline or HIV-1 RNA <400 copies per milliliter. Secondary outcomes included the change from baseline in HIV-1 RNA and CD4 lymphocyte count. Of the 53 subjects in the SAT arm and 88 subjects in the DAART arm, 52 and 82, respectively, provided blood samples at 6 months post-intervention. The DAART (n = 88) and SAT (n = 53) arms did not differ on virologic success (DAART 58.0% vs. SAT 56.6%, P = 0.64), mean reduction in log10 HIV-1 RNA (-0.79 vs. -0.31 log10 copies/mL, P = 0.53), or mean change in CD4 lymphocyte count (+60.2 vs. -15.4 cells/mL, P = 0.12). In the multivariate analysis, only high levels of social support significantly predicted virologic success. This analysis, from the first randomized controlled trial of DAART among active drug users, failed to show the persistence of the DAART intervention at improving virologic outcomes. Additional strategies are needed to ensure the on-treatment benefits persist following the cessation of DAART. Maru D, Bruce R, Walton M, Springer S, Altice F. Persistence of virologic benefits following directly administered antiretroviral therapy among drug users: results from a randomized controlled trial. J Acquir Immune Defic Syndr. 2009;50(2):176-81.

Important Economic Differences Found in This Study of Male and Female Methadone Maintenance Clients

Although the number of women entering drug treatment has increased in recent years, it remains considerably lower than the estimated number of women needing such treatment. Thus, the large numbers of out-of-treatment opioid-dependent women are unable to benefit from the proven ability of drug-abuse treatment—particularly methadone maintenance treatment—to reduce drug use, HIV-risk behaviors, and crime. For this study, gender differences were explored among 355 in- and out-of-treatment opioid-addicted adults in Baltimore. Addiction Severity Index and other variables were compared among: 1) in-treatment women vs. out-of-treatment women; 2) out-of-treatment: women vs. men; and, 3) in-treatment: women vs. men. Analysis indicated that in-treatment and out-of-treatment women worked less and used more cocaine than their male counterparts ($p < .01$). Moreover, out-of-treatment women used heroin and cocaine more often, spent more money on drugs, earned more illegal income, and had fewer treatments than in-treatment women ($p < .01$). It is important to note that in the analysis of gender differences, women reported more difficulties in employment than men. Findings indicate greater severity of drug and employment problems of opioid-addicted women and underline the need for gender-specific drug-treatment

services. Kelly S, Schwartz R, O 'Grady K, Mitchell S, Reisinger H, Peterson J, Agar M, Brown B. Gender differences among in- and out-of-treatment opioid-addicted individuals. Am J Drug Alcohol Abuse. 2009;35(1):38-42.

Clinicians' Attitudes Toward Evidence-Based Treatment Practices

To better understand the extent that empirically supported and promising substance abuse treatment approaches are implemented in community settings, a sample of California treatment providers were surveyed regarding their perceptions and use of several psychosocial and pharmacological treatment interventions. Program directors (n=30) and staff members (n=331) from diverse community settings rated the effectiveness and extent of use of various treatment interventions, and provided information on program and workforce characteristics via self-administered questionnaires. On average, program directors and staff rated the psychosocial treatment interventions as effective, with the exception of vouchers/motivational incentives. About half of the treatment providers did not know the effectiveness of certain pharmacological treatments, including buprenorphine and naltrexone. Respondents from the majority of programs (55%-80%) reported using Motivational Enhancement Therapy, Community Reinforcement Approach, and Supportive Expressive Psychotherapy. The extent that programs used several of the treatment interventions was related to organizational training and information resources. Variability in clinician ratings and use of these practices suggests the need for more aggressive and standardized training and research dissemination efforts. Herbeck D, Hser Y, Teruya C. Empirically supported substance abuse treatment approaches: a survey of treatment providers ' perspectives and practices. Addict Behav. 2008;33(5):699-712.

The Waterpipe: A Rapidly Developing Public Health Threat

This is a commentary by the author, a world authority on nicotine and tobacco, and a NIDA international grantee. The waterpipe, known in many cultures under different shapes and names (e.g. hookah, shisha, narghile), is a centuries-old tobacco use method that is witnessing a world-wide surge in popularity. This popularity is most noticeable among youths, and is surpassing cigarette smoking among this group in some societies. Many factors may have contributed to the recent waterpipe spread, including the introduction of sweetened/flavored waterpipe tobacco (known as Maassel), its reduced-harm perception, the thriving cafŽ culture, mass media and the internet. The passage of smoke through water on its way to the smoker underlies much of the common misperception that waterpipe use is less harmful than cigarettes. The health/addictive profile of waterpipe compared to cigarettes is largely un-researched and is likely to be influenced by the properties of smoke, duration and frequency of use, type of tobacco used, volume of smoke inhaled and the contribution of charcoal. However, the accumulation of evidence about the harmful and addictive potential of waterpipe use is outpacing the public health response to this health risk. A timely public health and policy action is needed in order to curb the emerging waterpipe smoking epidemic. Maziak W. The waterpipe: time for action. Addiction. 2008;103(11):1763-7.

First Study of Prevalence and Correlates of Illicit Methadone Use in New York City

Despite growing concern about illicit methadone use in the US and other countries, there is little data about the prevalence and correlates of methadone use in large urban areas. The authors assessed the prevalence and examined correlates of lifetime and recent illicit methadone use in New York City (NYC). 1,415 heroin, crack, and cocaine users aged 15-40 years were recruited in NYC between 2000 and 2004 to complete interviewer-administered questionnaires.

The researchers found that in multivariable logistic regression, non-injection drug users who used illicit methadone were more likely to be heroin dependent, less than daily methamphet-amine users and to have a heroin using sex partner in the last two months. Injection drug users who used illicit methadone were more likely to use heroin daily, share injection paraphernalia and less likely to have been in a detoxification program and to have not used marijuana in the last six months. The results overall suggest that illicit (or street) methadone use is likely not a primary drug of choice, but is instead more common in concert with other illicit drug use. Ompad D, Fuller C, Chan C, Frye V, Vlahov D, Galea S. Correlates of illicit methadone use in New York City: a cross-sectional study. BMC Public Health. 2008;8:375-81.

Psychiatric Disorders and Repeat Incarcerations: The Revolving Prison Door

Although numerous investigations have reported substantially elevated rates of psychiatric disorders among prison inmates compared with the general population, it is unclear whether mental illness is a risk factor for multiple episodes of incarceration. The authors examined this association in a retrospective cohort study of the nation's largest state prison system. The study population included 79,211 inmates who began serving a sentence between September 1, 2006, and August 31, 2007. Data on psychiatric disorders, demographic characteristics, and history of incarceration for the preceding 6-year period were obtained from statewide medical information systems and analyzed. Inmates with major psychiatric disorders (major depressive disorder, bipolar disorders, schizophrenia, and non-schizophrenic psychotic disorders) had substantially increased risks of multiple incarcerations over the 6-year study period. The greatest increase in risk was observed among inmates with bipolar disorders, who were 3.3 times more likely to have had four or more previous incarcerations compared with inmates who had no major psychiatric disorder. Prison inmates with major psychiatric disorders are more likely than those without to have had previous incarcerations. The authors recommend expanding interventions to reduce recidivism among mentally ill inmates. They discuss the potential benefits of continuity of care reentry programs to help mentally ill inmates connect with community-based mental health programs at the time of their release, as well as a greater role for mental health courts and other diversion strategies. Baillargeon J, Binswanger I, Penn J, Williams B, Murray O. Psychiatric disorders and repeat incarcerations: the revolving prison door. Am J Psychiatry. 2009;166(1):103-9.

Impact of Patient Race on Patient Experiences of Access and Communication in HIV Care

Patient-centered care--including the domains of access and communication--is an important determinant of positive clinical outcomes. The purpose of this study was to explore associations between race and HIV-infected patients' experiences of access and communication. This was a cross-sectional survey. Nine hundred and fifteen HIV-infected adults receiving care at 14 U.S. HIV clinics participated in the study. Dependent variables included patients' reports of travel time to their HIV care site and waiting time to see their HIV provider (access) and ratings of their HIV providers on always listening, explaining, showing respect, and spending enough time with them (communication). Multivariate logistic regression was used to estimate associations between patient race and dependent variables, and random effects models to estimate site-level contributions. Patients traveled a median 30 minutes (range 1-180) and waited a median 20 minutes (range 0-210) to see their provider. On average, blacks and Hispanics reported longer travel and wait times compared with whites. Adjusting for HIV care site attenuated this association. HIV care sites that provide services to a greater proportion of blacks and Hispanics may be more difficult to access for all patients. The majority of patients rated

provider communication favorably. Compared to whites, blacks reported more positive experiences with provider communication. Racial disparities were observed in patients' experience of access to care but not in patient-provider communication. Disparities were explained by poor access at minority-serving clinics. Efforts to make care more patient-centered for minority HIV-infected patients should focus more on improving access to HIV care in minority communities than on improving cross-cultural patient-provider interactions. Korthuis P, Saha S, Fleishman J, McGrath M, Josephs J, Moore R, Gebo K, Hellinger J, Beach M, Beach, M. Impact of patient race on patient experiences of access and communication in HIV care. J Gen Intern Med. 2008;23(12):2046-52.

Psychiatric Disorders, Particularly Alcohol Use Disorders, Are Common in College-Aged Populations

Although young adulthood is often characterized by rapid intellectual and social development, college-aged individuals are also commonly exposed to circumstances that place them at risk for psychiatric disorders. The objectives of this study are to assess the 12-month prevalence of psychiatric disorders, sociodemographic correlates, and rates of treatment among individuals attending college and their non-college-attending peers in the United States. Face-to-face interviews were conducted in the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (N = 43,093). Analyses were done for the subsample of college-aged individuals, defined as those aged 19 to 25 years who were both attending (n = 2188) and not attending (n = 2904) college in the previous year. The main measures were sociodemographic correlates and prevalence of 12-month DSM-IV psychiatric disorders, substance use, and treatment seeking among college-attending individuals and their non-college-attending peers. The investigators found that almost half of college-aged individuals had a psychiatric disorder in the past year. The overall rate of psychiatric disorders was not different between college-attending individuals and their non-college-attending peers. However, the unadjusted risk of alcohol use disorders was significantly greater for college students than for their non-college-attending peers (odds ratio = 1.25; 95% confidence interval, 1.04-1.50), although not after adjusting for background sociodemographic characteristics (adjusted odds ratio = 1.19; 95% confidence interval, 0.98-1.44). College students were significantly less likely (unadjusted and adjusted) to have a diagnosis of drug use disorder or nicotine dependence or to have used tobacco than their non-college-attending peers. Bipolar disorder was less common in individuals attending college. College students were significantly less likely to receive past-year treatment for alcohol or drug use disorders than their non-college-attending peers. Psychiatric disorders, particularly alcohol use disorders, are common in the college-aged population. Although treatment rates varied across disorders, overall fewer than 25% of individuals with a mental disorder sought treatment in the year prior to the survey. These findings underscore the importance of treatment and prevention interventions among college-aged individuals. Blanco C, Okuda M, Wright C, Hasin D, Grant B, Liu S, Olfson M. Mental health of college students and their non-college-attending peers: results from the National Epidemiologic Study on Alcohol and Related Conditions. Arch Gen Psychiatry. 2008; 65(12):1429-37.

Review of Adolescent Opioid Dependence: No Quick Fix - Despite Short Duration of Opioid Use

This review reports the results of an NIH-funded multisite randomized clinical trial of 2-week vs. 12-week buprenorphine-naloxone treatment of opioid-dependent patients aged 15 to 21 years (mean age, 19 years), in which both groups had their medication tapered at the end of their respective treatments. Nearly half reported injection use, and one-fifth had evidence of hepatitis C infection. The median duration of their opioid use was 1 year. The primary

finding is that the 12-week treatment with buprenorphine-naloxone was associated with greater treatment retention and decreased illicit opioid use—but only during the period that medication was provided. The study used a multisite design, appropriate eligibility criteria, rigorous methods, and cogent outcomes and provided long-term follow-up. The study had a number of methodological limitations, including the trial was too small to make strong conclusions regarding the safety of buprenorphine-naloxone in this population. Despite these concerns, it is apparent that adolescent opioid-dependent patients have greater abstinence while receiving buprenorphine-naloxone. The most important finding of this study is the rate of relapse in both treatment groups following the medication taper. Past-week opioid use did not differ by treatment condition at 12 weeks or 12 months and was reported by 38% to 55% and 53% to 72% of participants, respectively. This finding is of concern given the young age of the participants and their relatively short duration of opioid use. The implication is that adolescent opioid-dependent patients, like their adult counterparts, will likely need long-term, rather than short-term, opioid agonist treatment. This is consistent with trials in adults that have compared brief methadone and buprenorphine tapers with long-term treatment (6 months to 1 year) and have consistently demonstrated better outcomes with long-term treatment. Abstinence rates and retention in treatment are uniformly improved with provision of medication over longer periods of time. These trials, conducted in adults with longer durations of opioid dependence (e.g., 5-10 years), were not previously thought to be generalizable to adolescents. The unique finding of the study by Woody et al., that young opioid-dependent patients with relatively short durations of opioid use have high rates of relapse when provided with either brief or longer tapers of agonist medications, is sobering. The results of this trial should prompt clinicians to use caution when tapering buprenorphine-naloxone in adolescent patients who receive this medication. Supportive counseling; close monitoring for relapse; and, in some cases, naltrexone should be offered following buprenorphine tapers. From a research perspective, additional efforts are needed to provide a stronger evidence base from which to make recommendations for adolescents who use opioids. There is limited research on prevention of opioid experimentation and effective strategies to identify experimentation and intercede to disrupt the transition from opioid use to abuse and dependence. No information is available regarding the efficacy of treatment with medications such as methadone or buprenorphine-naloxone compared with non-agonist approaches (e.g., naltrexone) or non-pharmacologic approaches such as short-term rehabilitation or partial hospitalization programs. The high rate of relapse seen with both medication taper protocols in the current trial involving opioid-dependent adolescents, combined with the adverse social, legal, and infectious consequences of opioid dependence—and the risk for overdose with relapse—makes the need for rigorous evidence in this area urgent. These findings are another important reminder that there are no quick fixes for opioid dependence. Fiellin D. Treatment of adolescent opioid dependence: no quick fix. JAMA. 2008;300(17):2057-9.

Analysis of NSDUH Data Suggests Link between Ecstasy Use and Poor Academic Achievement

Data on 65,294 adolescents from the 2002-2005 National Survey on Drug Use and Health were used to examine the academic achievement of adolescents who reported using ecstasy (n=1,743) compared with those who did not use drugs (n=33,497), only used alcohol and/or tobacco (n=17,015), or used marijuana but did not use ecstasy. Multinomial regressions adjusting for demographics and survey year revealed that ecstasy users were four times the odds of reporting moderate grades as non-drug users to and 12 times the odds of reporting low grades (average grade of D or lower). This compares with marijuana users who had three and six times the odds of reporting moderate and low grades and alcohol/tobacco users who had less than 2 times the odds

of reporting either. Although this analysis did not establish causality, it does suggest that further research into the causal relationship between ecstasy use and academic achievement be investigated. Martins S, Alexandre P. The association of ecstasy use and academic achievement among adolescents in two U.S. national surveys. Addict Behav. 2009;34(1):9-16.

Barriers to Participation in Criminally-Mandated Treatment

This study addresses why some California Proposition 36 offenders did not enter drug treatment. Self-reported and administrative data were analyzed to compare the characteristics, perceptions, and re-arrest rates of 124 untreated and 1,335 treated offenders assessed by 30 sites in five California counties. Offenders were comparable in many domains at assessment; however, untreated offenders were younger, not employed, more criminally severe, and less motivated for treatment. Avoiding incarceration was the primary reason for choosing Proposition 36, but there were fewer untreated offenders who felt ready for treatment (12.9% vs. 35.7%) . Reasons for not entering treatment included re-arrest (31.6%), no desire for treatment (23.9%), and assignment to a program that was too far away (11.1%). Both groups had fewer total arrests after assessment, but recidivism was higher among untreated offenders. Evans E, Li L, Hser Y. Treatment entry barriers among California's Proposition 36 offenders. J Subst Abuse Treat. 2008;35:410-8.

Gender Differences in Generalized Anxiety Disorder: Results from a National Survey

The goals of this study were to assess gender differences in the epidemiology, comorbidity, and treatment-seeking patterns of DSM-IV generalized anxiety disorder (GAD) in the United States. The authors analyzed data derived from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions, a large cross-sectional survey of a representative sample (N = 43,093) of the U.S. population. The lifetime and 12-month male:female prevalence ratios of DSM-IV GAD were 1:1.9 and 1:2.2, respectively. Men with GAD had significantly higher rates of comorbid alcohol and drug use disorders, nicotine dependence, and antisocial personality disorder. Women with GAD had significantly higher rates of comorbid mood disorders (except bipolar disorder) and anxiety disorders (except social anxiety disorder). Men with GAD reported greater use of alcohol and drugs to help relieve GAD symptoms. GAD in women was associated with higher rates of family history of depression. Disability associated with GAD was greater in women than in men. Rates of treatment seeking for DSM-IV GAD were low for both genders, but particularly low among men. There are significant gender differences in the prevalence, comorbidity pattern, sociodemographic and clinical correlates, course, and treatment-seeking rates of persons with DSM-IV GAD. Increased recognition and treatment of GAD, particularly among men, could lead to substantial reductions in the societal and personal burden and improve the quality of life of those afflicted with this disorder. Vesga-L—pe O, Schneier F, Wang S, Heimberg R, Liu S, Hasin D, Blanco C. Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). J Clin Psychiatry. 2008;69(10):1606-16.

Integrating Buprenorphine Treatment Into Office-Based Practice: A Qualitative Study

Despite the availability and demonstrated effectiveness of office-based buprenorphine maintenance treatment (BMT), the systematic examination of physicians' attitudes towards this new medical practice has been largely neglected. To study this, the authors identified facilitators and barriers to the potential or actual implementation of BMT by office-based medical providers.

To accomplish this, a qualitative study using individual and group semi-structured interviews was undertaken. Twenty-three practicing office-based physicians in New England were studied. Interviews of these physicians were audiotaped, transcribed, and entered into a qualitative software program. The transcripts were thematically coded using the constant comparative method by a multidisciplinary team. It was found that: eighty percent of the physicians were white; 55% were women. The mean number of years since graduating medical school was 14 (SD = 10). The primary areas of clinical specialization were internal medicine (50%), infectious disease (20%), and addiction medicine (15%). Physicians identified physician, patient, and logistical factors that would either facilitate or serve as a barrier to their integration of BMT into clinical practice. Physician facilitators included promoting continuity of patient care, positive perceptions of BMT, and viewing BMT as a positive alternative to methadone maintenance. Physician barriers included competing activities, lack of interest, and lack of expertise in addiction treatment. Physicians' perceptions of patient-related barriers included concerns about confidentiality and cost, and low motivation for treatment. Perceived logistical barriers included lack of remuneration for BMT, limited ancillary support for physicians, not enough time, and a perceived low prevalence of opioid dependence in physicians' practices. It was concluded that addressing physicians' perceptions of facilitators and barriers to BMT is crucial to supporting the further expansion of BMT into primary care and office-based practices. Barry D, Irwin K, Fiellin D. Integrating buprenorphine treatment into office-based practice: a qualitative study. J Gen Intern Med. 2009;24(2):218-25.

Interest by Patients in Smoking Cessation Treatments

The authors surveyed 884 Vermont (VT) tobacco smokers by random digit dialing to determine past and future use of treatment. Among those who had recently attempted to quit, 61% had ever used a treatment, 21% had ever used a psychosocial treatment, and 57% had used a medication. Among those who planned to quit in the next month, 68% stated they would use a treatment, 35% would use a psychosocial treatment, and 62% would use a medication. The major predictors of past or future use of treatment were greater cigarettes per day, older age, being a woman, and seeing a health professional. Although this survey suggests many smokers have used or plan to use a smoking cessation treatment, program data indicate less than 10% of VT smokers who try to quit use the state quitline, counseling, or free medication provision. This study posed the follow-up question of; despite availability and awareness of their existence, why do smokers not use smoking cessation treatments, and can this be changed? Hughes J, Marcy T, Naud S. Interest in treatments to stop smoking. J Subst Abuse Treat. 2009;36(1):18-24.

Psychological Mediators of Bupropion Sustained-Release Treatment for Smoking Cessation

This study aimed to test simultaneously the understanding of the effects of bupropion sustained-release (SR) treatment on putative mediators and the understanding of determinants of post-quit abstinence, including withdrawal distress, cigarette craving, positive affect and subjective reactions to cigarettes smoked during a lapse. The specificity of bupropion SR effects was also tested in exploratory analyses. The study was performed using data from a randomized, placebo-controlled clinical trial of bupropion SR. Results were submitted to mediation analyses at the Center for Tobacco Research and Intervention, Madison, WI, USA. A total of 403 adult, daily smokers without contraindications to bupropion SR use were studied. Participants were assigned randomly to receive a 9-week course of bupropion SR or placebo pill and to receive eight brief individual counseling sessions or no counseling. Ecological momentary assessment ratings of smoking behavior and putative mediators

were collected pre- and post-quit. Results of structural equation and hierarchical linear models did not support the hypothesis that bupropion SR treatment improves short-term abstinence by reducing withdrawal distress or affecting the subjective effects of a lapse cigarette, but provided partial support for mediation by cigarette craving reduction and enhanced positive affect. Bupropion SR effects on point-prevalence abstinence at 1 month post-quit were also mediated partially by enhanced motivation to quit and self-efficacy. Results of this study provide some support for models of bupropion SR treatment and relapse and suggested that motivational processes may partially account for bupropion SR efficacy. McCarthy D, Piasecki T, Lawrence D, Jorenby D, Shiffman S, Baker T. Psychological mediators of bupropion sustained-release treatment for smoking cessation. Addiction. 2008;103(9):1521-33.

Government Databases Offer Accurate and Valuable Outcomes Data for Addiction Treatment Systems of Care

Using administrative data to evaluate health care outcomes has become increasingly common, but the reliability and validity of outcome measures based on cross-system data linkage have been little scrutinized. Applying a deterministic data matching methodology, records for 6545 Californians admitted to 43 substance abuse treatment programs between 2000 and 2001 were matched to administrative data acquired from three state agency databases for motor vehicle driving incidents, criminal history, and mental health services utilization. Administrative data confirmed self-report results in some measures (e.g., percent of people using mental health services, percent ever arrested) and augmented and improved accuracy for results in others (e.g., frequency of service utilization, and frequency of arrests). Agreement statistics between self-report and administrative data ranged from a low of 72% for lifetime psychiatric admissions (inpatient and outpatient) to 96 and 98% for past month and past 6-month mental health hospitalizations. Criminal justice data ranged between a low of 79% for lifetime arrests to 92% for arrests in the past month. Similar to findings based on the interview data, the administrative data also revealed improvements in several domains 1-year post-treatment compared to 1-year pre-treatment. Findings illustrate the value of using administrative records for substance abuse treatment outcome evaluation, while highlighting areas for improvement for future cross-system data linkage efforts. Hser Y, Evans E. Cross-system data linkage for treatment outcome evaluation: lessons learned from the California Treatment Outcome Project. Eval Program Plann. 2008;31(2):125-35.

Initiation Associated with Adolescent Treatment Outcomes in Models that Adjust for Selection Bias

419 adolescents who presented for intake at one of four Kaiser Permanente Northern California intensive structured outpatient chemical dependency programs were followed for 12 months to determine the relationship between treatment initiation and drug use and other behavioral outcomes. Initiation was operationalized as two treatment visits within 60 days of intake. As has been done in studies of other medical treatments but rarely in studies of substance abuse treatment, instrumental variable techniques using distance to the treatment facility and difficulties in transportation as instruments were used to address selection bias. In multivariate models controlling for baseline measurements of outcomes, individual and family characteristics, referral sources, and community and site characteristics, initiation was significantly associated with school attendance, employment, and abstinence. Patients who had initiated had a 48 percentage point higher probability of attending school and a 56 percentage point lower probability of being employed at 12 months than those who had not initiated. Patients who initiated also had a 19 percentage point higher probability of being abstinent at 12 months. The study

suggests the importance of testing for selection bias and controlling for it when necessary. Balsa AI, Homer JF, French MT, Weisner CM. Substance use, education, employment and criminal activity outcomes of adolescents in outpatient chemical dependency programs. J Behav Health Serv Res. 2009;36(1):75-95.

Correlates of HIV Testing Among South African Women with High Sexual and Substance-use Risk Behaviors

Despite its importance in raising awareness of HIV risk behavior and in linking HIV-positive individuals to care and treatment, research findings indicate that the HIV antibody testing rate in the general South African population remains relatively low, although knowledge of HIV testing services is high. The identification of important correlates of testing behavior can be used to improve HIV testing campaigns by refining messages that target individuals at highest risk for infection. This study uses data from an ongoing prevention intervention study in Pretoria, South Africa to identify factors that may have a greater influence on facilitating or hindering HIV testing among South African women who face a high risk for infection. The data for this study (n=425) are derived from the baseline interviews and HIV test results collected between June 2004 and January 2007. HIV testing for this study was significantly associated with education level, alcohol and cannabis use, sex trading, number of STI symptoms, physical abuse and number of visits to a clinic for medical treatment. Results suggest that more focused efforts need to be made to provide HIV testing to women who report substance use behavior, experience violence and report high-risk sexual behavior. Interventions also need to address denial of HIV infection and fear to test for HIV. Luseno W, Wechsberg W. Correlates of HIV testing among South African women with high sexual and substance-use risk behaviors. AIDS Care. 2009;21(2):178-84.

High Rate of Cigarette and Waterpipe Smoking Among Medical Students in Syria: A Cross-sectional Study

This study was performed to investigate tobacco use, beliefs and attitudes among medical students in Syria. Specifically, a cross-sectional study of a random sample of 570 medical students (first and fifth year) registered at the Damascus University Faculty of Medicine in 2006-2007 were given a self-administered questionnaire for demographic information, smoking behavior (cigarette, waterpipe), family and peer smoking, attitudes and beliefs about smoking and future role in advising patients to quit smoking. The authors found that the overall prevalence of tobacco use was 10.9% for cigarettes (15.8% men, 3.3% women), 23.5% for waterpipe (30.3% men, 13.4% women) and 7.3% for both (10.1% men, 3.1% women). Both smoking methods were more popular among the fifth year students (15.4% and 27%) compared to their younger counterparts (6.6% and 19.7%). Regular smoking patterns predominated for cigarettes (62%), while occasional use patterns predominated for waterpipes (83%). More than two thirds of students (69%) thought they might not address or would have difficulty addressing smoking in their future patients. From these findings, it was concluded that the level of tobacco use among Syrian medical students is alarming and highlights the rapidly changing patterns of waterpipe use, especially among female students. It was further suggested that medical schools should highlight this phenomenon and address it more efficiently in their curricula. Almerie M, Matar H, Salam M, Morad A, Abdulaal M, Koudsi A, Maziak W. Cigarettes and waterpipe smoking among medical students in Syria: a cross-sectional study. Int J Tuberc Lung Dis. 2008;12(9):1085-91. Benefit Limits in Health Insurance Plans in 2003 Provide Baseline against Which to Measure Success of Parity Data from a nationally-representative sample of health insurance plans (n=368) were used to determine the state of behavioral health care benefit limits and cost sharing in 2003. The survey revealed that among the plans 62%

of plans that imposed day limits, 50% imposed a 60 day limit on care for all behavioral health care combined, while 50% imposed day limits below that amount. Among the 16% that imposed separate day limits on substance abuse treatment, approximately 9% had limits of 60 days, 40% had limits of 30 days while 50% had limits of less than 30 days. Data from the survey also revealed that the average out-of-pocket costs of 20 substance abuse treatment limits was $400, the costs for 50 visits were $2,400. Hodgkin D, Horgan C, Garnick D, Merrick E. Benefit limits for behavioral health care in private health plans. Adm Policy Ment Health. 2009;36(1):15-23.

Health-related Quality of Life in HIV-infected Patients: The Role of Substance Use

HIV infection and substance use disorders are chronic diseases with complex contributions to health-related quality of life (HRQOL). A cross-sectional survey was conducted of 951 HIV-infected adults receiving care at 14 HIV Research Network sites in 2003 to estimate associations between HRQOL and specific substance use among HIV-infected patients. HRQOL was assessed by multi-item measures of physical and role functioning, general health, pain, energy, positive affect, anxiety, and depression. Mental and physical summary scales were developed by factor analysis. Linear regression was used to estimate adjusted associations between HRQOL and current illicit use of marijuana, analgesics, heroin, amphetamines, cocaine, sedatives, inhalants, hazardous/binge alcohol, and drug use severity. Current illicit drug use was reported by 37% of subjects. Mental HRQOL was reduced for current users [adjusted beta coefficient -9.66, 95% confidence interval [(CI]) -13.4, -5.94] but not former users compared with never users. Amphetamines and sedatives were associated with large decreases in mental (amphetamines: beta = -22.8 [95% CI -33.5, -12.0], sedatives: beta = -18.6 [95% CI -26.2, -11.0]), and physical HRQOL (amphetamines: beta = -11.5 [95% CI -22.6, -0.43], sedatives: beta = -13.2 [95% CI -21.0, -5.36]). All illicit drugs were associated with decreased mental HRQOL: marijuana (beta = -7.72 [95% CI -12.0, -3.48]), non-prescription analgesics (beta = -13.4 [95% CI -20.8, -6.07]), cocaine (beta = -10.5 [95% CI -16.4, -4.67]), and inhalants (beta = -14.0 [95% CI -24.1, -3.83]). Facilitating sobriety for patients with attention to specific illicit drugs represents an important avenue for elevating HRQOL in patients living with HIV. Korthuis P, Zephyrin L, Fleishman J, Saha S, Josephs J, McGrath M, Hellinger J, Gebo K, for the HIV Research Network. Health-related quality of life in HIV-infected patients: the role of substance use. AIDS Patient Care STDs. 2008;22(11):859-67.

The Dynamic Assessment and Referral System for Substance Abuse (DARSSA): Computer System to Screen and Refer Patients to Treatment

The Dynamic Assessment and Referral System for Substance Abuse (DARSSA) conducts a computerized substance abuse assessment; prints personalized summary reports that include tailored substance abuse treatment referral lists; and, for individuals who provide authorization, automatically faxes their contact information to a "best match" substance abuse treatment provider (dynamic referral). After piloting the program, the authors enrolled a sample of 85 medical patients. The DARSSA identified 48 (56%) participants who were risky substance users, many of whom had not been identified during their routine medical assessment. Mean satisfaction scores for all domains ranged between "Good" to "Excellent" across patients, nurses, doctors, and substance abuse treatment providers. The median completion time was 13min. Of the 48 risky substance using participants, 20 (42%) chose to receive a dynamic referral. These findings show that DARSSA provides a user-friendly, desirable service for patients and providers. It has the potential to improve identification of substance abuse in medical settings and to provide referrals that would not

routinely be provided. Future studies are planned to establish its efficacy at promoting treatment initiation and abstinence. Boudreaux E, Bedek K, Gilles D, Baumann B, Hollenberg S, Lord S, Grissom G. The dynamic assessment and referral system for substance abuse (DARSSA): development, functionality, and end-user satisfaction. Drug Alcohol Depend. 2009;99(1-3):37-46.

Emergency Department Initiated Treatments for Tobacco (EDITT): A Pilot Study

Emergency departments (EDs) have strong potential to initiate tobacco interventions with economically disadvantaged populations. The authors piloted three ED-initiated tobacco interventions and derived parameter estimates for future trials. The study enrolled adult patients being treated in an urban ED who were daily smokers. Exclusion criteria included severe illness or pain, isolation (for contagion), altered mental status, an insurmountable language barrier, temporary residence, and lack of telephone access. Subjects in the Bedside + Booster group received motivational counseling by a trained counselor at the bedside, up to three telephone sessions post-visit, and a self-help guide. Subjects in the Faxed Referral group had their personal contact information faxed to the hospital's tobacco dependence clinic, whereupon they received identical treatment as the Bedside + Booster group, but all sessions occurred over the telephone (i.e., no bedside counseling). The Standard Referral group received the self-help guide and a referral to the hospital's tobacco dependence clinic. A 2:2:1 randomization schedule was used to maximize the experience with the motivational interventions. Outcomes were assessed at 1 and 3 months. The study enrolled 90 subjects. Of the 36 subjects assigned to the Bedside + Booster condition, 31 (87%) completed bedside counseling and at least one booster session, while 22 (61%) completed the maximum four sessions. Of the 37 subjects assigned to the Faxed Referral group, 28 (76%) completed at least one telephone session, while 19 (51%) completed the maximum four sessions. Quit attempts over the 3 months ranged from 18% (Standard Referral) to 57% (Faxed Referral). Seven-day abstinence was attained by 8% (Bedside + Booster), 14% (Faxed Referral), and 6% (Standard Referral) at 3 months. These preliminary findings show Motivational cessation counseling can be feasibly initiated during the ED encounter with minimal medical staff involvement. Adequately powered trials are needed to study ED-initiated interventions that include post-visit follow-up. Boudreaux E, Baumann B, Perry J, Marks D, Francies S, Camargo C, Ziedonis D. Emergency department initiated treatments for tobacco (EDITT): a pilot study. Ann Behav Med. 2008;36(3):314-25.

Training Physicians to Treat Substance Use Disorders

The importance of training physicians to effectively assess and manage substance use disorders has become increasingly recognized. The authors highlight published studies that enhance medical curricula and common teaching practices are identified. Preferable curricula incorporate interactive teaching methods along with experiential and didactic components. Addiction specialists serve an important role in training programs designed for medical students and residents (i.e., role models) and practicing physicians (i.e., clinical support). Further integration of online training into current programs may expand and enhance training opportunities. Polydorou S, Gunderson E, Levin F. Training physicians to treat substance use disorders. Curr Psychiatry Rep. 2008;10(5):399-404.

Promoting Substance Use Education Among Generalist Physicians: An Evaluation of the Chief Resident Immersion Training (CRIT) Program

Education about substance use (SU) disorders remains inadequate in medical training. The purpose of this paper is to describe the Chief Resident Immersion Training (CRIT) program in addiction medicine and to evaluate its impact on chief resident (CR) physicians' substance use knowledge, skills, clinical practice, and teaching. The authors conducted a controlled educational study of CRIT programs (2003, 2004, and 2005) for incoming CRs in generalist disciplines. Intervention CRs were trained to diagnose, manage, and teach about SU. The control CRs sought but did not receive the intervention. The study group consisted of eighty-six CR applicants to the CRIT program. The program was evaluated by baseline and 6-month questionnaires assessing substance use knowledge, skills, clinical practice, and teaching. Outcomes were compared within groups from baseline to follow-up and between groups at follow-up. It was found that the intervention (n = 64) and control (n = 22) CRs were similar demographically. At 6-month follow-up, the intervention CRs reported a significant increase in SU knowledge, confidence, and preparedness to diagnose, manage, and teach and an increase in SU clinical and teaching practices compared to their baseline and control CRs. This study shows that intensive training for chief residents (CRs) improved knowledge, confidence, and preparedness to diagnose, manage, and teach about substance use (SU), affecting both the CRs' SU clinical and teaching practices. The CRIT program was an effective model for dissemination of SU knowledge and skills to educators in a key position to share this training with a broader audience of medical trainees. This model holds potential to address other high priority medical, yet under-addressed, content areas as well. Alford D, Bridden C, Jackson A, Saitz R, Amodeo M, Barnes H, Samet J. Promoting substance use education among generalist physicians: an evaluation of the Chief Resident Immersion Training (CRIT) Program. J Gen Intern Med. 2009;24(1):40-7.

Latent Class Pattern Mixture Models Offer a Superior Method for Analyzing Therapeutic Groups With Rolling Attendance

Historically, difficulties in analyzing treatment outcome data from open-enrollment groups have led to their avoidance in use in federally funded treatment trials despite the fact that 79% of treatment programs use open-enrollment groups. Latent class pattern mixture models (LCPMM) have shown promise as a defensible approach for making overall (and attendance-class-specific) inferences from open-enrollment groups with membership turnover. A statistical simulation study was conducted that compared LCPMMs to the commonly used longitudinal growth model (LGM) to understand when both frameworks are likely to produce conflicting inferences concerning overall treatment efficacy. LCPMMs performed well under all conditions examined; meanwhile, LGMs produced problematic levels of bias and Type I errors under two joint conditions: moderate to high dropout (30%-50%) and treatment by attendance class interactions exceeding Cohen's d approximately .2. This study highlights key concerns about using LGM for open-enrollment data: treatment effect overestimation and advocacy for treatments that may be ineffective in reality. Morgan Lopez AA, Fals-Stewart W. Consequences of mis-specifying the number of latent treatment attendance classes in modeling group membership turnover within ecologically valid behavioral treatment trials. J Subst Abuse Treat. 2008;35:396-409.

Long-term Strategic Planning Buffers Job Stress For Clinic Directors

Performance demands and pressure to make decisions via a centralized vertical chain of command were shown to cause emotional exhaustion and subsequent intent to quit among a large randomly-selected, national sample of 766 directors of drug abuse treatment provider organizations. Structural equation modeling showed that directors who engaged in long-term strategic planning were less likely to show emotional exhaustion and turnover intention than

those who did not strategically plan (RMSEA=.04, SRMR=.041, CFI=.95, TLI=.94, BIC=47919.14). Knudsen HK, Ducharme LJ, Roman PM. Turnover intention and emotional exhaustion at the top: adapting the job demands resources model to leaders of addiction treatment organizations. Journal of Occupational Health Psychology. 2009;14(1):84-95.

Labor Outcomes For An Intensive Case Management Program Targeting TANF Applicants With Substance Use Disorders

The authors examined abstinence rates among substance-dependent women receiving Temporary Assistance for Needy Families (TANF) in intensive case management (ICM) over 24 months and whether ICM yielded significantly better employment outcomes compared with a screen-and-refer program (i.e., usual care). Substance-dependent (n = 302) and non-substance dependent (n = 150) TANF applicants in Essex County, New Jersey, were recruited. The study procedure randomly assigned substance-dependent women to ICM or usual care and interviewed women at 3, 9, 15, and 24 months. Abstinence rates were higher for the ICM group than for the usual care group through 24 months of follow-up (odds ratio [OR] = 2.11; 95% confidence interval [CI] = 1.36, 3.29). A statistically significant interaction between time and group on number of days employed indicated that the rate of improvement over time in employment was greater for the ICM group than for the usual care group (incidence rate ratio = 1.03; 95% CI = 1.02, 1.04). Additionally, there were greater odds of being employed full time for those in the ICM group (OR = 1.68; 95% CI = 1.12, 2.51). ICM is a promising intervention for managing substance dependence among women receiving TANF and for improving employment rates among this vulnerable population. Morgenstern J, Neighbors C, Kuerbis A. Abstinence and employment outcomes for substance-dependent women receiving temporary assistance for needy families with intensive case management. Am J Public Health. 2009;99(2):328-33.

Trends in Use of Prescription Opioid Medication by the Type of Noncancer Pain, From 2000-2005, Among Arkansas Medicaid and Health-Core Enrollees: Results From the TROUP Study

Use of prescription opioids for noncancer pain has increased significantly in recent years, but it is not known if trends differ among the most common noncancer pain conditions. The researchers examined trends in opioid prescribing for the years 2000 through 2005 for individuals with arthritis/joint pain, back pain, neck pain, and headaches by type and number of pain diagnoses, using data from claims records from 2 health insurers: HealthCore commercially insured members (N = 3,768,223) and Arkansas Medicaid (N = 127,866). Rates of headache, back pain, and neck pain diagnoses increased significantly in Arkansas Medicaid enrollees but more modestly among HealthCore enrollees. Rates of opioid use increased in both groups, with long-term use (>90 days '' supply per year) increasing at twice the rate of any use. It was found that rates of opioid use did not differ widely between noncancer pain conditions, but long-term opioid use rates doubled with each additional pain diagnosis. Mean days supply and cumulative yearly dose increased between 2000 and 2005 for all pain types and with increasing number of pain diagnoses, but dose per day supply remained relatively stable. The greatest increases in dose among all the pain conditions were seen in short-acting DEA Schedule II opioids. This study demonstrates increased use of opioids, particularly long-term use, in noncancer pain over a 6-year period among those with multiple pain types. These results appear to reflect a general increase in use of prescription opioids for noncancer pain rather than a condition-specific change in prescribing practices. Braden J, Fan M, Edlund M, Martin B, DeVries A, Sullivan M. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and Health-Core enrollees: results from the TROUP study. J Pain. 2008;9(11):1026-35.

Smoking, Barriers to Quitting, and Smoking-Related Knowledge, Attitudes, and Patient Practices Among Male Physicians in China

Successful interventions to reduce the high rate of smoking among male physicians in China might contribute to reduction in tobacco use in the country overall. Better characterization of smoking, barriers to quitting, and smoking-related knowledge, attitudes, and patient practices in this physician population will help plan such interventions and provide baseline data to evaluate their effectiveness. The authors conducted a self-administered survey of smoking-related knowledge, attitudes, behaviors, and patient practices among health care professionals in 2 large teaching hospitals in China. It was found that of 103 male physicians, those who smoked (n = 51) had a more limited knowledge of smoking-related disease and were less likely to advise patients to quit smoking compared with nonsmoking physicians (n = 52). More than one-fourth (29%) of nonsmoking physicians accepted gift cigarettes, and these physicians were less likely to ask their patients about their smoking status than those who did not accept gift cigarettes. Seventy-five percent of smokers reported that their hospitals did not help them quit, and only 19% reported receiving training in how to help their patients quit. From this study it can be concluded that high rates of smoking, gifting of cigarettes, limited support for physician quitting, and limited training on cessation approaches may compromise the ability of male physicians in China to effectively treat their patients who smoke. Ceraso M, McElroy J, Kuang X, Vila P, Du X, Lu L, Ren H, Qian N, Jorenby D, Fiore M. Smoking, barriers to quitting, and smoking-related knowledge, attitudes, and patient practices among male physicians in China. Prev Chronic Dis. 2009; 6(1):A06-A08.

Individual and Community Risk Factors and Sexually Transmitted Diseases Among Arrested Youths: A Two-Level Analysis

High rates of infection for chlamydia and gonorrhea have been noted among youths involved in the juvenile justice system. Although both individual and community-level factors have been found to be associated with sexually transmitted disease (STD) risk, their relative importance has not been tested in this population. Study participants were newly arrested juveniles aged 12-18 processed at the Hillsborough County, FL Juvenile Assessment Center (HJAC) (a centralized intake facility) (male n = 506; female n = 442). A two-level logistic regression analysis was completed to assess the influence of individual-level and community-level predictors on STD test results among arrested youths processed at a centralized intake facility. Results from weighted two level logistic regression analyses indicated individual-level factors of gender (being female), age, race (being African American), and criminal history predicted the youths' positive STD status. Although marijuana and cocaine use, as assessed by UA, were significantly associated with STD status in bivariate analyses, these variables did not emerge as significant in multivariate analyses. For the community-level predictors, concentrated disadvantage significantly and positively predicted the youths' STD status. Implications of these findings for future research and public health policy are discussed. Dembo RSB, Childs S, Wareham J, Schmeilder J. Individual and community risk factors and sexually transmitted diseases among arrested youths: a two level analysis. J Behav Med. 2009;1-14.

Treatment Cost Analysis Tool for Directors Successfully Adapted From Research

A Microsoft¨ Excel-based workbook designed for research analysts to use in a national study was retooled for treatment program directors and financial officers to allocate, analyze, and estimate outpatient treatment costs in the

U.S. This instrument can also be used as a planning and management tool to optimize resources and forecast the impact of future changes in staffing, client flow, program design, and other resources. The Treatment Cost Analysis Tool (TCAT) automatically provides feedback and generates summaries and charts using comparative data from a national sample of non-methadone outpatient providers. TCAT was used by program staff in 115 programs across 9 states to capture and allocate both economic and accounting costs, and outpatient service costs are reported for a sample of 70 programs. Costs for an average episode of treatment in regular, intensive, and mixed types of outpatient treatment were $882, $1310, and $1381 respectively (based on 20% trimmed means and 2006 dollars). An hour of counseling cost $64 in regular, $85 intensive, and $86 mixed. Group counseling hourly costs per client were $8, $11, and $10 respectively for regular, intensive, and mixed. Future directions include use of a web-based interview version, much like some of the commercially available tax preparation software tools, and extensions for use in other modalities of treatment. Flynn PM, Broome KM, Beaston-Blaackman A, Knight DK, Horgan CM, Shepard DS. Treatment cost analysis tool (TCAT) for estimating costs of outpatient treatment services. Drug Alcohol Depend. 2009;100:47-53.

Levels of Patient-Counselor Rapport Are Reflected in Topics Discussed in Therapy

Counselor ratings of rapport with 330 private, for-profit methadone clients found that topics addressed in counseling sessions were influenced by rapport. Higher rapport was associated with addressing clients with a more "supportive approach" that emphasized relapse prevention and strengths-building while lower rapport was associated with a punitive counseling style that stressed program rules and compliance. The influences of client background, counselor differences, and during-treatment positive urines were also examined. Although counselors differed in their general manner of dealing with clients, each also showed flexibility determined in part by client behavior (such as continued cocaine use). Joe GW, Simpson DD, Rowan-Szal GA. Interaction of counseling rapport and topics discussed in sessions with methadone treatment clients. Subst Use Misuse. 2009;44:3-17.

Key Informant Surveys Less Costly, Just as Accurate as Other Cost Data Collection Methods

Cost data were collected from a convenience sample of 27 methadone programs in 12 states to determine if there were any differences in information obtained via 3 methods: A key informant method, a staff time survey method, and a staff time allocation method. The key informants, the program directors, were asked to fill out the Substance Abuse Services Cost Analysis Program survey which has been used in other costing studies. The staff survey was given to primary staff including counselors, case managers, and medical, management and administrative staff. Each primary staff person was asked to allocate his or her time across the services and activities as those represented in the SASCAP based on a typical week over the past month. In the staff diary method, each primary staff was asked to record actual hours worked for 7 consecutive days and to allocate his or her time across the same service and activity categories. For most service and activity categories, the cost estimates were statistically indistinguishable from one another. However there were differences in the initial patient assessment and initial medical services activities. For these services, key informants estimated that each staff member participated in less than 6 sessions per week which lasted more than 100 minutes per session. Both staff surveys and staff diaries suggested that staff members took part in more than 20 sessions per week, spending less than 50 minutes per session. This likely is because the key informant was reporting on an entire session, while the staff members were reporting on the component

parts in which they may have participated. This was not an issue for other services which were usually provided by one person. Because the key informants estimates of these issues matched the number of admissions per week the key informant method was deemed most accurate. Given that the key informant method requires far less staff time to complete, and that response rates were higher for this method than the other methods, these findings suggest that it may be the most economical way to collect accurate data. Zarkin G, Dunlap L, Wedehase B, Cowell A. The effect of alternative staff time data collection methods on drug treatment service cost estimates. Eval Program Plan. 2008;31(4):427-35.

Explaining Job Turnover Among Treatment Program Administrators

Although there is a growing literature on job stress and burnout among addiction treatment counselors, there has been no analogous research on the top administrators of addiction treatment programs. Stability in these occupations is important as administrators make key decisions about service delivery, including the adoption and implementation of evidence-based practices. Using a sample of 410 administrators of public and private sector specialty care programs, the authors estimated a structural equation model to examine the impact of job demands and job resources on emotional exhaustion and intent to leave the organization. The study's findings indicated that burnout and intent to quit were higher among administrators who were under pressure to meet financial performance targets; maintained centralized decision making structures; failed to engage in long-range strategic planning; and expressed lower tolerance for risk and innovation. Knudsen HK, Ducharme LJ, Roman PM. Turnover intention and emotional exhaustion at the top: adapting the job demands-resources model to leaders of addiction treatment organizations. J Occup Health Psychol. 2009;14:84-95.

The Importance of Examining the Role of Quality of Life Satisfaction in Addiction Recovery

Quality of life (QOL) remains the missing measurement in the addictions arena and is generally underutilized as an outcome variable in addiction health services research. The few studies conducted to date show that QOL is typically poor during active addiction and improves as a function of remission. An intriguing question bears on the role of QOL in subsequent remission status. Reasoning that higher life satisfaction may "increase the price" of future use and thus enhance the likelihood of sustained remission, this exploratory study tests the hypotheses that QOL satisfaction prospectively predicts sustained remission, and that motivational constructs mediate the association. Inner city residents (N = 289, 53.6% male, mean age 43) remitting from chronic and severe histories of dependence to crack and/or heroin were interviewed three times at yearly interval beginning in April 2003. Logistic regression findings generally support the authors' hypotheses: Controlling for other relevant variables, baseline life satisfaction predicted remission status 1 and 2 years later and the association was partially mediated by motivation (commitment to abstinence) although the indirect effect did not reach statistical significance. Findings underline the importance of examining the role of QOL satisfaction in remission processes. Limitations of this exploratory study are discussed, including the use of a single-item global life satisfaction rating; suggestions for future studies are discussed including the need to embrace QOL as a bona fide clinical outcome and to use comprehensive standardized QOL measures that speak to individual dimensions of functioning. Implications are noted, especially the need for the addiction field to continue moving away from the pathology-focused model of care toward a broader model that embraces multiple dimensions of positive health as a key outcome. Laudet A, Becker J, White W. Don 'T Wanna Go Through That Madness No More: quality of life satisfaction as

predictor of sustained remission from illicit drug misuse. Subst Use Misuse. 2009;44(2) 227-52.

A Method for Longitudinal Analysis of Variable and Invariant Patient Factors Improves Validity and Clarity of Results

The analysis of longitudinal data to study changes in variables measured repeatedly over time has received considerable attention in many fields. This paper proposes a two-level structural equation model for analyzing multivariate longitudinal responses that are mixed continuous and ordered categorical variables. The first-level model is defined for measures taken at each time point nested within individuals for investigating their characteristics that are changed with time. The second level is defined for individuals to assess their characteristics that are invariant with time. The proposed model accommodates fixed covariates, nonlinear terms of the latent variables, and missing data. A maximum likelihood (ML) approach was developed for the estimation of parameters and model comparison. Results of a simulation were compared to an actual longitudinal study concerning cocaine use indicate that the performance of the ML estimation is satisfactory. Song X, Lee S, Hser Y. A Two-level structural equation model approach for analyzing multivariate longitudinal responses. Stat Med. 2008;27(16):3017-41.

The Use of Recursive Partitioning in the Analysis of Addiction Treatment Retention Data

Recursive Partitioning (RP) is a statistical technique that examines all available predictors and identifies a hierarchy of variables that are, in succession, most related to the outcome measure. It is an exploratory technique, not necessarily based on conceptual or theoretical modeling. The aim of this study is to demonstrate the utility of RP for analyzing process and outcome data in drug treatment research. The authors introduce the basic methodology of RP and apply the procedure to the prediction of treatment retention. In the data analysis, a total of 315 individuals randomly were assigned to one of two treatment conditions; 289 (91.7%) completed a comprehensive baseline assessment battery. Treatment retention was assessed at a 52-week follow-up interview. The RP approach was successful in generating a parsimonious decision tree that predicted drug treatment retention from the 195 input variables. Severity of drug use (as indicated by length of time speedballing, the concurrent use of heroin and cocaine mixed and injected intravenously), criminal behavior (as indicated by history of property crimes), level of insight (an assessment of an individual's understanding of the damage that their drug use was causing), social network, and age at intake were predictive of treatment retention. The model is estimated to explain 32% of the variability in the population. RP supports the notion that there are early indicators of treatment retention and that specific approaches that are tailored to individuals' needs will be potentially more successful in treatment engagement and retention than the typical "one size fits all" approach. The results also demonstrate the utility of RP for the detection of complex relationships between diverse and interdependent predictors. Hellemann G, Conner B, Anglin M, Longshore D. Seeing the trees despite the forest: applying recursive partitioning to the evaluation of drug treatment retention. J Subst Abuse Treat. 2009;36(1);59-64.

Health Insurance Plans Change Strategies for Managing Behavioral Health Care

Survey data from nationally-representative samples of health insurance plans in 1999 (n=434) and 2003 (n=368) were used to examine changes over time in how plans provide and managed behavioral health services. Among the

findings: Plans were more likely to contract with managed behavioral health organizations in 2003 than they were in 1999, moving from 58% of products to 72% of products. At the same time, the percentage of plans requiring prior authorization for outpatient detoxification, and outpatient rehabilitation declined by 15.9 and 22.8 percentage points respectively, which might increase access to care, while the percentage requiring prior authorization for intensive outpatient increased slightly by 2.8 percentage points. Cost sharing requirements for behavioral health care services, however, increased over the time period, as the percentage of plans with coinsurance requirements of greater than 20% and co-payments of greater than $20 per visit increased from 25.7% in 1999 to 42.1% in 2003. This may reduce access given that the demand for behavioral health care has been found to be quite price-sensitive. Horgan CM, Garnick DW, Merrick EL, Hodgkin D. Changes in how health plans provide behavioral health services. J Behav Health Serv Res. 2009;36(1):11-24.

Visualizations of Cognitive-Emotional Experience Is A Useful Tool for Structuring CBT

This article reviews the 20-plus year history and progress of node-link cognitive mapping as a useful strategic tool for cognitive therapists. Cognitive visualizations provided by patients can help structure more productive therapeutic sessions and also offers a useful tool for training new therapists. Mapping has been shown to enhance patient collaboration in treatment and improve engagement when used in conjunction with other approaches. Dansereau DF, Simpson, DD. A picture is worth a thousand words: the case for graphic representations. Professional Psychology: Reseach & Practice. 2009;40(1):104-110.

Criminal Thinking Style Is An Important Factor in UK Prison Addiction Treament

This study examines 199 male drug users diverted into criminal justice system treatment in Birmingham England to assess their treatment engagement and criminal thinking styles using the Texas Christian University Client Evaluation of Self and Treatment scale and the Criminal Thinking Scale. UK inmates scored similar to US norms for average desire for help and need for treatment, but slightly higher than US inmates on treatment readiness. UK inmates reported higher treatment engagement and satisfaction than US samples. An association was found between higher criminal thinking and both poorer engagement in treatment and worse client functioning ($r=-.28$; $p<.001$). The key implication is that to address offending-prone behavior as a determinant of ongoing drug use. Results indicated that criminal thinking styles are an important element in inmate engagement in addiction treatment. Best D, Day E, Campbell A, Flynn PM, Simpson DD. Relationship between drug treatment engagement and criminal thinking style among drug-using offenders. Eur Addict Res. 2009;15:71-7.

Epidemiology of Chronic Prescription Opioid Use: Results From a Major National, Population-Based Survey

Chronic pain occurs commonly and accounts for significant suffering and costs. Although use of opioids for treatment of chronic pain is increasing, little is known about patients who use opioids regularly. The researchers report data from the second wave of the Healthcare for Communities survey (2000-2001), a large, nationally representative household survey. They compared regular users of prescription opioids to nonusers of opioids and calculated the percentage of individuals within a given demographic or disease state that reported chronic opioid use. Approximately 2% of the 7,909 survey

respondents reported use of opioid medications for at least a month, which the Healthcare for Communities survey defined as "regular use." It was found that opioid users were more likely than nonusers to report high levels of pain interference with their daily lives and to rate their health as fair or poor. Arthritis and back pain were the most prevalent chronic, physical health conditions among users of opioids, with 63% of regular users of opioids reporting arthritis and 59% reporting back pain. The majority of regular users of opioids had multiple pain conditions (mean=1.9 pain conditions). This study indicates that regular opioid users appear to have an overall lower level of health status and to have multiple, chronic physical health disorders. Hudson T, Edlund M, Steffick D, Tripathi S, Sullivan M. Epidemiology of regular prescribed opioid use: results from a national, population-based survey. J Pain Symptom Manage. 2008;36(3):280-8.

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

Research Findings - CTN-Related Research

Facilitating Involvement in Twelve-Step Programs

Twelve-step programs represent a readily available resource for individuals with substance use disorders. These programs have demonstrated considerable effectiveness in helping substance abusers achieve and maintain abstinence and improve their overall psychosocial functioning and recovery. Despite these positive benefits associated with increased involvement in twelve-step self-help programs, many substance abusers do not affiliate or do so for only a short period of time before dropping out. Because of this, clinicians and researchers have sought ways to increase involvement in such self-help groups by facilitating meeting attendance and engagement in other twelve-step activities. The present chapter reviews the impact of treatment program orientation and specific interventions designed to facilitate twelve-step program involvement, subsequent meeting attendance, engagement in twelve-step activities, and alcohol and drug use. The findings of studies evaluating these approaches indicate that it is possible to increase twelve-step involvement and that doing so results in reduced substance use. The results suggest that incorporating these evidence-based interventions into standard treatment programs may lead to improved outcomes. Donovan DM, Floyd AS. Facilitating involvement in twelve-step programs. Recent Dev Alcohol. 2008;18:303-20.

Measurement and Data Analysis in Research Addressing Health Disparities in Substance Abuse

This article describes concrete strategies for conducting substance abuse research with ethnic minorities. Two issues associated with valid analysis, measurement and data analysis, are included. Both empirical (e.g., confirmatory factor analysis, item response theory, and regression) and nonempirical (e.g., focus groups, expert panels, pilot studies, and translation equivalence) approaches to improve measures are described. A discussion of the use of norms and cutoff scores derived from a different ethnic group along with the effects of the ethnicity of the interviewer or coder on measurement is included. The section on data analysis describes why the use of race-comparison designs may lead to misleading conclusions. Alternatives to race-comparison analysis including within-group and between-group analyses are described. The shortcomings of combining ethnic groups for analyses are discussed. The article ends with a list of recommendations for research with ethnic minorities. Burlew AK, Feaster D, Brecht ML, Hubbard R. Measurement and data analysis in research addressing health disparities in substance abuse. J Subst Abuse Treat. 2009;36(1):25-43. Epub 2008 Jun 11.

Motivational and Skills Training HIV/Sexually Transmitted Infection Sexual Risk Reduction Groups For Men

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The effectiveness of a motivational and skills training HIV/AIDS group intervention designed for men in substance abuse treatment was evaluated. Men in methadone maintenance (n = 288) or outpatient psychosocial treatment (n = 302) completed assessments at baseline, 2 weeks, 3 months, and 6 months postintervention. Participants were randomly assigned to attend either Real Men Are Safe (REMAS; five sessions containing information, motivational exercises, and skills training) or HIV education (HIV-Ed; one session containing HIV prevention information). REMAS participants engaged in significantly fewer unprotected vaginal and anal sexual intercourse occasions (USO) during the 90 days prior to the 3- and 6-month follow-ups than HIV-Ed participants. Completing REMAS resulted in an even stronger effect: Completers reduced their number of USO by 21% from baseline to 6-month follow-up. In contrast, HIV-Ed completers increased the number of USO by 2%. A motivational and skills training HIV prevention intervention designed for men was associated with greater sexual risk reduction over standard HIV-Ed. Substance abuse treatment programs can therefore help reduce sexual risk among their clientele by providing a more intensive intervention than what is traditionally provided. Calsyn DA, Hatch-Maillette M, Tross S, Doyle SR, Crits-Christoph P, Song YS, Harrer JM, Lalos G, Berns SB. Motivational and skills training HIV/sexually transmitted infection sexual risk reduction groups for men. J Subst Abuse Treat. 2009; Jan 14. [Epub ahead of print].

Buprenorphine Tapering Schedule and Illicit Opioid Use

The aims of this study were to compare the effects of a short or long taper schedule after buprenorphine stabilization on participant outcomes as measured by opioid-free urine tests at the end of each taper period. This multi-site study sponsored by Clinical Trials Network (CTN, a branch of the US National Institute on Drug Abuse) was conducted from 2003 to 2005 to compare two taper conditions (7 days and 28 days). Data were collected at weekly clinic visits to the end of the taper periods, and at 1-month and 3-month post-taper follow-up visits. The setting included eleven out-patient treatment programs in 10 US cities. The intervention was non-blinded dosing with Suboxone during the 1-month stabilization phase included 3 weeks of flexible dosing as determined appropriate by the study physicians. A fixed dose was required for the final week before beginning the taper phase. Measurements obtained were the percentage of participants in each taper group providing urine samples free of illicit opioids at the end of the taper and at follow-up. At the end of the taper, 44% of the 7-day taper group (n = 255) provided opioid-free urine specimens compared to 30% of the 28-day taper group (n = 261; P = 0.0007). There were no differences at the 1-month and 3-month follow-ups (7-day = 18% and 12%; 28-day = 18% and 13%, 1 month and 3 months, respectively). The authors conclude that for individuals terminating buprenorphine pharmacotherapy for opioid dependence, there appears to be no advantage in prolonging the duration of taper. Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, Jenkins J, Hasson A, Annon J, Saxon A, Selzer J, Boverman J, Bilangi R. Buprenorphine tapering schedule and illicit opioid use. Addiction. 2009;104(2):256-65.

A Centralized Informatics Infrastructure for the National Institute on Drug Abuse Clinical Trials Network

Clinical trial networks (CTNs) were created to provide a sustaining infrastructure for the conduct of multisite clinical trials. As such, they must withstand changes in membership. Centralization of infrastructure including knowledge management, portfolio management, information management, process automation, work policies, and procedures in clinical research networks facilitates consistency and ultimately research. In 2005, the National Institute on Drug Abuse (NIDA) CTN transitioned from a distributed data management

model to a centralized informatics infrastructure to support the network's trial activities and administration. This paper describes the centralized informatics infrastructure and discusses challenges that were encountered to inform others considering such an endeavor. During the migration of a clinical trial network from a decentralized to a centralized data center model, descriptive data were captured and are presented here to assess the impact of centralization. Authors present the framework for the informatics infrastructure and evaluative metrics. The network has decreased the time from last patient-last visit to database lock from an average of 7.6 months to 2.8 months. The average database error rate decreased from 0.8% to 0.2%, with a corresponding decrease in the interquartile range from 0.04%-1.0% before centralization to 0.01-0.27% after centralization. Centralization has provided the CTN with integrated trial status reporting and the first standards-based public data share. A preliminary cost-benefit analysis showed a 50% reduction in data management cost per study participant over the life of a trial. Since a single clinical trial network comprising addiction researchers and community treatment programs was assessed these findings may not be applicable to other research settings. The authors conclude that the identified informatics components provide the information and infrastructure needed for our clinical trial network. Post centralization data management operations are more efficient and less costly, with higher data quality. Pan JJ, Nahm M, Wakim P, Cushing C, Poole L, Tai B, Pieper CF. A centralized informatics infrastructure for the National Institute on Drug Abuse Clinical Trials Network. Clin Trials. 2009;6(1):67-75.

Understanding Attitudes Toward Use of Medication in Substance Abuse Treatment: A Multilevel Approach

Individual and organizational variables influence attitudes towards use of naltrexone, methadone, and buprenorphine for the treatment of alcohol and drug disorders. Prior research has not considered both sets of influences simultaneously. Hierarchical linear modeling tested the contribution of individual and organizational variables using data the National Drug Abuse Treatment Clinical Trials Network treatment unit and workforce surveys (n = 2,269 staff nested within 247 treatment units), done as part of protocol CTN-0008, "Assessment of the National Drug Abuse Clinical Trials Network: A Baseline for Investigating Diffusion of Innovation." Individual-level variables consistently had more influence on attitudes, but a unique blend of variables existed for each medication. One predictor, support for psychiatric medications, influenced attitudes across all medications. Staff attitudes towards addiction medications varied significantly between treatment units. Implications for increasing the appropriate use of addiction medications are discussed. Fitzgerald JP, McCarty D. Understanding attitudes toward use of medication in substance abuse treatment: a multilevel approach. Psychological Services. 2009;6(1):74-84.

Substance Abuse Treatment Clinician Opinions and Infectious Disease Service Delivery

Substance abuse treatment programs are an important platform for delivery of services for infectious diseases associated with drug and alcohol use. However, important components of infectious disease care are not universally provided. Clinician training often focuses on information about infectious diseases and less attention is paid to provider opinions and attitudes that may be barriers to providing infectious diseases services. In a national multi-site trial conducted by the National Drug Abuse Treatment Clinical Trials Network (CTN), the authors investigated the relationship between clinician opinions and the delivery of services for human immunodeficiency virus, hepatitis C virus, and sexually transmitted infections in substance abuse treatment settings. Survey data were collected from 1,723 clinicians at 269 CTN treatment programs.

Clinician opinion was found to be significantly related to infectious disease service delivery. Implications for training are discussed. Tracy K, Brown LS, Kritz S, Alderson D, Robinson J, Bini EJ, Levy M, Calsyn D, Rieckmann T, Fuller B, McAuliffe P, Rotrosen J. Substance abuse treatment clinician opinions and infectious disease service delivery. J Addict Dis. 2009;28(1):8-12.

Correlates of Stimulant Treatment Outcome Across Treatment Modalities

This study evaluated variables associated with stimulant use outcomes in stimulant users (N = 800) receiving care in community outpatient psychosocial or methadone maintenance treatment clinics as part of a national multi-site clinical trial. Results from the full sample were examined first, and then predictors were examined separately in the two treatment modalities. A cocaine-positive urine sample at study intake was the most robust and consistent correlate of stimulant use outcome in all analyses. Psychiatric distress, social environment and employment had differential effects on outcome across modalities. This study confirms that intake assessments have considerable value in identifying problems to be addressed in treatment. Peirce JM, Petry NM, Roll JM, Kolodner K, Krasnansky J, Stabile PQ, Brown C, Stitzer ML. Correlates of stimulant treatment outcome across treatment modalities. Am J Drug Alcohol Abuse. 2009;35(1):48-53.

Factor Structure of the Condoms Barriers Scale with a Sample of Men at High Risk for HIV

This study assesses the psychometric properties of the Condom Barriers Scale (CBS), an instrument originally designed to measure womenÕs perceptions and attitudes regarding male condom use, with a sample of men at high risk for human immunodeficiency virus (HIV). Participants include 590 male patients in drug abuse treatment involved in a gender-specific HIV prevention intervention for teaching safer sex skills (protocol CTN-0018). Second-order confirmatory factor analysis generally supported the underlying four-factor subscale structure of the CBS. However, exploratory factor analysis revealed a few specific discrepancies in the factor structure between men and women. Internal consistency and test-retest reliability estimates were moderate to high in value. CBS scores correlated with use of condoms for men with high-risk sexual partners, supporting criterion-related validity. Overall, the analysis indicates that the CBS is a potentially valid and reliable instrument and has utility for assessing barriers to condom use with men, but may need some item content modifications to allow appropriate assessment of gender differences and comparisons across studies. Doyle SR, Calsyn DA, Ball SA. Factor structure of the Condoms Barriers Scale with a sample of men at high risk for HIV. Assessment. 2009;16(1):3-15. Epub 2008 Aug 8.

Motivation Enhancement Therapy with Pregnant Substance-Abusing Women: Does Baseline Motivation Moderate Efficacy?

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 goal were 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 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] 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 SM, Wang Y. Motivation Enhancement Therapy with pregnant substance-abusing women: does baseline motivation moderate efficacy? Drug Alcohol Depend. 2009;101(1-2):74-9. Epub 2008 Dec 19.

Construct, Concurrent and Predictive Validity of the URICA: Data from Two Multi-Site Clinical Trials

A better understanding of how to measure motivation to change and how it relates to behavior change in patients with drug and alcohol dependence would broaden our understanding of the role of motivation in addiction treatment. Two multi-site, randomized clinical trials comparing brief motivational interventions with standard care were conducted in the National Institute on Drug Abuse Clinical Trials Network. Patients with primary drug dependence and alcohol dependence entering outpatient treatment participated in a study of either Motivational Enhancement Therapy (n=431) or Motivational Interviewing (n=423). The construct, concurrent, and predictive validity of two composite measures of motivation to change derived from the University of Rhode Island Change Assessment (URICA): Readiness to Change (RTC) and Committed Action (CA) were evaluated. Confirmatory factor analysis confirmed the a priori factor structure of the URICA. RTC was significantly associated with measures of addiction severity at baseline (r=.12-.52, p<.05). Although statistically significant (p<.01), the correlations between treatment outcomes and RTC were low (r=-.15 and -18). Additional analyses did not support a moderating or mediating effect of motivation on treatment retention or substance use. The construct validity of the URICA was confirmed separately in a large sample of drug- and alcohol-dependent patients. However, evidence for the predictive validity of composite scores was very limited and there were no moderating or mediating effects of either measure on treatment outcome. Thus, increased motivation to change, as measured by the composite scores of motivation derived from the URICA, does not appear to influence treatment outcome. Field CA, Adinoff B, Harris TR, Ball SA, Carroll KM. Construct, concurrent and predictive validity of the URICA: data from two multi-site clinical trials. Drug Alcohol Depend. 2009;101(1-2):115-23. Epub 2009 Jan 20.

Supervision Mediates Counselor Burnout

Extends previous research on emotional exhaustion and turnover intention among counselors by estimating the associations between clinical supervision and these variables in a large national sample (N = 823) drawn from the NIDA Clinical Trials Network. Clinical supervision was negatively associated with both emotional exhaustion and turnover intention (RMSEA =.037, SRMR = .042; chi-square=1873.64, df = 878, p<.001), accounting for 31% of the variance in

exhaustion reports, and 46% of intent to quit. Perceived quality of clinical supervision was strongly associated with counselors' perceptions of job autonomy, procedural justice, and distributive justice, which are, in turn, associated with emotional exhaustion and turnover intention. These data offer support for the protective role of clinical supervision in substance abuse treatment counselors' turnover and occupational well-being. Knudsen HK, Ducharme LJ, Roman PM. Clinical supervision, emotional exhaustion, and turnover intention: a study of substance abuse treatment counselors in the Clinical Trials Network of the National Institute on Drug Abuse. J Subst Abuse Treat. 2008;35:387-95.

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

Research Findings - International Research

Publications by Former NIDA Hubert H. Humphrey Fellows

Understanding Post 9/11 Drug Control Policy and Politics in Central Asia
Latypov A. International Journal on Drug Policy. 2009 January 2. [Epub ahead of print]
HHH Fellow: Alisher Latypov, Republic of Tajikistan, 2002-2003
This paper exposes contemporary drug policy challenges in Central Asia by focusing on a single point in the history of drug control, in a single region of the global war against drugs and terrorism, and on one agency whose mission is to help make the world safer from crime, drugs and terrorism. By looking closely at the post 9/11 security-oriented donor priorities, I conclude that, in Central Asia, the rhetoric of the taking a more 'balanced approach' to drug policy is bankrupt. When enacted by the national law enforcement agencies in the Central Asian republics, the 'Drug Free' aspirational goal is driving the HIV epidemic among IDUs. The face-saving 'containment' thesis does not reflect the drug situation in this region but rather the failure to adopt an evidence-based approach. The harm reduction agenda continues to face many challenges including resistance to substitution treatment, the harm from drug treatment, from poorly designed drug prevention programmes and from repressive counter-narcotics policies and practices. PMID: 19121928 [PubMed - as supplied by publisher].

The Characteristics of Depressive Symptoms in Medical Students During Medical Education and Training: A Cross-Sectional Study
Baldassin S, Alves TC, de Andrade AG, Nogueira Martins LA. BMC Medical Education. 2008 December 11;8:60.
HHH Fellow: Arthur Guerra de Andrade, Brazil, 1991-1992
Medical education and training can contribute to the development of depressive symptoms that might lead to possible academic and professional consequences. The authors aimed to investigate the characteristics of depressive symptoms among 481 medical students (79.8% of the total who matriculated). The Beck Depression Inventory (BDI) and cluster analyses were used in order to better describe the characteristics of depressive symptoms. Medical education and training in Brazil is divided into basic (1st and 2nd years), intermediate (3rd and 4th years), and internship (5th and 6th years) periods. The study organized each item from the BDI into the following three clusters: affective, cognitive, and somatic. Statistical analyses were performed using analysis of variance (ANOVA) with post-hoc Tukey corrected for multiple comparisons. There were 184 (38.2%) students with depressive symptoms (BDI > 9). The internship period resulted in the highest BDI scores in comparison to both the basic ($p < .001$) and intermediate ($p < .001$) periods. Affective, cognitive, and somatic clusters were significantly higher in the internship period. An exploratory analysis of possible risk factors showed that

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females (p = .020) not having a parent who practiced medicine (p = .016), and the internship period (p = .001) were factors for the development of depressive symptoms. The authors conclude that there is a high prevalence towards depressive symptoms among medical students, particularly females, in the internship level, mainly involving the somatic and affective clusters, and not having a parent who practiced medicine. The active assessment of these students in evaluating their depressive symptoms is important in order to prevent the development of co-morbidities and suicide risk. PMID: 19077227 [PubMed - indexed for MEDLINE].

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

Research Findings - Intramural Research

Biomedical Informatics Section, Administrative Management Branch

Automation in an Addiction Treatment Research Clinic: Computerized Contingency Management, Ecological Momentary Assessment, and a Protocol Workflow System

IRP researchers have automated several major functions of our outpatient treatment research clinic for studies in drug abuse and dependence to enhance efficient operations, adherence to protocol and better communications among research staff. IRP researchers describe three such specialized applications within an integrated platform: the Automated Contingency Management (ACM) system for delivery of behavioral interventions, the Transactional Electronic Diary (TED) system for management of behavioral assessments, and the Protocol Workflow System (PWS) for computerized workflow automation and guidance of each participant's daily clinic activities. ACM and TED have each permitted us to conduct research that was not previously possible. In addition, the time to data analysis at the end of each study is substantially shorter. With the implementation of the PWS, the authors have been able to manage a research clinic with an 80-patient capacity having an annual average of 18,000 patient-visits and 7,300 urine collections with a research staff of five. Finally, automated data management has considerably enhanced the authors' ability to monitor and summarize participant-safety data for research oversight.
Vahabzadeh M, Lin JL, Mezghanni M, Epstein DH, Preston KL. Automation in an addiction treatment research clinic: Computerised contingency management, ecological momentary assessment and a protocol workflow system. Drug Alcohol Rev. 2009;28(1):3-11.

Office of the Scientific Director

EEG and Cerebral Blood Flow Velocity Abnormalities in Chronic Cocaine Users

EEG and cerebral blood flow abnormalities occur in chronic cocaine users, but the relationship between these two phenomena is not well studied. IRP scientists evaluated this issue in 99 adult, chronic, heavy cocaine users tested within 5 days of admission to a closed research unit and 42 healthy, non-drug-using, age-matched controls. Absolute power in 6 frequency bands of resting EEG was compared with blood flow velocity in the middle cerebral artery as measured by transcranial Doppler sonography (which uses focused, high-frequency sound waves). The cocaine users had decreased blood flow velocity during cardiac diastole (relaxation), increased pulsatility index (a measure of small blood vessel resistance), and decreased high-frequency EEG power in posterior brain regions. The greater the amount of recent cocaine use, the greater the pulsatility index and the lower the low-frequency EEG power. Only

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high-frequency EEG power was significantly correlated with pulsatility index. These findings suggest that EEG and cerebral blood flow velocity changes during early cocaine abstinence reflect related physiological processes. Copersino ML, Herning RI, Better W, Cadet J-L, Gorelick DA. EEG and cerebral blood flow velocity abnormalities in chronic cocaine users. Clin EEG Neurosci. 2009;40(1):39-42.

Cellular Pathobiology Section, Cellular Neurobiology Research Branch

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 researchers present a hypothetical signaling scheme that might be triggered by the binding of DMT to sigma-1 receptors. Su TP, Hayashi T, Vaupel DB. When the endogenous hallucinogenic trace amine N,N-dimethyltryptamine meets the sigma-1 receptor. Sci Signal. 2009;2(61):pe12.

MAM: More Than Just a Housekeeper

The physical association between the endoplasmic reticulum (ER) and mitochondria, which is known as the mitochondria-associated ER membrane (MAM), has important roles in various cellular 'housekeeping' functions including the non-vesicular transports of phospholipids. It has recently become clear that the MAM also enables highly efficient transmission of Ca(2+) from the ER to mitochondria to stimulate oxidative metabolism and, conversely, might enable the metabolically energized mitochondria to regulate the ER Ca(2+) homeostasis. Recent studies have shed light on molecular chaperones such as calnexin, calreticulin, ERp44, ERp57, grp75 and the sigma-1 receptor at the MAM, which regulate the association between the two organelles. The MAM thus integrates signal transduction with metabolic pathways to regulate the communication and functional interactions between the ER and mitochondrion. Hayashi T, Rizzuto R, Hajnoczky G, Su TP. MAM: more than just a housekeeper. Trends Cell Biol. 2009;19(2):81-8.

Electrophysiology Section, Cellular Neurobiology Research Branch

Properties of Distinct Ventral Tegmental Area Synapses Activated Via Pedunculopontine or Ventral Tegmental

Anatomical studies indicate that synaptic inputs from many cortical and subcortical structures converge on neurons of the ventral tegmental area (VTA). Although in vitro electrophysiological studies have examined synaptic inputs to dopamine (DA) and non-DA neurons in the VTA, they have largely relied upon local electrical stimulation to activate these synapses. This provides little information regarding the distinct properties of synapses originating from different brain areas. Using whole-cell recordings in parasagittal rat brain slices that preserved subcortical axons from the pedunculopontine nucleus (PPN) to the VTA, IRP scientists compared these synapses with those activated by intra-VTA stimulation. PPN-evoked currents demonstrated longer latencies than intra-VTA-evoked currents, and both VTA and PPN responses were mediated by GABA(A) and AMPA receptors. However, unlike VTA-evoked currents, PPN currents were exclusively mediated by glutamate in 25-40% of the VTA neurons. Consistent with a cholinergic projection from the PPN to the VTA, nicotinic acetylcholine receptors (nAChR) were activated by endogenous acetylcholine released during PPN, but not VTA, stimulation. This was seen as a

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reduction of PPN-evoked, and not VTA-evoked, synaptic currents by the alpha7-nAChR antagonist methyllycaconitine (MLA) and the agonist nicotine. The beta2-nAChR subunit antagonist dihydro-beta-erythroidine had no effect on VTA- or PPN-evoked synaptic currents. The effects of MLA on PPN-evoked currents were unchanged by the GABA(A) receptor blocker picrotoxin, indicating that alpha7-nAChRs presynaptically modulated glutamate and not GABA release. These differences in physiological and pharmacological properties demonstrate that ascending PPN and presumed descending inputs to VTA utilize distinct mechanisms to differentially modulate neuronal activity and encode cortical and subcortical information. Good CH, Lupica CR. Properties of distinct ventral tegmental area synapses activated via pedunculopontine or ventral tegmental. The Journal of Physiology. 2009;587(Pt 6):1233-47.

Neurophysiology Section, Cellular Neurobiology Research Branch

Generalized Tetracycline Induced Cre Recombinase Expression

Through the ROSA26 Locus of Recombinant Mice Inducible Cre recombinase systems have been developed to bypass initial lethal phenotypes and to provide access to later embryonic or adult phenotypes. Here IRP investigators describe the generation of a recombinant mouse that combines a tetracycline dependent switch with generalized Cre recombinase expression by targeting the ubiquitously expressed ROSA26 locus. This transgenic strain was developed using a simplified gene delivery system integrating both elements, the reverse tetracycline controlled trans-activator (rtTA) and rtTA inducible promoter into a single vector. In this transgenic strain, the endogenous ROSA26 promoter drives rtTA expression through a splice acceptor site. The tetracycline inducible promoter, cloned in opposite orientation to the ROSA26 locus and separated from the rtTA element by a 5 kb human p53 intron, drives Cre recombinase expression. Crossing these mice with a Cre reporter strain showed that Cre DNA-mediated recombination was ubiquitously and effectively induced during various prenatal developmental windows. Background Cre recombinase expression levels were observed in some tissues in the absence of the inducer, mostly during late embryonic developmental stages and in adult animals. Background recombination levels were low during development and most prominent in nervous tissue. Cre recombinase expression could not be effectively induced in adult animals. While rtTA mRNA levels were high in developmental and adult tissues, Cre recombinase mRNA levels remained low after doxycycline treatment. The mouse strain described here provides a valuable tool to further analyze the function of genes during specific developmental windows, by allowing the effective inactivation of their function throughout defined stages of embryonic development. BŠckman CM, Zhang Y, Malik N, Shan L, Hoffer BJ, Westphal H, Tomac AC. Generalized tetracycline induced Cre recombinase expression through the ROSA26 locus of recombinant mice. J Neurosci Methods. 2009;176(1):16-23.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Direct Profiling of Tissue Lipids by MALDI-TOFMS

Advances in matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) have allowed for the direct analysis of biological molecules from tissue. Although most of the early studies of direct tissue profiling by MALDI-TOFMS have focused on proteins and peptides, analysis of lipids has increased dramatically in recent years. This review gives an overview of the factors to consider when analyzing lipids directly from tissue and some recent examples of the use of MALDI-TOFMS for the direct profiling of lipids in tissue. Jackson SN, Woods AS. Direct profiling of tissue lipids by MALDI-TOFMS. J Chromatogr B Analyt Technol Biomed Life Sci. 2008; Nov 28. [Epub ahead of print].

Integrated Signaling in Heterodimers and Receptor Mosaics of Different Types of GPCRs of the Forebrain: Relevance for Schizophrenia

Receptor-receptor interactions within receptor heterodimers and receptor mosaics formed by different types of GPCRs represent an important integrative mechanism for signaling in brain networks at the level of the plasma membrane. The malfunction of special heterodimers and receptor mosaics in the ventral striatum containing D(2) receptors and 5-HT(2A) receptors in cortical networks may contribute to disturbances of key pathways involving ventral striato-pallidal GABA neurons and mediodorsal thalamic prefrontal glutamate neurons that may lead to the development of schizophrenia. The ventral striatum transmits emotional information to the cerebral cortex through a D(2) regulated accumbal-ventral pallidal-mediodorsal-prefrontal circuit which is of special interest to schizophrenia in view of the reduced number of glutamate mediodorsal-prefrontal projections associated with this disease. This circuit is especially vulnerable to D(2) receptor activity in the nucleus accumbens, since it produces a reduction in the prefrontal glutamate drive from the mediodorsal nucleus. The following D(2) receptor containing heterodimers/receptor mosaics are of special interest to schizophrenia: A(2A)-D(2), mGluR5-D(2), CB(1)-D(2), NTS(1)-D(2) and D(2)-D(3) and are discussed in this review. Fuxe K, Marcellino D, Woods AS, Giuseppina L, Antonelli T, Ferraro L, Tanganelli S, Agnati LF. Integrated signaling in heterodimers and receptor mosaics of different types of GPCRs of the forebrain: relevance for schizophrenia. J Neural Transm. 2009; Jan 21. [Epub ahead of print].

Building A New Conceptual Framework for Receptor Heteromers

Receptor heteromers constitute a new area of research that is reshaping our thinking about biochemistry, cell biology, pharmacology and drug discovery. In this commentary, IRP scientists recommend clear definitions that should facilitate both information exchange and research on this growing class of transmembrane signal transduction units and their complex properties. The authors also consider research questions underlying the proposed nomenclature, with recommendations for receptor heteromer identification in native tissues and their use as targets for drug development. FerrŽ S, Baler R, Bouvier M, Caron MG, Devi LA, Durroux T, Fuxe K, George SR, Javitch JA, Lohse MJ, Mackie K, Milligan G, Pfleger KD, Pin JP, Volkow ND, Waldhoer M, Woods AS, Franco R. Building new conceptual framework for receptor heteromers. Nat Chem Biol. 2009;5(3):131-4.

Anatomy and Cell Biology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Pedunculopontine and Laterodorsal Tegmental Nuclei Contain Distinct Populations of Cholinergic, Glutamatergic and GABAergic Neurons in the Rat

The pedunculopontine tegmental nucleus (PPTg) and laterodorsal tegmental nucleus (LDTg) provide cholinergic afferents to several brain areas. This cholinergic complex has been suggested to play a role in sleep, waking, motor function, learning and reward. To have a better understanding of the neurochemical organization of the PPTg/LDTg IRP researchers characterized the phenotype of PPTg/LDTg neurons by determining in these cells the expression of transcripts encoding choline acetyltransferase (ChAT), glutamic acid decarboxylase (GAD) or the vesicular glutamate transporters (vGluT1, vGluT2 and vGluT3). Within the PPTg/LDTg complex the authors found neurons expressing ChAT, vGluT2 or GAD transcripts, these neuronal phenotypes were intermingled, but not homogeneously distributed within the PPTg or LDTg. Previous studies suggested the presence of either glutamate or gamma-aminobutyric acid (GABA) immunolabeling in a large number of PPTg/LDTg cholinergic neurons, leading to the widespread notion that PPTg/LDTg cholinergic neurons co-release acetylcholine together with either glutamate or GABA. To assess the glutamatergic or GABAergic nature of the PPTg/LDTg

cholinergic neurons, the authors combined in situ hybridization (to detect vGluT2 or GAD transcripts) and immunohistochemistry (to detect ChAT), and found that over 95% of all PPTg/LDTg cholinergic neurons lack transcripts encoding either vGluT2 mRNA or GAD mRNA. As the vast majority of PPTg/LDTg cholinergic neurons lack transcripts encoding essential proteins for the vesicular transport of glutamate or for the synthesis of GABA, co-release of acetylcholine with either glutamate or GABA is unlikely to be a major factor in the interactions between acetylcholine, glutamate and GABA at the postsynaptic site. Wang HL, Morales M. Pedunculopontine and laterodorsal tegmental nuclei contain distinct populations of cholinergic, glutamatergic and GABAergic neurons in the rat. Eur J Neurosci. 2009;29(2):340-58.

Clinical Psychopharmacology Section, Chemical Biology Research Branch

Studies of the Biogenic Amine Transporters 13. Identification of "Agonist" and "Antagonist" Allosteric Modulators of Amphetamine-Induced Dopamine Release

Recent studies identified novel allosteric modulators of the dopamine transporter (DAT). N-(diphenylmethyl)-2-phenyl-4-quinazolinamine (SoRI-9804), N-(2,2-diphenylethyl)-2-phenyl-4-quinazolinamine (SoRI-20040), and N-(3,3-diphenylpropyl)-2-phenyl-4-quinazolinamine (SoRI-20041) partially inhibited [(125)I]RTI-55 binding, slowed the dissociation rate of [(125)I]RTI-55 from the DAT, and partially inhibited [(3)H]dopamine uptake. In the present study IRP scientists report that SoRI-9804 and SoRI-20040, at doses that do not alter release, partially inhibited D-amphetamine-induced DAT-mediated release of [(3)H]MPP(+) or [(3)H]dopamine from striatal synaptosomes ("DAT-mediated DA release") in a dose-dependent manner. SoRI-20041, which does not alter DAT-mediated DA release measured with [(3)H]DA, reversed the effect of SoRI-20040. SoRI-20040 and SoRI-9804 also partially inhibited DAT-mediated DA release induced by DA or (+/-)-3,4-methylenedioxyamphetamine, demonstrating that the observed partial inhibition is not specific for a particular DAT substrate. SoRI-9804 and SoRI-20040 did not attenuate D-amphetamine-induced release of [(3)H]5-HT from serotonergic, or [(3)H]MPP(+) from noradrenergic, nerve terminals. Kinetic experiments demonstrated that SoRI-9804, in contrast to cocaine, slowed D-amphetamine-induced release of [(3)H]MPP(+) from dopaminergic nerve terminals without altering the apparent rate constants. The two major findings of this paper are: 1) the identification of both "agonist" (SoRI-9804, SoRI-20040) and "antagonist" (SoRI-20041) allosteric modulators of D-amphetamine-induced DAT-mediated DA release, and 2) [(3)H]DA uptake and D-amphetamine-induced DAT-mediated efflux can be separately modulated. Such agents may have therapeutic potential for the treatment of stimulant addiction, parkinson's disease and other psychiatric disorders. Rothman RB, Dersch CM, Ananthan S, Partilla JS. J Pharmacol Exp Ther. 2009; (Epub ahead of print)

Evidence for the Involvement of Dopamine Transporters in Behavioral Stimulant Effects of Modafinil

Modafinil is prescribed for numerous medical conditions, but the drug's mechanism of action is unclear. Here IRP investigstors examined the interaction of modafinil with receptors and transporters in vitro, and compared pharmacological effects of the drug to those produced by indirect dopamine (DA) agonists, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR12909) and (+)-methamphetamine (METH). Modafinil was screened at various receptors and transporters using binding assays. Transporter-mediated uptake and release were examined in rat brain synaptosomes. Effects of modafinil on motor activity and neurochemistry were determined in rats undergoing in vivo microdialysis in n. accumbens. Of the receptors and transporters assayed, modafinil displayed measurable potency only at DA transporters (DAT), inhibiting [(3)H]DA uptake with an IC50 of 4.0

microM. Accordingly, modafinil pretreatment (10 microM) antagonized METH-induced release of the DAT substrate [(3)H]1-methyl-4-phenylpyridinium. Intravenous modafinil (20 & 60 mg/kg) produced dose-dependent increases in motor activity and extracellular DA, without affecting serotonin (5-HT). Analogous results were observed for GBR12909 (1 & 3 mg/kg), whereas METH (0.3 & 1 mg/kg) increased DA and 5-HT. Locomotor effects of all drugs were positively correlated with dialysate DA ($P<0.001$). Interestingly, modafinil pretreatment reduced METH-induced ambulation and DA release. These data show that modafinil interacts with DAT sites in rat brain, a property shared with agonist medications under investigation for treating cocaine dependence. Non-dopaminergic mechanisms may also contribute to the pharmacology of modafinil. Finally, the results suggest that modafinil should be tested as an adjunct for treating METH addiction. Zolkowska D, Jain R, Rothman RB, Partilla JS, Roth BL, Setola V, Prisinzano TE, Baumann MH. J Pharmacol Exp Ther. 2009; (Epub ahead of print).

Selective Suppression of Cocaine- versus Food-Maintained Responding by Monoamine Releasers in Rhesus Monkeys: Benzylpiperazine, (+)Phenmetrazine, and 4- Benzylpiperidine

Monoamine releasers constitute one class of drugs currently under investigation as potential agonist medications for the treatment of cocaine dependence. The efficacy and safety of monoamine releasers as candidate medications may be influenced in part by their relative potency to release dopamine and serotonin, and we reported previously that releasers with approximately 30-fold selectivity for dopamine vs. serotonin release may be especially promising. The present study examined the effects of the releasers benzylpiperazine, (+)phenmetrazine and 4-benzylpiperidine, which have 20-48-fold selectivity in vitro for releasing dopamine vs. serotonin. In an assay of cocaine discrimination, rhesus monkeys were trained to discriminate 0.4 mg/kg cocaine i.m. from saline in a two-key, food-reinforced procedure. Each of the releasers produced a dose- and time-dependent substitution for cocaine. 4-Benzylpiperidine had the most rapid onset and shortest duration of action. Phenmetrazine and benzylpiperazine had slower onsets and longer durations of action. In an assay of cocaine self-administration, rhesus monkeys were trained to respond for cocaine injections and food pellets under a second- order FR2(VR16:S) schedule. Treatment for 7 days with each of the releasers produced a dose-dependent and selective reduction in self-administration of cocaine (0.01 mg/kg/inj). The most selective effects were produced by phenmetrazine. Phenmetrazine also produced a downward shift in the cocaine self-administration dose effect curve, virtually eliminating responding maintained by a 30-fold range of cocaine doses (0.0032-0.1 mg/kg/inj) while having only small and transient effects on food-maintained responding. These findings support the potential utility of dopamine-selective releasers as candidate treatments for cocaine dependence. Negus SS, Baumann MH, Rothman RB, Mello NK, Blough BE. J Pharm Exp Ther. 2009; (Epub ahead of print).

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

The Future of Endocannabinoid-Oriented Clinical Research After CB(1) Antagonists

Great interest has been shown by the medical community and the public in the cannabinoid CB(1) receptor antagonists, such as rimonabant, for treatment of obesity, metabolic syndrome, and possibly drug addiction. This novel class of drug has therapeutic potential for other disorders, as the endocannabinoid system is involved in various health conditions. However, rimonabant, the first clinically available member of this class of drugs, has been linked to increased risk of anxiety, depression, and suicidality. Due to those risks, the European Medicines Agency called for its withdrawal from the market in October, 2008.

Shortly after this decision, several pharmaceutical companies (Sanofi-aventis, Merck, Pfizer, Solvay) announced that they would stop further clinical research on this class of drug. Here, IRP scientists provide an overview of those events and make several suggestions for continuing such clinical research, while safeguarding the safety of patients and clinical trial subjects. Le Foll B, Gorelick DA, Goldberg SR. The future of endocannabinoid-oriented clinical research after CB(1) antagonists. Psychopharmacology. 2009;Mar 20; Epub ahead of print.

The Endocannabinoid System: A New Molecular Target for the Treatment of Tobacco Addiction

Tobacco addiction is one of the leading preventable causes of mortality in the world and nicotine appears to be the main critical psychoactive component in establishing and maintaining tobacco dependence. Several lines of evidence suggest that the rewarding effects of nicotine, which underlie its abuse potential, can be modulated by manipulating the endocannabinoid system. For example, pharmacological blockade or genetic deletion of cannabinoid CB(1) receptors reduces or eliminates many behavioral and neurochemical effects of nicotine that are related to its addictive potential. This review will focus on the recently published literature about the role of the endocannabinoid system in nicotine addiction and on the endocannabinoid system as a novel molecular target for the discovery of medications for tobacco dependence. Scherma M, Fadda P, Le Foll B, Forget B, Fratta W, Goldberg SR, Tanda G. The endocannabinoid system: a new molecular target for the treatment of tobacco addiction. CNS Neurol Disord Drug Targets. 2008;7(5):468-81.

Endogenous Fatty Acid Ethanolamides Suppress Nicotine-induced Activation of Mesolimbic Dopamine Neurons Through Nuclear Receptors

Nicotine stimulates the activity of mesolimbic dopamine neurons, which is believed to mediate the rewarding and addictive properties of tobacco use. Accumulating evidence suggests that the endocannabinoid system might play a major role in neuronal mechanisms underlying the rewarding properties of drugs of abuse, including nicotine. Here, IRP scientists investigated the modulation of nicotine effects by the endocannabinoid system on dopamine neurons in the ventral tegmental area with electrophysiological techniques in vivo and in vitro. They discovered that pharmacological inhibition of fatty acid amide hydrolase (FAAH), the enzyme that catabolizes fatty acid ethanolamides, among which the endocannabinoid anandamide (AEA) is the best known, suppressed nicotine-induced excitation of dopamine cells. Importantly, this effect was mimicked by the administration of the FAAH substrates oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), but not methanandamide, the hydrolysis resistant analog of AEA. OEA and PEA are naturally occurring lipid signaling molecules structurally related to AEA, but devoid of affinity for cannabinoid receptors. They blocked the effects of nicotine by activation of the peroxisome proliferator-activated receptor-alpha (PPAR-alpha), a nuclear receptor transcription factor involved in several aspects of lipid metabolism and energy balance. Activation of PPAR-alpha triggered a nongenomic stimulation of tyrosine kinases, which might lead to phosphorylation and negative regulation of neuronal nicotinic acetylcholine receptors. These data indicate for the first time that the anorexic lipids OEA and PEA possess neuromodulatory properties as endogenous ligands of PPAR-alpha in the brain and provide a potential new target for the treatment of nicotine addiction. Melis M, Pillolla G, Luchicchi A, Muntoni AL, Yasar S, Goldberg SR, Pistis M. Endogenous fatty acid ethanolamides suppress nicotine-induced activation of mesolimbic dopamine neurons through nuclear receptors. J Neurosci. 2008;28(51):13985-94.

Interactions Between Environmental Aversiveness and the Anxiolytic Effects of Enhanced Cannabinoid Signaling by FAAH Inhibition in Rats

Since the discovery of endogenous cannabinoid signaling, the number of studies exploring its role in health and disease has increased exponentially.

Fatty acid amide hydrolase (FAAH), the enzyme responsible for degradation of the endocannabinoid anandamide, has emerged as a promising target for anxiety-related disorders. FAAH inhibitors (e.g., URB597) increase brain levels of anandamide and induce anxiolytic-like effects in rodents. Recent findings, however, questioned the efficacy of URB597 as an anxiolytic. IRP scientists tested here the hypothesis that conflicting findings are due to variations in the stressfulness of experimental conditions employed in various studies. They found that URB597 (0.1-0.3 mg/kg) did not produce anxiolytic effects when the aversiveness of testing procedures was minimized by handling rats daily before experimentation, by habituating them to the experimental room, or by employing low illumination during testing. In contrast, URB597 had robust anxiolytic effects when the aversiveness of the testing environment was increased by eliminating habituation to the experimental room or by employing bright lighting conditions. Unlike URB597, the benzodiazepine chlordiazepoxide (5 mg/kg) had anxiolytic effects under all testing conditions. The anxiolytic effects of URB597 were abolished by the cannabinoid CB1-receptor antagonist AM251, showing that they were mediated by CB1 receptors. Close inspection of experimental conditions employed in earlier reports suggests that conflicting findings with URB597 can be explained by different testing conditions, such as those manipulated in the present study. These findings show that FAAH inhibition does not affect anxiety under mildly stressful circumstances but protects against the anxiogenic effects of aversive stimuli. Haller J, Barna I, Barsvari B, Gyimesi Pelczer K, Yasar S, Panlilio LV, Goldberg S. Interactions between environmental aversiveness and the anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rats. Psychopharmacology. 2009;Mar 4; Epub ahead of print.

Building a New Conceptual Framework for Receptor Heteromers

Receptor heteromers constitute a new area of research that is reshaping our thinking about biochemistry, cell biology, pharmacology and drug discovery. In this commentary, IRP researchers recommend clear definitions that should facilitate both information exchange and research on this growing class of transmembrane signal transduction units and their complex properties. They also consider research questions underlying the proposed nomenclature, with recommendations for receptor heteromer identification in native tissues and their use as targets for drug development. FerrŽ S, Baler R, Bouvier M, Caron MG, Devi LA, Durroux T, Fuxe K, George SR, Javitch JA, Lohse MJ, Mackie K, Milligan G, Pfleger KD, Pin JP, Volkow ND, Waldhoer M, Woods AS, Franco R. Building a new conceptual framework for receptor heteromers. Nat Chem Biol. 2009;5(3):131-4.

GDNF Control of the Glutamatergic Cortico-Striatal Pathway Requires Tonic Activation of Adenosine A Receptors

Glial cell line-derived neurotrophic factor (GDNF) affords neuroprotection in Parkinson's disease in accordance with its ability to bolster nigrostriatal innervation. IRP scientists previously found that GDNF facilitates dopamine release in a manner dependent on adenosine A(2A) receptor activation. As motor dysfunction also involves modifications of striatal glutamatergic innervation, they now tested if GDNF and its receptor system, Ret (rearranged during transfection) and GDNF family receptor alpha1 controlled the cortico-striatal glutamatergic pathway in an A(2A) receptor-dependent manner. GDNF (10 ng/mL) enhanced (by approximately 13%) glutamate release from rat striatal nerve endings, an effect potentiated (up to approximately 30%) by the A(2A) receptor agonist CGS 21680 (10 nM) and prevented by the A(2A) receptor antagonist, SCH 58261 (50 nM). Triple immunocytochemical studies revealed that Ret and GDNF family receptor alpha1 were located in 50% of rat striatal glutamatergic terminals (immunopositive for vesicular glutamate transporters-1/2), where they were found to be co-located with A(2A) receptors. Activation of the glutamatergic system upon in vivo electrical stimulation of the rat cortico-striatal input induced striatal Ret phosphorylation that was prevented by pre-treatment with the A(2A) receptor antagonist, MSX-

3 (3 mg/kg). The results provide the first functional and morphological evidence that GDNF controls cortico-striatal glutamatergic pathways in a manner largely dependent on the co-activation of adenosine A(2A) receptors. Gomes CA, Sim›es PF, Canas PM, Quiroz C, Sebasti‹o AM, FerrŽ S, Cunha RA, Ribeiro JA. GDNF control of the glutamatergic cortico-striatal pathway requires tonic activation of adenosine A receptors. J Neurochem. 2009;108(5):1208-19.

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

Age at Menarche and Weight Concerns in Adolescent Smokers

Many girls adopt dieting and other practices (i.e. cigarette smoking) to control weight during puberty. This analysis explored the relationship between age at menarche and onset of daily smoking, and whether this relationship was influenced by weight concerns among treatment seeking female adolescents. The sample consisted of 71 participants enrolled in a smoking cessation trial (age 15.2±1.3 years; 74.7% European American, baseline BMI 24.7±5.4, age at menarche 11.7±1.3 years, Fagerstršm Test for Nicotine Dependence score 7.0±1.2). Over 60% of participants reported weight concerns at baseline, based on responses to the Eating Disorders module from the Diagnostic Interview for Children and Adolescents. Linear regression analyses revealed a significant association between age at menarche and age of onset of daily smoking (β=0.18±0.09, p=0.038). Having weight concerns did not modify the relationships between age at menarche and smoking trajectory/severity or abstinence. Findings support previous research showing that early maturation represents a risk factor for substance use. Further study in larger samples that include non-treatment-seeking adolescent female smokers is warranted. Jaszyna-Gasior M, Schroeder JR, Thorner ED, Heishman SJ, Collins CC, Lo S, Moolchan ET. Addictive Behaviors. 2009;34:92-5.

Behavioral Neuroscience Research Branch

Rapid Morphological Brain Abnormalities During Acute Methamphetamine Intoxication in the Rat: An Experimental Study Using Light and Electron Microscopy

This study describes morphological abnormalities of brain cells during acute methamphetamine (METH) intoxication in the rat and demonstrates the role of hyperthermia, disruption of the blood-brain barrier (BBB) and edema in their development. Rats with chronically implanted brain, muscle and skin temperature probes and an intravenous (i.v.) catheter were exposed to METH (9 mg/kg) at standard (23 ¡C) and warm (29 ¡C) ambient temperatures, allowing for the observation of hyperthermia ranging from mild to pathological (38-42 ¡C). When brain temperature peaked or reached a level suggestive of possible lethality (>41.5 ¡C), rats were injected with Evans blue (EB), rapidly anesthetized, perfused, and their brains were taken for further analyses. Four brain areas (cortex, hippocampus, thalamus and hypothalamus) were analyzed for EB extravasation, water and electrolyte (Na+, K+, Cl-) contents, immunostained for albumin and glial fibrillary acidic protein (GFAP), and examined for neuronal, glial and axonal alterations using standard light and electron microscopy. These examinations revealed profound abnormalities in neuronal, glial, and endothelial cells, which were stronger with METH administered at 29 ¡C than 23 ¡C and tightly correlated with brain and body hyperthermia. These changes had some structural specificity, but in each structure they tightly correlated with increases in EB levels, the numbers of albumin-positive cells, and water and ion contents, suggesting leakage of the BBB, acutely developing brain edema, and serious shifts in brain ion homeostasis as leading factors underlying brain abnormalities. While most of these acute structural and functional abnormalities appear to be reversible, they could trigger subsequent cellular alterations in the brain and accelerate neurodegeneration—the most dangerous complication of chronic amphetamine-

like drug abuse. Sharma, HS, Kiyatkin, EA. Rapid morphological brain abnormalities during acute methamphetamine intoxication in the rat: An experimental study using light and electron microscopy. Journal of Chemical Neuroanatomy. 2009;37:18-32.

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 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 scientists 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 corticotroping-releasing factor network. Biological Psychiatry. 2009; Feb 27 [E-pub ahead of print].

Long-Lasting Incubation of Conditioned Fear in Rats

In 1937, Diven (1) reported that human fear responses to cues previously paired with shock progressively increase or incubate over 24 hours. Since then, fear incubation has been demonstrated in both humans and nonhumans. However, the difficulty of demonstrating long-lasting fear incubation in rodents has hampered the study of the underlying mechanisms of this incubation. Here, IRP investigators describe a rat procedure where fear reliably incubates over time. They trained food-restricted rats to lever-press for food pellets in daily 90-min sessions. They then gave each rat one-hundred 30-s tones co-terminating with a 0.5-s, 0.5 mA footshock over 10 days (10 pairings per day). Groups of rats (n=10-15) were then given 4 presentations of the tone (the fear cue) 2, 15, 31 or 61 days after fear conditioning training and were assessed for conditioned suppression of lever-pressing. The authors found that conditioned fear responses were significantly higher 31 and 61 days after fear training than after 2 or 15 days. In control experiments, the authors showed that extensive tone-shock pairing is necessary for the emergence of fear incubation, and that it is unlikely that non-associative factors contribute to this incubation. The authors describe a procedure for generating reliable and long-lasting conditioned fear incubation. This procedure can be used to study mechanisms of fear incubation, and may provide a model for studying the mechanisms of delayed-onset posttraumatic stress disorder that occur in a sub-population of people previously exposed to chronic stressors. Pickens CL, Golden SA, Adams-Deutsch T, Nair SG, Shaham Y. Long-lasting incubation of conditioned fear in rats. Biological Psychiatry. 2009; Jan 22 Epub ahead of print].

Ventral mPFC Neuronal Activity Plays an Important Role in the Incubation of Cocaine Craving

Cue-induced drug-seeking in rodents progressively increases after withdrawal from cocaine, suggesting that cue-induced cocaine craving incubates over time. Here, IRP scientists explored the role of the medial prefrontal cortex (mPFC, a brain area previously implicated in cue-induced cocaine seeking) in this incubation. They trained rats to self-administer cocaine for 10 d (6 h/d, infusions were paired with a tone-light cue), and then assessed after 1 or 30 withdrawal days the effect of exposure to cocaine cues on lever presses in extinction tests. They found that cue-induced cocaine-seeking in the extinction tests was higher after 30 withdrawal days than after 1 day. The time-dependent increases in extinction responding were associated with large (ventral mPFC) or modest (dorsal mPFC) increases in ERK phosphorylation (a measure of ERK activity and an index of neuronal activation). After 30 withdrawal days, ventral but not dorsal injections of muscimol+baclofen (GABAa+GABAb receptor agonists that inhibit neuronal activity) decreased extinction responding. After 1 withdrawal day, ventral but not dorsal mPFC injections of bicuculline+saclofen (GABAa+GABAb receptor antagonists that increase neuronal activity) strongly increased extinction responding. Finally, muscimol+baclofen had minimal effect on extinction responding after 1 day, and in cocaine-experienced rats, ventral mPFC injections of muscimol+baclofen or bicuculline+saclofen had no effect on lever presses for an oral sucrose solution. The present results indicate that ventral mPFC neuronal activity plays an important role in the incubation of cocaine craving. Koya E, Uejima JL, Wihbey KA, Bossert JM, Hope BT, Shaham Y. Neuropharmacology. 2009;56(S1):177-185.

Chemical Biology Research Branch

Mechanisms of Withdrawal-Associated Increases in Heroin Self-Administration: Pharmacologic Modulation of Heroin vs Food Choice in Heroin-Dependent Rhesus Monkeys

Opioid withdrawal can produce a constellation of physiological and behavioral signs, including an increase in opioid self-administration. Different mechanisms mediate different withdrawal signs, and the present study used pharmacologic tools to assess mechanisms underlying withdrawal-associated increases in opioid reinforcement. Five rhesus monkeys were rendered heroin dependent via daily 21-h heroin self-administration sessions. One hour after each heroin self-administration session, monkeys chose between heroin (0-0.1 mg/kg per injection) and food (1 g pellets) during 2-h choice sessions. Under these conditions, heroin maintained a dose-dependent increase in heroin choice, such that monkeys responded primarily for food when low heroin doses were available (0-0.01 mg/kg per injection) and primarily for heroin when higher heroin doses were available (0.032-0.1 mg/kg per injection). Periods of spontaneous withdrawal were intermittently introduced by omitting one 21-h heroin self-administration session, and test drugs were administered during these withdrawal periods. Untreated withdrawal robustly increased heroin choice during choice sessions. Withdrawal-associated increases in heroin choice were completely suppressed by the mu opioid agonist morphine (0.032-0.32 mg/kg/h, i.v.), but not by the alpha-2 noradrenergic agonist clonidine (0.01-0.1 mg/kg/h, i.v.), the dopamine/ norepinephrine releaser amphetamine (0.032-0.1 mg/kg/h, i.v.), or the kappa-opioid antagonist 5'-guanidinonaltrindole (1.0 mg/kg, i.m.). The corticotropin-releasing factor 1 antagonist antalarmin (1.0-10 mg/kg per day, i.m.) produced a morphine-like suppression of withdrawal-associated increases in heroin choice in one of three monkeys. These results suggest that mechanisms of withdrawal-associated increases in the relative reinforcing efficacy of opioid agonists may be different from mechanisms of many other somatic, mood-related, and motivational signs of opioid withdrawal. Negus SS, Rice KC. Mechanisms of withdrawal-associated increases in heroin self-administration: pharmacologic modulation of heroin vs

food choice in heroin-dependent rhesus monkeys. Neuropsychopharmacology. 2009;4(4):899-911.

Pharmacological Properties and Discriminative Stimulus Effects of a Novel and Selective 5-HT2 Receptor Agonist AL-38022A [(S)-2-(8,9-dihydro-7H-pyrano[2,3-g]indazol-1-yl)-1-methylethylamine]

PAL-38022A is a novel synthetic serotonergic (5-HT) ligand that exhibited high affinity for each of the 5-HT2 receptor subtypes (Ki ² 2.2 nM), but a significantly lower (> 100-fold less) affinity for other 5-HT receptors. In addition, AL-38022A displayed a very low affinity for a broad array of other receptors, neurotransmitter transport sites, ion channels, and second messenger elements, making it a relatively selective agent. AL-38022A potently stimulated functional responses via native and cloned rat (EC50 range: 1.9-22.5 nM) and human (EC50 range: 0.5-2.2 nM) 5-HT2 receptor subtypes including [Ca2+]i mobilization and tissue contractions with apparently similar potencies and intrinsic activities and was a full agonist at all 5-HT2 receptor subtypes. The CNS activity of AL-38022A was assessed by evaluating its discriminative stimulus effects in both a rat and a monkey drug discrimination paradigm using DOM as the training drug. AL-38022A fully generalized to the DOM stimulus in each of these studies; in monkeys MDL 100907 antagonized both DOM and AL-38022A. The pharmacological profile of AL-38022A suggests that it could be a useful tool in defining 5-HT2 receptor signaling and receptor characterization where 5-HT may function as a neurotransmitter. May, JA, Sharif, NA, Chen, H-H, Liao JC, Kelly CR, Glennon RA, Young R, Li JX, Rice KC, France C. Pharmacological properties and discriminative stimulus effects of a novel and selective 5-HT2 receptor agonist AL-38022A [(S)-2-(8,9-dihydro-7H-pyrano[2,3-g]indazol-1-yl)-1-methylethylamine]. Pharmacol Biochem Behav. 2009;91:307-14.

Corticotropin-Releasing Factor-1 Receptor Antagonists Decrease Heroin Self-Administration in Long- but not Short-Access Rats

Dysregulation of the stress-related corticotropin-releasing factor (CRF) system has been implicated in the development of drug dependence. The present study examined the effects of administering CRF type 1 (CRF1) receptor antagonists on heroin self-administration in animals allowed short (1 hour) or long (8-12 hours) access to intravenous heroin self-administration sessions. The nonpeptide CRF1 antagonists MJL-1-109-2 (1 hour versus 8 hours access) or R121919 (1 hour versus 12 hours access) were systemically injected in both short- and long-access rats. MJL-1-109-2 (10 mg/kg) and R121919 (10 and 20 mg/kg) reduced heroin self-administration in long-access animals without altering heroin intake in short-access animals. Both MJL-1-109-2 and R121919 decreased first-hour intravenous heroin self-administration selectively in long-access rats, with R121919 decreasing cumulative heroin intake across the 12-hour session. The results demonstrate that blockade of the CRF-CRF1 receptor system attenuates the increased heroin intake of rats with extended access to the drug. Greenwell TN, Funk CK, Cottone P, Richardson HN, Chen SA, Rice KC, Zorrilla EP, Koob GF. Corticotropin-releasing factor-1 receptor antagonists decrease heroin self-administration in long- but not short-access rats. Addiction Biology. 2009;14:130-43.

Role of Delta Opioid Efficacy as a Determinant of Mu/Delta Opioid Interactions in Rhesus Monkeys

Delta opioid agonists can selectively enhance the antinociceptive effects of mu opioid agonists without enhancing some other, potentially undesirable mu agonist effects. However, the degree of delta receptor efficacy required to produce this profile of interactions is unknown. To address this issue, the present study examined interactions produced by the mu agonist fentanyl and the intermediate-efficacy delta opioid MSF61 in rhesus monkeys. For comparison, interactions were also examined between fentanyl and the relatively high-efficacy delta agonist SNC243A and the delta antagonist naltrindole, which has negligible efficacy at delta receptors. Two different

behavioral procedures were used: (a) a warm-water tail-withdrawal assay of thermal nociception, and (b) an assay of schedule-controlled responding for food reinforcement. Drug interactions within each procedure were evaluated using dose-addition analysis to compare experimental results with expected additivity. Drug interactions across procedures were evaluated using dose-ratio analysis to assess relative potencies to produce antinociception vs. response-rate suppression. As expected, dose-addition analysis found that fentanyl/SNC243A interactions were superadditive in the assay of antinociception but additive in the assay of schedule-controlled responding. Conversely, fentanyl/MSF61 interactions were generally additive in both procedures, and fentanyl/naltrindole interactions were additive or subadditive in both procedures. Dose-ratio analysis found that fentanyl alone produced antinociception and rate suppression with similar potencies. Some fentanyl/SNC243A mixtures produced antinociception with up to 4-fold greater potency than rate-suppression. However, fentanyl/MSF61 and fentanyl/naltrindole mixtures produced antinociception with lower potency than rate suppression. These results suggest that relatively high delta receptor efficacy is required for mu/delta antinociceptive synergy. Negus SS, Bear AE, Folk JE, Rice KC. Role of Delta Opioid Efficacy as a Determinant of Mu-Delta Opioid Interactions in Rhesus Monkeys. Role of Delta Opioid Efficacy as a Determinant of Mu/Delta Opioid Interactions in Rhesus Monkeys. Eur J Pharmacol 2009;602:92-100.

The Selective Non-Peptidic Delta Opioid Agonist SNC80 does not Facilitate Intracranial Self-Stimulation in Rats

Delta opioid receptor agonists are under development for a variety of clinical applications, and some findings in rats raise the possibility that agents with this mechanism have abuse liability. The present study assessed the effects of the non-peptidic delta opioid agonist SNC80 in an assay of intracranial self-stimulation (ICSS) in rats. ICSS was examined at multiple stimulation frequencies to permit generation of frequency-response rate curves and evaluation of curve shifts produced by experimental manipulations. Drug-induced leftward shifts in ICSS frequency-rate curves are often interpreted as evidence of abuse liability. However, SNC80 (1.0-10 mg/kg s.c.; 10-56 mg/kg i.p.) failed to alter ICSS frequency-rate curves at doses up to those that produced convulsions in the present study or other effects (e.g. antidepressant effects) in previous studies. For comparison, the monoamine releaser d-amphetamine (0.1-1.0 mg/kg, i.p.) and the kappa agonist U69,593 (0.1-0.56 mg/kg, i.p.) produced dose-dependent leftward and rightward shifts, respectively, in ICSS frequency-rate curves, confirming the sensitivity of the procedure to drug effects. ICSS frequency-rate curves were also shifted by two non-pharmacological manipulations (reductions in stimulus intensity and increases in response requirement). Thus, SNC80 failed to facilitate or attenuate ICSS-maintained responding under conditions in which other pharmacological and non-pharmacological manipulations were effective. These results suggest that non-peptidic delta opioid receptor agonists have negligible abuse-related effects in rats. Do Carmo GP, Folk JE, Rice KC, Chartoff E, Carlezon WA, Negus SS. The Selective Non-Peptidic Delta Opioid Agonist SNC80 does not Facilitate Intracranial Self-Stimulation in Rats. Eur J Pharmacol. 2009;604:58-65.

Discriminative Stimulus Effects of 1-(2,5-Dimethoxy-4-Methylphenyl)-2-Aminopropane in Rhesus Monkeys: Antagonism and Apparent pA2 Analyses

Discriminative stimulus effects of the serotonin (5-HT) receptor agonist 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) have been studied in rats and, more recently, in rhesus monkeys. This study examined DOM, 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7), and dipropyltryptamine hydrochloride (DPT) alone and in combination with three antagonists, MDL100907 [(±)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]], ketanserin [3-[2-[4-(4-fluorobenzoyl) piperidin-1-yl]ethyl]-1H-quinazoline-2,4-

dione], and ritanserin [6-[2-[4-[bis(4-fluorophenyl) methylidene]piperidin-1-yl]ethyl]-7-methyl-[1,3]thiazolo[2,3-b]pyrimidin-5-one], to identify the 5-HT receptor subtype(s) that mediates the discriminative stimulus effects of these 5-HT receptor agonists. Four adult rhesus monkeys discriminated between 0.32 mg/kg s.c. DOM and vehicle while responding under a fixed ratio 5 schedule of stimulus shock termination. DOM, 2C-T-7, and DPT dose-dependently increased responding on the DOM-associated lever. MDL100907 (0.001-0.01 mg/kg), ketanserin (0.01-0.1 mg/kg), and ritanserin (0.01-0.1 mg/kg) each shifted the dose-response curves of DOM, 2C-T-7, and DPT rightward in a parallel manner. Schild analysis of each drug combination was consistent with a simple, competitive, and reversible interaction. Similar apparent affinity (pA2) values were obtained for MDL100907 in combination with DOM (8.61), 2C-T-7 (8.58), or DPT (8.50), for ketanserin with DOM (7.67), 2C-T-7 (7.75), or DPT (7.71), and for ritanserin with DOM (7.65), 2C-T-7 (7.75), or DPT (7.65). Potency of antagonists in this study was correlated with binding affinity at 5-HT2A receptors and not at 5-HT2C or {alpha}1 adrenergic receptors. This study used Schild analysis to examine receptor mechanisms mediating the discriminative stimulus effects of hallucinogenic drugs acting at 5-HT receptors; results provide quantitative evidence for the predominant, if not exclusive, role of 5-HT2A receptors in the discriminative stimulus effects of DOM, 2C-T-7, and DPT in rhesus monkeys. Li J-X, Rice KC, France CP. Discriminative stimulus effects of 1-(2,5-Dimethoxy-4-Methylphenyl)-2-Aminopropane in rhesus monkeys: antagonism and apparent pA2 analyses. J Pharmacol Exp Ther. 2009;328:976-81.

Presynaptic CRF1 Receptors Mediate the Ethanol Enhancement of GABAergic Transmission in the Mouse Central Amygdala

Corticotropin-releasing factor (CRF) is a 41-amino-acid neuropeptide involved in stress responses initiated from several brain areas, including the amygdala formation. Research shows a strong relationship between stress, brain CRF, and excessive alcohol consumption. Behavioral studies suggest that the central amygdala (CeA) is significantly involved in alcohol reward and dependence. IRP scientists recently reported that the ethanol augmentation of GABAergic synaptic transmission in rat CeA involves CRF1 receptors, because both CRF and ethanol significantly enhanced the amplitude of evoked GABAergic inhibitory postsynaptic currents (IPSCs) in CeA neurons from wild-type (WT) and CRF2 knockout (KO) mice, but not in neurons of CRF1 KO mice. The present study extends these findings using selective CRF receptor ligands, gene KO models, and miniature IPSC (mIPSC) analysis to assess further a presynaptic role for the CRF receptors in mediating ethanol effects in the CeA. In whole-cell patch recordings of pharmacologically isolated GABAAergic IPSCs from slices of mouse CeA, both CRF and ethanol augmented evoked IPSCs in a concentration-dependent manner, with low EC50s. A CRF1 (but not CRF2) KO construct and the CRF1-selective nonpeptide antagonist NIH-3 (LWH-63) blocked the augmenting effect of both CRF and ethanol on evoked IPSCs. Furthermore, the new selective CRF1 agonist stressin1, but not the CRF2 agonist urocortin 3, also increased evoked IPSC amplitudes. Both CRF and ethanol decreased paired-pulse facilitation (PPF) of evoked IPSCs and significantly enhanced the frequency, but not the amplitude, of spontaneous miniature GABAergic mIPSCs in CeA neurons of WT mice, suggesting a presynaptic site of action. The PPF effect of ethanol was abolished in CeA neurons of CRF1 KO mice. The CRF1 antagonist NIH-3 blocked the CRF- and ethanol-induced enhancement of mIPSC frequency in CeA neurons. These data indicate that presynaptic CRF1 receptors play a critical role in permitting or mediating ethanol enhancement of GABAergic synaptic transmission in CeA, via increased vesicular GABA release, and thus may be a rational target for the treatment of alcohol abuse and alcoholism. Nie Z, Zorrilla EP, Madamba SG, Rice KC, Roberto M, Siggins GR. Presynaptic CRF1 receptors mediate the ethanol enhancement of GABAergic transmission in the mouse central amygdala. The ScientificWorld JOURNAL. 2009;9:68-85.

Synthesis of 2-(5Z,8Z,11Z,14Z)-Icosa-5,8,11,14-tetraenamidoethyl-d4 Dihydrogen Phosphate, Tetra-deuterated pAEA

A labile intermediate phospho-anandamide (2-(5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenamidoethyl dihydrogen phosphate, pAEA) has been identified in mouse brain and macrophages, but its precise quantitation was difficult because of its low concentration and chemical instability. IRP researchers report the synthesis of tetra-deuterated pAEA from 2-aminoethyl dihydrogen phosphate-1,1,2,2-d4 and (5Z,8Z,11Z,14Z)-2,5-dioxopyrrolidin-1-yl icosa-5,8,11,14-tetraenoate. The compound will be used to quantitate the pAEA necessary for a novel biosynthetic pathway. Cheng K, Saha B, Mahadevan A, Razdan RK, Kunos G, Jacobson AE, Rice KC. Synthesis of 2-(5Z,8Z,11Z,14Z)-Icosa-5,8,11,14-tetraenamidoethyl-d4 dihydrogen phosphate, tetra-deuterated pAEA. J Labelled Comp Radiopharm. 2008;51(12):389-90.

Probes for Narcotic Receptor Mediated Phenomena. 37.(1) Synthesis and Opioid Binding Affinity of the Final Pair of Oxide-Bridged Phenylmorphans, the Ortho- and Para-b-Isomers and their N-Phenethyl Analogues, and the Synthesis of the N-Phenethyl Analogues of the Ortho- and Para-d-Isomers

In the isomeric series of 12 racemic topologically rigid N-methyl analogues of oxide-bridged phenylmorphans, all but two of the racemates, the ortho- and para-b-oxide-bridged phenylmorphans 20 and 12, have remained to be synthesized. The b-isomers were very difficult to synthesize because of the highly strained 5,6-trans-fused ring junction that had to be formed. The authors' successful strategy required functionalization of the position para (or ortho) to a fluorine atom on the aromatic ring using an electron-withdrawing nitro group to activate that fluorine. The racemic N-phenethyl analogues 24 and 16 were moderately potent κ-receptor antagonists in the [35S]GTPϒS assay. IRP researchers synthesized the N-phenethyl-substituted oxide-bridged phenylmorphans in the ortho- and para-d-oxide-bridged phenylmorphan series (51 and 52) which had not been previously evaluated using contemporary receptor binding assays to see whether they also have higher affinity for opioid receptors than their N-methyl relatives 46 and 47. Kurimura M, Liu H, Sulima A, Hashimoto A, Przybyl AK, Ohshima E, Kodato S, Deschamps JR, Dersch C M, Rothman RB, Lee YS, Jacobson AE, Rice KC. Probes for Narcotic Receptor Mediated Phenomena. 37. (1) Synthesis and opioid binding affinity of the final pair of oxide-bridged phenylmorphans, the ortho- and para-b-isomers and their n-phenethyl analogues, and the synthesis of the n-phenethyl analogues of the ortho- and para-d-isomers. J Med Chem. 2008; 51(24):7866-81.

Genetic and Early Environmental Factors Interact to Influence Ethanol's Motivational Effects

To explore these issues, a reciprocal cross-fostering paradigm was applied to Fischer and Lewis rats. The adult female offspring received vehicle or the kappa opioid antagonist nor-BNI (1 mg/kg) followed by assessments of conditioned taste aversion (CTA), blood alcohol concentrations (BACs) and hypothermia induced by 1.25 g/kg intraperitoneal ethanol. CTA acquisition in the in-fostered Fischer and Lewis animals did not differ; however, the Fischer maternal environment produced stronger acquisition in the cross-fostered Lewis rats versus their in-fostered counterparts. CTAs in the Fischer rats were not affected by cross-fostering. In extinction, the in-fostered Lewis animals displayed stronger aversions than the Fischer groups on two trials (of 12) whereas the cross-fostered Lewis differed from the Fischer groups on nine trials. Despite these CTA effects, Lewis rats exhibited higher BACs and stronger hypothermic responses than Fischer with no cross-fostering effects in either strain. No phenotypes were affected by nor-BNI. These data extend previous findings dissociating the aversive and peripheral physiological effects of ethanol in female Fischer and Lewis rats, and highlight the importance of genetic and early environmental factors in shaping subsequent responses to alcohol's motivational effects in adulthood. Roma PG, Rinker JA, Serafine KM, Chen S A, Barr CS, Cheng K, Rice, KC, Riley AL. Genetic and early environmental factors

interact to influence ethanol's motivational effects. Pharmacol Biochem Behav. 2008;91(1):134-39.

Discriminative Stimulus Properties of Naloxone in Long-Evans Rats: Assessment with the Conditioned Taste Aversion Baseline of Drug Discrimination Learning

The characterization of the discriminative stimulus properties of naloxone has focused primarily on its actions at the mu opioid receptor, although naloxone also displays an affinity for delta and kappa receptor subtypes. The present study extends this characterization of the naloxone cue by investigating if relatively specific antagonists for the mu (naltrexone: 0.10-0.56 mg/kg), delta (naltrindole: 1-18 mg/kg), and kappa (MR2266: 1.8-10 mg/kg) opioid receptor subtypes will substitute for naloxone in animals trained to discriminate naloxone from its vehicle. The temporal nature of the naloxone cue was examined by varying pretreatment time points (15, 30, 45, 60 min). Finally, various doses of naltrexone methobromide (1-18 mg/kg) were assessed to determine peripheral mediation of the cue. Female Long-Evans rats (N = 30) received an injection of naloxone (1 mg/kg; i.p.) 15 min prior to a pairing of saccharin (20-min access) and the emetic LiCl (1.8 mEq; i.p.; n = 16, group NL) or vehicle (n = 14, group NW); on other days, they were injected with saline prior to saccharin alone. Substitution tests with compounds with various receptor affinities and selective CNS and PNS actions were then assessed. Only naloxone and naltrexone produced dose-dependent decreases in saccharin consumption. Naloxone administered at 15 and 30 min before saccharin produced decreases in consumption similar to that displayed on training days. Naltrexone methobromide substituted only at the highest dose tested (18 mg/kg). Naloxone's stimulus effects appear to be mediated centrally via activity at the mu opioid receptor. Davis CM, Stevenson GW, Ca–adas F, Ullrich T, Rice KC, Riley AL. Discriminative stimulus properties of naloxone in Long-Evans rats: assessment with the conditioned taste aversion baseline of drug discrimination learning. Psychopharmacology. 2009;203(2):421-29.

Synthesis and Pharmacological Effects of the Enantiomers of the N-phenethyl Analogues of the Ortho and Para e- and f-oxide-bridged Phenylmorphans

The N-phenethyl analogues of (1R*,4aR*,9aS*)-2-phenethyl-1,3,4,9a-tetrahydro-2H-1,4a-propanobenzofuro[2,3-c]pyridin-6-ol and 8-ol and (1R*,4aR*,9aR*)-2-phenethyl-1,3,4,9a-tetrahydro-2H-1,4a-propanobenzofuro[2.3-c]pyridin-6-ol and 8-ol, the ortho- (43) and para-hydroxy e- (20), and f-oxide-bridged 5-phenylmorphans (53 and 26) were prepared in racemic and enantiomerically pure forms from a common precursor, the quaternary salt 12. Optical resolutions were accomplished by salt formation with suitable enantiomerically pure chiral acids or by preparative HPLC on a chiral support. The N-phenethyl (-)- para-e enantiomer (1S,4aS,9aR-(-)-20) was found to be a mu-opioid agonist with morphine-like antinociceptive activity in a mouse assay. In contrast, the N-phenethyl (-)-ortho-f enantiomer (1R,4aR,9aR-(-)-53) had good affinity for the mu-opioid receptor (K(i) = 7 nM) and was found to be a mu-antagonist both in the [(35)S]GTP-gamma-S assay and in vivo. The molecular structures of these rigid enantiomers were energy minimized with density functional theory at the level B3LYP/6-31G* level, and then overlaid on a known potent mu-agonist. This superposition study suggests that the agonist activity of the oxide-bridged 5-phenylmorphans can be attributed to formation of a seven membered ring that is hypothesized to facilitate a proton transfer from the protonated nitrogen to a proton acceptor in the mu-opioid receptor. Zezula J, Singer L, Przyby AK, Hashimoto A, Dersch CM, Rothman, RB, Deschamps, J, Lee YS, Jacobson AE, Rice, KC. Synthesis and pharmacological effects of the enantiomers of the N-phenethyl analogues of the ortho and para e- and f-oxide-bridged phenylmorphans. Org Biomol Chem. 2008;6(16):2868-83.

Integration of In Vivo and In Vitro Approaches to Characterize the

Toxicity of Antalarmin, a Corticotropin-Releasing Hormone Receptor Antagonist

Non-clinical studies were conducted to evaluate the toxicity of Antalarmin, a corticotropin-releasing hormone type 1 receptor antagonist being developed for therapy of stress-related pathologies. Antalarmin was not genotoxic in bacterial mutagenesis assays, mammalian cell mutagenesis assays, or in vivo DNA damage assays. In a 14-day range-finding study in rats, Antalarmin doses >or=500 mg/kg/day (3,000 mg/m(2)/day) induced mortality. In a 90-day toxicity study in rats, no gross toxicity was seen at doses of 30, 100, or 300 mg/kg/day (180, 600, or 1,800 mg/m(2)/day, respectively). Antalarmin (300 mg/kg/day) induced mild anemia, increases in serum gamma-glutamyl transferase activity, and microscopic hepatic pathology (bile duct hyperplasia and epithelial necrosis, periportal inflammation). Microscopic renal changes (cortical necrosis, inflammation, hypertrophy, nephropathy) were observed in rats at all Antalarmin doses. In a 14-day range-finding study in dogs, Antalarmin doses >or=50mg/kg/day (1,000 mg/m(2)/day) induced repeated emesis and bone marrow suppression. In a 90-day toxicity study in dogs, Antalarmin (4, 8, or 16 mg/kg/day (80, 160, or 320 mg/m(2)/day, respectively)) induced bone marrow and lymphoid depletion, but no gross toxicity. Comparative in vitro studies using rat, dog, and human neutrophil progenitors demonstrated that canine bone marrow cells are highly sensitive to Antalarmin cytotoxicity, while rat and human bone marrow cells are relatively insensitive. As such, the bone marrow toxicity observed in dogs is considered likely to over-predict Antalarmin toxicity in humans. The hepatic and renal toxicities seen in rats exposed to Antalarmin identify those tissues as the most likely targets for Antalarmin toxicity in humans. Horn TL, Harder JB, Johnson WD, Curry PT, Parchment RE, Morrissey RL, Mellick PW, Calis KA, Gold PW, Rice KC, Contoreggi C, Charney DS, Cizza G, Glaze ER, Tomaszewski JE, McCormick DL. Integration of in vivo and in vitro approaches to characterize the toxicity of Antalarmin, a corticotropin-releasing hormone receptor antagonist. Toxicology. 2008;248(1):8-17.

Non-Stereoselective Reversal of Neuropathic Pain by Naloxone and Naltrexone: Involvement of Toll-Like Receptor 4 (TLR4)

Although activated spinal cord glia contribute importantly to neuropathic pain, how nerve injury activates glia remains controversial. It has recently been proposed, on the basis of genetic approaches, that toll-like receptor 4 (TLR4) may be a key receptor for initiating microglial activation following L5 spinal nerve injury. The present studies extend this idea pharmacologically by showing that TLR4 is key for maintaining neuropathic pain following sciatic nerve chronic constriction injury (CCI). Established neuropathic pain was reversed by intrathecally delivered TLR4 receptor antagonists derived from lipopolysaccharide. Additionally, (+)-naltrexone, (+)-naloxone, and (-)-naloxone, which we show here to be TLR4 antagonists in vitro on both stably transfected HEK293-TLR4 and microglial cell lines, suppressed neuropathic pain with complete reversal upon chronic infusion. Immunohistochemical analyses of spinal cords following chronic infusion revealed suppression of CCI-induced microglial activation by (+)-naloxone and (-)-naloxone, paralleling reversal of neuropathic pain. Together, these CCI data support the conclusion that neuron-to-glia signaling through TLR4 is important not only for initiating neuropathic pain, as suggested previously, but also for maintaining established neuropathic pain. Furthermore, these studies suggest that the novel TLR4 antagonists (+)-naloxone and (-)-naloxone can each fully reverse established neuropathic pain upon multi-day administration. This finding with (+)-naloxone is of potential clinical relevance. This is because (+)-naloxone is an antagonist that is inactive at the (-)-opioid selective receptors on neurons that produce analgesia. Thus, these data suggest that (+)-opioid antagonists such as (+)-naloxone may be useful clinically to suppress glial activation, yet (-)-opioid agonists suppress pain. Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, Sholar PW, Patel SJ, Crysdale NY, Harrison JA, Maier SF, Rice KC, Watkins LR. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone:

involvement of toll-like receptor 4 (TLR4). Eur J Neurosci. 2008;28(1):20-9.

Evidence for a Mu-Delta Opioid Receptor Complex in CHO Cells Co-Expressing Mu and Delta Opioid Peptide Receptors

Based on non-competitive binding interactions IRP scientists suggested that mu and delta receptors associate as a mu/delta receptor complex in rat brain. They hypothesized that the same non-competitive binding interactions observed in rat brain will be seen in CHO cells that co-express mu and delta receptors, but not in cells that express just mu or delta receptors. They used CHO cells expressing the cloned human mu receptor, cloned human delta receptor, or cloned mouse delta/human mu ("dimer cell"). Cell membranes were prepared from intact cells pretreated with 100nM SUPERFIT. [(3)H][d-Ala(2),d-Leu(5)]enkephalin binding assays followed published procedures. SUPERFIT, a delta-selective irreversible ligand, decreased [(3)H][d-Ala(2),d-Leu(5)]enkephalin binding to delta receptors by approximately 75% and to mu receptors by approximately 50% in dimer cells. SUPERFIT treatment did not decrease [(3)H][d-Ala(2),d-Leu(5)]enkephalin binding to mu cells. The IC(50) values observed in SUPERFIT-treated dimer cells were: [d-Pen(2),d-Pen(5)]enkephalin (1820nM) and morphine (171nM). Saturation binding experiments with SUPERFIT-treated dimer cells showed that [d-Pen(2),d-Pen(5)]enkephalin (5000nM) was a competitive inhibitor. In contrast, morphine (1000nM) lowered the B(max) from 1944fmol/mg to 1276fmol/mg protein (35% decrease). Both [d-Pen(2),d-Pen(5)]enkephalin and morphine competitively inhibited [(3)H][d-Ala(2),d-Leu(5)]enkephalin binding to SUPERFIT-treated mu cells. The results indicate that the mu-delta opioid receptor complex defined on the basis of non-competitive binding interactions in rat brain over 20 years ago likely occurs as a consequence of the formation of mu-delta heterodimers. SUPERFIT-treated dimer cells may provide a useful model to study the properties of mu-delta heterodimers. Rutherford JM, Wang J, Xu H, Dersch CM, Partilla JS, Rice KC, Rothman RB. Evidence for a mu-delta opioid receptor complex in CHO cells co-expressing mu and delta opioid peptide receptors. Peptides. 2008 Aug;29(8):1424-31.

Behavioral Pharmacology of the Mu/Delta Opioid Glycopeptide MMP2200 in Rhesus Monkeys

H(2)N-Tyr-D-Thr-Gly-Phe-Leu-Ser-(O-beta-D-lactose)-CONH(2) (MMP2200) is a novel glycopeptide opioid agonist with similar affinities for mu and delta receptors. Glycosylation promoted brain penetration and production of centrally mediated behavioral effects in mice; however, it is unknown whether the magnitude of enhanced brain penetration is sufficient to permit central mediation of drug effects and production of synergistic mu/delta antinociceptive interactions after systemic administration in primates. To address this issue, the present study compared the effects of MMP2200 and the mu-agonist morphine in four behavioral procedures in rhesus monkeys. In an assay of thermal nociception, morphine (1.0-5.6 mg/kg) produced dose-dependent antinociception, whereas MMP2200 (10-56 mg/kg) was ineffective. In an assay of capsaicin-induced thermal allodynia, both morphine (0.01-1.0 mg/kg) and MMP2200 (0.032-3.2 mg/kg) produced dose-dependent antiallodynic effects. MMP2200-induced antiallodynia was blocked by the moderately mu-selective antagonist naltrexone (0.01 mg/kg), the delta-selective antagonist naltrindole (1.0 mg/kg), and the peripherally selective opioid antagonist quaternary naltrexone (0.32 mg/kg). In an assay of schedule-controlled behavior, both morphine (0.01-1.0 mg/kg) and MMP2200 (10-56 mg/kg) decreased response rates. Morphine effects were antagonized by naltrexone (0.001-0.01 mg/kg); however, the effects of MMP2200 were not antagonized by either naltrexone (0.01 mg/kg) or naltrindole (1.0 mg/kg). In an assay of drug self-administration, morphine (0.0032-0.32 mg/kg/injection) produced reinforcing effects, whereas MMP2200 (0.032-0.32 mg/kg/injection) did not. These results suggest that systemically administered MMP2200 acted as a peripheral, mu/delta-opioid agonist with limited distribution to the central nervous system in rhesus monkeys. These results also suggest the existence of

species differences in the pharmacokinetics and brain penetration of glycopeptides. Do Carmo GP, Polt R, Bilsky EJ, Rice KC, Negus SS. Behavioral pharmacology of the mu/delta opioid glycopeptide MMP2200 in rhesus monkeys. J Pharmacol Exp Ther. 2008;326(3):939-48.

Probes for Narcotic Receptor Mediated Phenomena. 38. An Expeditious Synthesis of rac-cis-4a-Ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol and rac-cis-2-Methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol
A high-yielding five-step synthesis of cis-benzofuropyridin-6-ols provided an improved route to compounds with low to subnanomolar affinity at opioid receptors and high antinociceptive potency. This synthesis provided the known rac-cis-4a-ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (1a) in high yield, and the novel rac-cis-2-methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (1b). It was achieved using NBS to prepare the key intermediate 7. Di-demethylation followed by subsequent displacement of the bromine by the phenolic ion in hot Et3N gave the desired 1a. The structure of 1a was confirmed by X-ray crystallography. Iyer MR, Deschamps JR, Jacobson AE, Rice KC. Probes for narcotic receptor mediated phenomena. 38. An expeditious synthesis of rac-cis-4a-Ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol and rac-cis-2-Methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol. Heterocycles. 2009;78:1061-72.

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

Program Activities

NIDA PAs/RFAs

On March 4, 2009, NIH issued an RFA entitled **Recovery Act Limited Competition: NIH Challenge Grants in Health and Science Research (RC1) (RFA-OD-09-003)**. This Funding Opportunity Announcement (FOA) is developed as part of the American Recovery and Reinvestment Act of 2009 (Recovery Act), Pub. L. No. 111-5. All NIH Institutes and Centers with funding authority will participate with the NIH Office of the Director in this initiative. This FOA will be administered by the Office of the Director of the NIH (http://www.nih.gov). NIH has received new funds for Fiscal Years (FYs) 2009 and 2010 as part of the American Recovery and Reinvestment Act of 2009 (Recovery Act). NIH has designated at least $200 million for a new initiative called the **NIH Challenge Grants** in Health and Science Research (see http://grants.nih.gov/recovery/). This new program will support research on topic areas which address specific scientific and health research challenges in biomedical and behavioral research that would benefit from significant 2-year jumpstart funds. NIH Institute and Centers have selected specific Challenge Topics within each of the Challenge Areas. The research in these Challenge Areas should have a high impact in biomedical or behavioral science and/or public health. As part of the Recovery Act, the NIH invites, through this limited competition, NIH Challenge Grant (RC1) applications from domestic (United States) institutions/organizations proposing novel research in areas that address specific knowledge gaps, scientific opportunities, new technologies, data generation, or research methods that would benefit from an influx of funds to quickly advance the area in significant ways. This program is designed to support research in scientific areas identified by the Institutes and Centers, as described below. This FOA will utilize the NIH Challenge Grant (RC1) award mechanism.

On March 20, 2009, NIH issued an RFA entitled **Recovery Act Limited Competition for NIH Grants: Research and Research Infrastructure "Grand Opportunities" (RC2) (RFA-OD-09-004)**. This Funding Opportunity Announcement (FOA) is developed as part of the American Recovery & Reinvestment Act of 2009 (Recovery Act). NIH Institutes and Centers with funding authority listed below will participate with the NIH Office of the Director in this initiative. Reviews and awards will be administered by the participating Institutes and Centers. The NIH has received new funds for Fiscal Years (FYs) 2009 and 2010 as part of the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"). This is one of a number of NIH initiatives related to the Recovery Act. These are listed at the following site: http://grants.nih.gov/recovery/. Under the Recovery Act, the NIH has established a new program entitled **Research and Research Infrastructure "Grand Opportunities"** hereafter called the "GO" grants program. This new program will support projects that address large, specific biomedical and biobehavioral research endeavors that will benefit from significant 2-year funds without the expectation of continued NIH funding beyond two years. The research supported by the "GO" grants program should have high short-term impact, and a high likelihood of enabling growth and investment in biomedical research and development, public health, and health care delivery. This NIH Funding Opportunity Announcement (FOA), supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"), Public Law 111-5, solicits through this limited competition applications from domestic (United States) institutions/organizations proposing to develop and implement critical research innovations to advance the research enterprise, stimulate future growth and investments, and advance public health and health care delivery. The purpose of the "GO" grants program is to support

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high impact ideas that lend themselves to short-term funding, and may lay the foundation for new fields of investigation. The "GO" grants program will support large-scale research projects that accelerate critical breakthroughs, early and applied research on cutting-edge technologies, and new approaches to improve the synergy and interactions among multi and interdisciplinary research teams. The initiative seeks novel approaches in areas that address specific knowledge gaps, scientific opportunities, new technologies, data generation, or research methods that would benefit from an influx of funds to quickly advance the area in significant ways. Applicants may propose to address either a specific research question or propose the creation of a unique infrastructure/resource designed to accelerate scientific progress in the future. This program is a trans-NIH effort supported by Recovery Act funds. For those projects that span the missions of Institutes, Centers and Offices (ICs), support may come from Recovery Act funds allocated to the Common Fund.

On March 30, 2009, NIH issued an RFA entitled **Recovery Act Limited Competition: Supporting New Faculty Recruitment to Enhance Research Resources through Biomedical Research Core Centers (P30) (RFA-OD-09-005)**. This NIH Funding Opportunity Announcement (FOA), supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"), Public Law 111-5, invites applications from U.S academic institutions/organizations to support the hiring of newly-recruited faculty to develop research projects within the context of Biomedical Core Centers. For this announcement, a Biomedical Core Center is defined as a community of multidisciplinary researchers focusing on areas of biomedical research relevant to NIH, such as centers, departments, programs, and/or trans-departmental collaborations or consortia. . These awards are designed to enhance innovative programs of excellence by providing scientific and programmatic support for promising research faculty and their areas of research. Specifically for the purposes of this announcement, Core Center Grants are institutional awards that provide funding to hire, provide appropriate start-up packages, and develop pilot research projects for newly independent investigators, with the goal of augmenting and expanding the institution's community of multidisciplinary researchers focusing on areas of biomedical research relevant to NIH. This FOA will utilize the NIH Core Center Grant (P30) mechanism.

On April 20, NIH issued an RFA entitled **Recovery Act Limited Competition: Academic Research Enhancement Award (R15) (RFA-OD-09-007)**. This NIH Funding Opportunity Announcement (FOA) is supported by funds provided to the NIH under the American Recovery & Reinvestment Act of 2009 ("Recovery Act" or "ARRA"), Public Law 111-5. The purpose of the Academic Research Enhancement Award (AREA) program is to stimulate research in educational institutions that provide baccalaureate or advanced degrees for a significant number of the Nation's research scientists, but that have not been major recipients of NIH support. These AREA grants create opportunities for scientists and institutions otherwise unlikely to participate extensively in NIH programs, to contribute to the Nation's biomedical and behavioral research effort. AREA grants are intended to support small-scale health-related research projects proposed by faculty members of eligible, domestic institutions. This FOA will utilize the Academic Research Enhancement Award (AREA) R15 award mechanism.

On April 1, 2009, NIH issued an RFA entitled **Novel Statistical Methods for Human Gene Expression Quantitative Trait Loci (eQTL) Analysis (R01) (RFA-RM-09-006)**. This FOA solicits applications to develop innovative statistical methods to detect the influence of genetic variation on tissue-specific gene expression and regulation. The goal of the FOA is to seek proposals to develop statistical methods to appropriately analyze the forthcoming complex data sets generated by the NIH Roadmap initiative entitled "Genotype-Tissue Expression (GTEx) Project". Applicants are encouraged to take advantage of existing tissue-specific gene expression datasets and/or simulated datasets, but will also be strongly encouraged to utilize GTEx-generated data, if and when it is available. This FOA will utilize the R01 grant mechanism.

On April 16, NIH issued a PA entitled **NIH Small Research Grant Program (Parent R03) (PA-09-163)**. The National Institutes of Health (NIH) Investigator-Initiated Small Grant (R03) funding opportunity supports small research projects that can be carried out in a short period of time with limited resources. Investigator-initiated research, also known as unsolicited research, is research funded as a result of an investigator submitting a research grant application to NIH in an investigator's area of interest and competency. The R03 grant mechanism supports different types of projects including pilot and feasibility studies; secondary analysis of existing data;

Planned Meetings

Publications

Staff Highlights

Grantee Honors

small, self-contained research projects; development of research methodology; and development of new research technology. All investigator-initiated small grant applications described in this announcement will be assigned to NIH Institutes and Centers (ICs) according to standard Public Health Service (PHS) referral guidelines and specific program interests. Investigators are strongly encouraged to consult the list of participating ICs and special research interests. This FOA will utilize the NIH Small Research Grant (R03) award mechanism.

NIH issued a PA entitled **NIH Exploratory/Developmental Research Grant Program (Parent R21) (PA-09-164)**. The Exploratory/Developmental Grant (R21) mechanism is intended to encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research. All investigator-initiated exploratory/developmental grant applications described in this announcement will be assigned to NIH Institutes and Centers (ICs) according to standard Public Health Service (PHS) referral guidelines and specific program interests. Investigators are strongly encouraged to consult the list of participating ICs and special research interests. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism.

New NIDA PAs and RFAs

On March 23, 2009, NIDA issued a PA entitled **Building System Capacity for Implementing Evidence-Based Practices in Substance Abuse Treatment and Prevention (R34) (PA-09-105)**. This Funding Opportunity Announcement (FOA) provides resources to facilitate research on the adoption, implementation, and sustainability of evidence-based clinical treatment practices, prevention approaches, and business practices in community-based service delivery settings. It is intended to foster collaboration between service providers and entities that directly influence their capacity to deliver such practices, including Single State Agencies, other funders, licensing and regulatory bodies, referral sources, educational entities, and other social services agencies that interact with the treatment and prevention systems. Applications are encouraged that will advance the field of implementation science while simultaneously building the capacity of systems and service providers to conduct process improvement research. Applicants may propose to pilot test proven clinical or business practices across service delivery settings, or to study the downstream effect of changes in State or other system-level policies on program capacity to implement evidence-based practices. This FOA encourages collection of preliminary data needed to inform approaches to the eventual scaling-up of selected practices to broader, sustained implementation. This FOA will utilize the R34 grant mechanism.

On April 6, 2009, NIDA issued a PA entitled **Pilot and Feasibility Studies in Preparation for Drug Abuse Prevention Trials (R34) (PA-09-146)**. This FOA for R34 applications seeks to support: (a) pilot and/or feasibility testing of new, revised, or adapted preventive intervention approaches targeting the initiation of drug use, the progression to abuse or dependence, and the acquisition or transmission of HIV infection among diverse populations and settings; and (b) pre-trial feasibility testing for prevention services and systems research. The NIDA R34 mechanism does not support the development of intervention protocols, manuals, or the standardization of protocols. It is expected that research conducted via this R34 mechanism will consist of early stage efficacy, effectiveness or services research that will provide intervention pilot and/or feasibility data that is a pre-requisite for submitting larger drug abuse and/or drug-related HIV prevention intervention studies. This FOA will utilize the NIH Planning Grant (R34) award mechanism and runs in parallel with FOAs of identical scientific scope, PA-08-217, PA-08-218, and PA-08-219 that encourage applications under the NIH Research Project Grant (R01), Exploratory/Developmental Grant (R21), and Small Research Grant (R03) award mechanisms, respectively.

On April 7, 2009, NIDA issued an RFA entitled **Economic Studies of Health Insurance Coverage on Drug Abuse Treatment Availability, Access, Costs, and Quality (R01) (RFA-DA-10-004)**. This FOA solicits research project grant (R01) applications from institutions/organizations that propose to conduct rigorous, theory-driven research on the effects of recent legislative and regulatory changes affecting insurance coverage for drug abuse treatment services. This FOA will utilize the R01 grant mechanism.

PAs/RFAs Issued with Other NIH Components/Agencies

On January 13, 2009, NIDA and NIAAA jointly issued a Program Announcement (PA) entitled **Senior Scientist Research and Mentorship Award (K05) (PA-09-076)**. This PA is intended to provide protected time for outstanding senior scientists who have demonstrated a sustained high level of productivity conducting biomedical research relevant to the scientific mission of the appropriate institute to focus on their research and to provide mentoring of new investigators. The overall goal of NIH-supported career development programs is to help ensure that a diverse pool of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation's biomedical, behavioral, and clinical research needs. This Funding Opportunity Announcement (FOA) will utilize the NIH Senior Scientist Award (K05) mechanism.

On January 22, 2009, NIDA, in collaboration with numerous other NIH components, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) and the Administration for Children and Families (ACF), issued a PA entitled **PHS 2009-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]) (PA-09-080)**. This Funding Opportunity Announcement (FOA) invites eligible United States small business concerns (SBCs) to submit Small Business Innovation Research (SBIR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH, CDC, FDA and ACF awarding components identified in this FOA are encouraged to submit SBIR grant applications in response to identified topics (see PHS 2009-2 SBIR/STTR Program Descriptions and Research Topics for NIH, CDC, FDA and ACF.) This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, Fast-Track, and Phase II Competing Renewal applications (NIH only), and runs in parallel with an FOA of identical scientific scope, PA-09-081, that solicits applications under the Small Business Technology Transfer (STTR) (R41/R42) grant mechanisms. Note: STTR applications are accepted ONLY by the NIH. The CDC, FDA and ACF do not participate in the STTR program. SBIR Fast-Track and Phase II Competing Renewal grant applications are accepted by the NIH only.

On January 22, 2009, NIDA, in conjunction with numerous other NIH components, issued a PA entitled **PHS 2009-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42]) (PA-09-081)**. This Funding Opportunity Announcement (FOA) invites eligible United States small business concerns (SBCs) to submit Small Business Technology Transfer (STTR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH awarding components identified in this FOA are encouraged to submit STTR grant applications in response to identified topics (see PHS 2009-2 SBIR/STTR Program Descriptions and Research Topics for NIH.) This FOA will utilize the STTR (R41/R42) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-09-080, that encourages applications under the Small Business Innovation Research (SBIR) (R43/R44) grant mechanisms.

On February 11, 2009, NIDA, in conjunction with a number of ther NIH components, issued a PA entitled **New Technologies for Liver Disease STTR (R41/R42) (PA-09-094)**. The purpose of this Funding Opportunity Announcement (FOA) is to solicit Small Business Innovation Research (STTR) grant applications from small business concerns (SBCs) that propose to develop resources, research tools, instrumentations, biomarkers, devices, drugs or new and innovative approaches to diagnosis, monitoring, management, treatment and prevention of liver diseases. Areas of interest include development of reliable and practical means of diagnosis of liver diseases; biomarkers for disease activity and stage; noninvasive tests for inflammation, fibrosis and fat in the liver; and drugs, complementary and alternative modalities, biologics or molecular reagents for the therapy or prevention of liver diseases. The goal of this announcement is to enlist members of the small business research community in advancing means of diagnosis, treatment and prevention of liver disease and facilitate the goals outlined in the trans-NIH Action Plan for Liver Disease Research. This FOA will utilize the STTR (R41/R42) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-09-095, that encourages applications under the Small Business Innovation Research (SBIR) (R43/R44) grant mechanisms.

On February 12, 2009, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **New Technologies for Liver Disease SBIR (R43/R44) (PA-09-095)**. The purpose of this Funding Opportunity Announcement (FOA) is to solicit Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose to develop resources, research tools, instrumentations,

biomarkers, devices, drugs or new and innovative approaches to diagnosis, monitoring, management, treatment and prevention of liver diseases. Areas of interest include development of reliable and practical means of diagnosis of liver diseases; biomarkers for disease activity and stage; noninvasive tests for inflammation, fibrosis and fat in the liver; and drugs, complementary and alternative modalities, biologics or molecular reagents for the therapy or prevention of liver diseases. The goal of this announcement is to enlist members of the small business research community in advancing means of diagnosis, treatment and prevention of liver disease and facilitate the goals outlined in the trans-NIH Action Plan for Liver Disease Research. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-09-094, which encourages applications under the Small Business Technology Transfer (STTR) (R41/R42) grant mechanisms.

On February 13, 2009, NIDA and NIAAA jointly issued a PA entitled **Mechanisms of Alcohol and Nicotine Co-Dependence (R21) (PA-09-098)**. This FOA encourages Exploratory/ Developmental (R21) applications from institutions/organizations that propose to study neurobiological and behavioral mechanisms contributing to concurrent alcohol and nicotine use and dependence. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism and runs in parallel with a FOA of identical scientific scope, PA-09-099, that encourages applications under the Research Project Grant (R01) mechanism.

On February 13, 2009, NIDA and NIAAA jointly issued a PA entitled **Mechanisms of Alcohol and Nicotine Co-Dependence (R01) (PA-09-099)**. This FOA encourages Research Project grants (R01) applications from institutions/organizations that propose to study neurobiological and behavioral mechanisms contributing to concurrent alcohol and nicotine use and dependence. This FOA will utilize the Research Project Grant (R01) award mechanism and runs in parallel with an FOA of identical scientific scope, PA-09-098, that encourages applications under the R21 mechanism.

On February 12, 2009, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **Energy Efficiency and Renewable Energy System Technology Research and Development (SBIR [R43/R44]) (PA-09-100)**. On December 19, 2007, President George W. Bush signed into law the "Energy Independence and Security Act of 2007 (Act), P.L. 110-140. This Act requires SBIR/STTR agencies, whenever possible and appropriate, to give high priority within the SBIR and STTR programs to energy efficiency or renewable energy system research and development projects (R&D). As part of the implementation of this Act, this Funding Opportunity Announcement (FOA) encourages eligible United States small business concerns (SBCs) whose biomedical research is related to energy efficiency or renewable energy systems, to submit SBIR Phase I, Phase II, and Fast-Track grant applications for R&D projects in those areas. Mechanism of Support. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, Fast-Track, and Phase II Competing Renewal applications (NIH only), and runs in parallel with an FOA of identical scientific scope, PA-09-101, that solicits applications under the Small Business Technology Transfer (STTR) (R41/R42) grant mechanisms.

On February 12, 2009, NIDA, in conjunction with numerous other NIH components, issued a PA entitled **Energy Efficiency and Renewable Energy System Technology Research and Development (STTR [R41/R42]) (PA-09-101)**. On December 19, 2007, President George W. Bush signed into law the "Energy Independence and Security Act of 2007 (Act), P.L. 110-140. This Act requires SBIR/STTR agencies, whenever possible and appropriate, to give high priority within the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs to energy efficiency or renewable energy system research and development projects (R&D). As part of the implementation of this Act, this Funding Opportunity Announcement (FOA) encourages eligible United States small business concerns (SBCs) whose biomedical research is related to energy efficiency or renewable energy systems, to submit STTR Phase I, Phase II, and Fast-Track grant applications for R&D projects in those areas. This FOA will utilize the STTR (R41/R42) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-09-100, which encourages applications under the SBIR (R43/R44) grant mechanisms.

On February 13, 2009, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **Centers for AIDS Research: D-CFAR, CFAR (P30) (PAR-09-103)**. This FOA solicits applications for the Centers for AIDS Research (CFAR) program to provide administrative and shared research support to enhance HIV/AIDS

research. Applications are being solicited for both standard CFARs and developmental CFARs (D-CFARs). Standard and D-CFARs provide core facilities, expertise, resources, and services not readily obtained otherwise through more traditional funding mechanisms. Additionally, D-CFARs provide support to assist investigators in the development of a competitive standard CFAR. The program emphasizes interdisciplinary collaboration, especially between basic and clinical investigators, translational research between the laboratory and the clinic and vice versa, inclusion of minority investigators, and inclusion of prevention and behavioral change research. This FOA will utilize the NIH Center Core Grants (P30) assistance mechanism.

On February 25, 2009, NIDA, in collaboration with NIMH, NIAAA, and NICHD, issued a PA entitled **Developmental Psychopharmacology (R01) (PA-09-111)**. The purpose of this Funding Opportunity Announcement (FOA) is to request research grant applications to examine the neurobiological impact of psychotherapeutic medications upon the immature brain, with particular emphasis upon mapping the precise developmental profile of physiological response to psychotropic agents used in the treatment of mental disorders in children. Relevant research includes studies in model systems, including animals, and in human populations. This FOA will utilize the NIH Research Project Grant (R01) award mechanism and runs in parallel with an FOA of identical scientific scope, PA-09-112, which encourages applications under the Exploratory/Developmental Grant (R21) award mechanism.

On February 25, 2009, NIDA, in collaboration with NIMH, NIAAA, and NICHD, issued a PA entitled **Developmental Psychopharmacology (R21) (PA-09-112)**. The purpose of this Funding Opportunity Announcement (FOA) is to request research grant applications to examine the neurobiological impact of psychotherapeutic medications upon the immature brain, with particular emphasis upon mapping the precise developmental profile of physiological response to psychotropic agents used in the treatment of mental disorders in children. Relevant research includes studies in model systems, including animals, and in human populations. This FOA will utilize the NIH Exploratory/Developmental (R21) award mechanism and runs in parallel with an FOA of identical scientific scope, PA-09-111, which encourages applications under the Research Project Grant (R01) award mechanism.

On February 19, 2009, NIDA in collaboration with NCI jointly issued a PA entitled **Testing Tobacco Products Promoted to Reduce Harm (R01) (PA-09-046)**. This funding opportunity announcement (FOA) invites applications that propose multidisciplinary research on potential reduced-exposure tobacco products, both smoked and smokeless. The multidisciplinary studies can span basic, biological, behavioral, surveillance, and epidemiology research. The tobacco industry is currently promoting several new products with claims that they: a) are less either harmful or less addictive; and b) purportedly deliver lower amounts of toxic, carcinogenic, and/or addictive agents to the user compared with conventional products. However, to date, the scientific evidence is insufficient to evaluate whether these new products actually reduce the users' exposure or risk for tobacco-related diseases. The overarching goal of this FOA is to determine whether potential reduced-exposure tobacco products provide a truly, less-harmful alternative to conventional tobacco products, both at the individual and population level. This FOA uses the NIH research project R01 grant mechanism and runs in parallel with an FOA of identical scientific scope, PA-09-047 that encourages applications under the NIH Exploratory/Developmental (R21) Grant mechanism.

On February 19, 2009, NIDA in collaboration with NCI jointly issued a PA entitled **Testing Tobacco Products Promoted to Reduce Harm (R21) (PA-09-047)**. This funding opportunity announcement (FOA) invites applications that propose multidisciplinary research on potential reduced-exposure tobacco products, both smoked and smokeless. The multidisciplinary studies can span basic, biological, behavioral, surveillance, and epidemiology research. The tobacco industry is currently promoting several new products with claims that they: a) are less either harmful or less addictive; and b) purportedly deliver lower amounts of toxic, carcinogenic, and/or addictive agents to the user compared with conventional products. However, to date, the scientific evidence is insufficient to evaluate whether these new products actually reduce the users' exposure or risk for tobacco-related diseases. The overarching goal of this FOA is to determine whether potential reduced-exposure tobacco products provide a truly, less-harmful alternative to conventional tobacco products, both at the individual and population level This FOA utilizes the NIH exploratory/developmental (R21) grant mechanism and runs in parallel with an FOA of identical scientific scope, PA-09-046, which uses the NIH Research Project Grant (R01) mechanism.

On February 26, 2009, NIDA, in collaboration with numerous other NIH components,

issued a PA entitled **Manufacturing Processes of Medical, Dental, and Biological Technologies (SBIR [R43/R44]) (PA-09-113)**. On February 26, 2004, Executive Order 13329 was signed by President George W. Bush requiring SBIR/STTR agencies, to the extent permitted by law and in a manner consistent with the mission of the Department, to give high priority within the SBIR and STTR programs to manufacturing-related research and development (R&D). In response to this Executive Order, NIH is expanding its focus by encouraging eligible United States small business concerns to submit SBIR Phase I, Phase II, and Fast-Track grant applications whose biomedical research is related to advanced processing, manufacturing processes, equipment and systems, and manufacturing workforce skills and protection. This FOA will utilize the SBIR (R43/R44) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-09-114, which encourages applications under the Small Business Technology Transfer (STTR) (R41/R42) grant mechanisms.

On February 26, 2009, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Manufacturing Processes of Medical, Dental, and Biological Technologies (STTR [R41/R42]) (PA-09-114)**. On February 26, 2004, Executive Order 13329 was signed by President George W. Bush requiring SBIR/STTR agencies, to the extent permitted by law and in a manner consistent with the mission of the Department, to give high priority within the SBIR and STTR programs to manufacturing-related research and development (R&D). In response to this Executive Order, NIH is expanding its focus by encouraging eligible United States small business concerns to submit STTR Phase I, Phase II, and Fast-Track grant applications whose biomedical research is related to advanced processing, manufacturing processes, equipment and systems, and manufacturing workforce skills and protection. This FOA will utilize the STTR (R41/R42) grant mechanisms for Phase I, Phase II, and Fast-Track applications and runs in parallel with a FOA of identical scientific scope, PA-09-113, that encourages applications under the Small Business Innovation Research (SBIR) (R43/R44) grant mechanisms.

On March 3, 2009, NIDA, in collaboration with NIAAA and NICHD, issued a PA entitled **Medications Development for the Treatment of Pregnant/Postpartum Women with Substance Related Disorders and/or In Utero Substance Exposed Neonates (R01) (PA-09-106)**. The purpose of this FOA is to foster the development of novel pharmacological strategies for the treatment of pregnant/postpartum women with Substance Related Disorders (SRDs) and/or in utero substance exposed neonates. This FOA will encourage applications to implement preclinical and clinical research directed towards: 1) the identification, evaluation, and development of safe and effective novel pharmacotherapies (e.g., new chemical entities or immunotherapies) for the treatment of pregnant/postpartum women with SRDs and/or in utero substance exposed neonates, and/or 2) the evaluation of the safety and efficacy of FDA approved medications (e.g., medications approved for a different indication) for the treatment of pregnant/postpartum women with SRDs and/or in utero substance exposed neonates. This FOA will use the NIH Research Project Grant (R01) mechanism and runs in parallel with a FOA of identical scientific scope, PA-09-107 that encourages applications under the Exploratory/Developmental (R21) grant mechanism.

On March 3, 2009, NIDA, in collaboration with NIAAA and NICHD, issued a PA entitled **Medications Development for the Treatment of Pregnant/Postpartum Women with Substance Related Disorders and/or In Utero Substance Exposed Neonates (R21) (PA-09-107)**. The purpose of this FOA is to foster the development of novel pharmacological strategies for the treatment of pregnant/postpartum women with Substance Related Disorders (SRDs) and/or in utero substance exposed neonates. This FOA will encourage applications to implement preclinical and clinical research directed towards: 1) the identification, evaluation, and development of safe and effective novel pharmacotherapies (e.g., new chemical entities or immunotherapies) for the treatment of pregnant/postpartum women with SRDs and/or in utero substance exposed neonates, and/or 2) the evaluation of the safety and efficacy of FDA approved medications (e.g., medications approved for a different indication) for the treatment of pregnant/postpartum women with SRDs and/or in utero substance exposed neonates. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism and runs in parallel with a FOA of identical scientific scope, PA-09-106 that encourages applications under the Research Project Grant (R01).

On March 27, 2009, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **Basic and Translational Research in Emotion (R01) (PA-09-137)**. This Funding Opportunity Announcement (FOA) encourages Research Project

Grant (R01) applications to expand basic and translational research on the processes and mechanisms involved in the experience, expression, and regulation of emotion. This FOA will utilize the NIH Research Project Grant (R01) award mechanism. Applications of identical scientific scope are encouraged also under the NIH Small Research Grant (R03) and the NIH Exploratory/Developmental Grant (R21) award mechanisms, responding to FOAs PA-06-180 and PA-06-181, respectively.

On April 18, 2009, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **Research on Teen Dating Violence (R01) (PA-09-169)**. This Funding Opportunity Announcement (FOA) encourages investigator-initiated research grant applications from institutions/organizations that propose to conduct behavioral and/or biomedical research aimed at better understanding the etiologies and precursors for, reducing risk for, and incidence of, teen dating violence (TDV). Research is also sought that examines the linkages and gaps among perceptions of appropriate responses to teen dating violence from service providers, the criminal justice system, teens themselves, victims, perpetrators and bystanders. This FOA will utilize the R01 grant mechanism and runs in parallel with a FOA of identical scientific scope, PA-09-170, which encourages applications under the R21 mechanism.

On April 18, 2009, NIDA, in conjunction with a number of other NIH components, issued a PA entitled **Research on Teen Dating Violence (R21) (PA-09-170)**. This Funding Opportunity Announcement (FOA) encourages investigator-initiated research grant applications from institutions/ organizations that propose to conduct behavioral and/or biomedical research aimed at better understanding the etiologies and precursors for, reducing risk for, and incidence of, teen dating violence (TDV). Research is also sought that examines the linkages and gaps among perceptions of appropriate responses to teen dating violence from service providers, the criminal justice system, teens themselves, victims, perpetrators and bystanders. This FOA will use the NIH Exploratory/Developmental (R21) grant mechanism and runs in parallel with a FOA of identical scientific scope, PA-09-169, which encourages applications under the R01 mechanism.

On April 24, 2009, NIDA, in collaboration with NIMH, NICHD and the AHRQ's Center for Primary Care Prevention and Clinical Partnerships, issued a PA entitled **Women's Mental Health in Pregnancy and the Postpartum Period (R01) (PA-09-174)**. In this Funding Opportunity Announcement (FOA), participating agencies encourage research on women's mental health in relation to pregnancy and the postpartum period. As illustrated by a few highly publicized cases, the consequences of severe untreated postpartum depression and psychosis can be devastating for individuals, families, and communities. A recent evidence-based practice report from the Agency for Healthcare Research and Quality noted that depression is also prevalent during pregnancy as well as the postpartum period, therefore research that occurs throughout pregnancy and the postpartum period (the perinatal period) is encouraged. This FOA will utilize the NIH Research Project Grant (R01) award mechanism and runs in parallel with an FOA of identical scientific scope, PA-09-175, that encourages applications under the Exploratory/Developmental (R21) award mechanism.

On April 24, 2009, NIDA, in collaboration with NIMH, NICHD and the AHRQ's Center for Primary Care Prevention and Clinical Partnerships, issued a PA entitled **Women's Mental Health in Pregnancy and the Postpartum Period (R21) (PA-09-175)**. In this Funding Opportunity Announcement (FOA), the participating agencies encourage research on women's mental health in relation to pregnancy and the postpartum period. As illustrated by a few highly publicized cases, the consequences of severe untreated postpartum depression and psychosis can be devastating for individuals, families, and communities. A recent evidence-based practice report from the Agency for Healthcare Research and Quality noted that depression is also prevalent during pregnancy as well as the postpartum period, therefore research that occurs throughout pregnancy and the postpartum period (the perinatal period) is encouraged. This FOA will use the NIH Exploratory/Developmental (R21) award mechanism and runs in parallel with an FOA of identical scientific scope, PA-09-174, that encourages applications under the Research Project Grant (R01) award mechanism.

Other Program Activities

Clinical Trials Network (CTN) Update

RFP: The RFP N01DA-9-2217, Data and Statistics Center for the NIDA Clinical Trials Network, was issued on March 23, 2009. Proposals are due May 7, 2009, with a planned award in August 2009.

Protocols: A total of 42 protocols have been initiated since 2001, including multi-site clinical trials (28), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). Twenty-three trials have completed data lock; one is in the follow-up, data-lock phase; three are currently enrolling and four are in development. In addition, 18 ancillary studies have been supported by CTN and non-CTN funds. Seven protocols are in the development phase. Over 10,000 participants have enrolled in studies.

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

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

Primary outcome papers are published or in press for:

- **Protocol CTN 0003**, Bup/Nx: Comparison of Two Taper Schedules
- **Protocol CTN 0004**, MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse
- **Protocol CTN 0008**, A Baseline for Investigating Diffusion of Innovation
- **Protocol CTN 0009**, Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs
- **Protocol CTN 0010**, Buprenorphine/Naloxone-Facilitated Rehabilitation for Heroin Addicted Adolescents/Young Adults
- **Protocol CTN 0011**, A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities
- **Protocol CTN 0012**, Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infection, and Sexually Transmitted Infections in Substance Abuse Treatment Programs
- **Protocol CTN 0013**, Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers
- **Protocol CTN 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.

In addition, the following protocols have submitted primary papers:

- **Protocol CTN 0015**, Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial
- **Protocol CTN 0017**, HIV and HCV Intervention in Drug Treatment Settings
- **Protocol CTN 0029**, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD)

The following protocols have locked the data:

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

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

- **Protocol CTN 0030**, Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phase, open-label, multi-center study in outpatient treatment settings. Pre-screening began in May 2006. The study is being carried out in 9 sites, and has randomized 653 participants into phase 1 and 360 participants into phase 2.
- CTN 0030A1, Collection of Economic Data for the Prescription Opioid Addiction Treatment Study. This ancillary study was conducted in collaboration with NIDA DESPR and it is in the data analysis phase.
- CTN 0030A2, Effects of Chronic Opioids is conducted in collaboration with NIDA DCNBR to obtain anatomical MR scans in subjects with a history of opioid use to evaluate neural changes that may occur with such use and compare with age/gender healthy controls. This study is in the data analysis phase.
- CTN 0030A3, POATS Long-Term Follow Up Study (LTFU) is being implemented at all POATS sites to examine long-term outcomes for individuals who participated in CTN-0030 with opioid analgesic (OA) dependence.

The following protocols are currently enrolling:

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

  CTN 0027A1, START Pharmacogenetics: Exploratory Genetic Studies In Starting Treatment With Agonist Replacement Therapies.

  CTN-0027A2, Retention of Suboxone Patients in START: Perspectives of Providers and Patients. The overall purposes of the supplemental study are to identify and assess barriers for retaining Suboxone patients.
- **Protocol CTN 0031**, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12): Evaluation of a Combined Individual-Group Intervention to Reduce Stimulant and Other Drug Use by Increasing 12-Step Involvement. As of February 28, 2009, all ten sites (three Wave 1, seven Wave 2) are actively recruiting and have randomized a total of 210 participants to either the STAGE-12 or the TAU condition.

  CTN 0031A1, An Evaluation of Neurocognitive Function, Oxidative Damage, and Their Association with Treatment Outcomes in Methamphetamine and Cocaine Abusers. Potential participants are being recruited at six sites.

  CTN 0031A2, The Role of Alcohol Consumption in Classifications of Alcohol Use Disorders: A Clinical Study. It investigates the utility of adding a frequency measure of alcohol consumption (i.e., the first three items of the Alcohol Use Disorders Identification Test [AUDIT-C]), to the DSM-IV diagnostic criteria for alcohol use disorders. This study is funded by an MOU between NIDA and NIAAA. Data will be collected for this study throughout the life of the main STAGE-12 study.

  CTN 0031A3, Organizational and Practitioner Influences on Implementation of STAGE-12. The study assesses the influence of counselor and organizational variables on fidelity of the STAGE-12 intervention during the clinical trial, tests the impact of fidelity on clinical trial participant outcomes, and explores the influence of counselor and organizational variables on sustainability of the STAGE-12 intervention

following completion of the clinical trial. Study staff has already collected the organizational and counselor level data from all ten STAGE-12 sites. The baseline data obtained in this research will form the foundation for an R01 grant application.

- **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 seeks to enroll more than 1,200 participants across approximately 12 sites in the US. All 12 sites are active in the study: Lexington/Richland Alcohol and Drug Council-LRADAC and Morris Village (Southern Consortium Node); Wheeler Clinic and Midwestern Connecticut Council on Alcoholism-MCCA (New England Node); Daymark Recovery Services, Inc. (Florida Node); CPCDA (Appalachian Tri-State Node); CODA (Oregon/Hawaii Node); La Frontera (California/Arizona Node); Gibson Recovery (Ohio Valley Node); Chesterfield CSB Substance Abuse Services and Glenwood Life Counseling Center (Mid-Atlantic Node); and The Life Link (Southwest Node). As of February 28, 2009, 419 participants were randomized.

  CTN 0032A1, Economic Analysis of HIV Rapid Testing in Drug Abuse Treatment Programs. This is an ancillary study to protocol CTN 0032, to conduct 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 Schakman. The project is in collaboration with NIDA's DESPR.
- **Protocol CTN 0033-Ot**, Methamphetamine Use among American Indians. The first area of research emphasis in the National Institute on Drug Abuse's Strategic Plan on Reducing Health Disparities (2004 Revision) is the epidemiology of drug abuse, health consequences and infectious diseases among minority populations. The study is a collaboration among four Nodes: Pacific NW, Southwest, Oregon/Hawaii, and Ohio Valley.
- **Protocol CTN 0035-Ot**, Access to HIV and Hepatitis Screening and Care among Ethnic Minority Drug Users In and Out of Drug Treatment. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the California/Arizona Node.
- **Protocol CTN 0036-Ot**, Epidemiology and Ethnographic Survey of "Cheese" Heroin Use among Hispanics in Dallas County. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and is being conducted in the Texas Node.

The following protocols are in the development phase:

- **Protocol CTN 0034-Ot**, Developing Research Capacity and Culturally Appropriate Research Methods: Community-based Participatory Research Manual for Collaborative Research in Drug Abuse for American Indians and Alaska Natives. This study is in collaboration with the NIH National Center for Minority Health and Health Disparities and will be conducted in the Pacific Northwest Node.
- **Protocol CTN 0037**, Exercise as a Treatment for Substance Use Disorders. This clinical trial will test the effectiveness of the addition of exercise in improving drug abuse treatment outcomes.
- **Protocol CTN-0038-Ot**, Barriers to Substance Abuse Treatment among Asian Americans and Pacific Islanders. The objective of this study is to gain a better understanding of the factors that may influence the under-utilization of substance abuse treatment services by Asian Americans and Pacific Islanders (AAPIs) and the readiness of substance abuse treatment programs serving AAPIs to participate in clinical trials and adopt evidence based practices (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.

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 2008

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Case, Patricia -- Fenway Community Health Center
Feasibility of Pharmacy-Based HIV Interventions among IDUs: Two New England Cities

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

Chen, Kevin -- University of Maryland, Baltimore
Treatment of Cocaine Addiction with Integrative Meditation

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

Coffman, Donna L. -- Pennsylvania State University, University Park
Causal Inference for Mediation Models in Substance Abuse Prevention Research

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

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

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

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

David, Sean P. -- Memorial Hospital of Rhode Island
Exploratory/Developmental Study of Pharmacogenetic Smoking Cessation Therapy

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

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

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

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

El-Hage, Nazira -- Virginia Commonwealth University
Oxidative Damage and Proteasome Activity: Role of Opioid in HIV-HCV Infection

Evans, David E. -- H. Lee Moffitt Cancer Center and Research Institute
Automatic Attention to Smoking Cues: Neural Correlates

Franklin, Teresa R. -- University of Pennsylvania
Dopaminergic Variants Involved in Smoking Behavior: A Perfusion fMRI Study

Friedmann, Peter D. -- Rhode Island Hospital (Providence, RI)
Continuum of Care for Drug-Involved Offenders

Garofalo, Robert -- Children's Memorial Hospital (Chicago)
Syndemic Development and HIV Risk among Vulnerable Young Men

Glass, Michael J. -- Weill Medical College of Cornell University
Glutamate Receptors and Opioid Dependence: Molecules, Circuits and Behavior

Hao, Shuanglin -- University of Michigan at Ann Arbor
Pathogenesis and Therapy of HIV-Related Neuropathic Pain

Heinzerling, Keith G. -- University of California, Los Angeles
Pilot Trial of Bupropion vs. Placebo for Methamphetamine Abuse in Adolescents

Higgins, Stephen T. -- University of Vermont and State Agriculture College
Modeling Initial Smoking Abstinence and Relapse Risk

Hooten, W. Michael -- Mayo Clinic College of Medicine, Rochester
Cognitive Behavioral Smoking Cessation Intervention for Adults with Chronic Pain

Horner, Kristen A. -- Mercer University, Macon
The Role of Mu Opioid Receptor Activation in Psychostimulant-Induced Gene Express

Hruby, Victor J. -- University of Arizona
New Modalities for Treatment of Pain and Drug Abuse

Hu, Xiu-Ti -- Rush University Medical Center
Chronic Cocaine Exposure and HIV-1 Tat: Dysregulation of the Medial Prefrontal Cortex

Hurd, Yasmin L. -- Mount Sinai School of Medicine of NYU
The Opioid Mesolimbic System in Heroin Abuse

Hussong, Andrea M. -- University of North Carolina, Chapel Hill
Internalizing Pathways to Drug Use: A Multi-Sample Analysis

Iacono, William G. -- University of Minnesota, Twin Cities
Twin Family Study of Vulnerability to Substance Abuse

Isgor, Ceylan -- Florida Atlantic University
Individual Differences in Relapse to Nicotine

Ivanov, Iliyan Stoyanov -- Mount Sinai School of Medicine of NYU
Activation of Neuronal Networks Related to Risk for Addiction: A fMRI Study

Johnson, Knowlton -- West Pacific Institute for Research and Evaluation
A Community Trial in Alaska to Prevent Youth's Use of Legal Products to Get High

Johnson, Matthew Wayne -- Johns Hopkins University
Development of a Novel Trial-By-Trial Consequence Human Delay Discounting Task

Kelley, Michelle L. -- Old Dominion University
Secondary Effects of Parent Treatment for Drug Abuse on Children

Kerr, Thomas -- University of British Columbia
Evaluating the Natural History of Injection Drug Use

Khan, Maria -- National Development and Research Institutes
Longitudinal Study of Substance Use, Incarceration, and STI in the U.S.

Kombe, Gilbert -- ABT Associates, Inc.
Feasibility of Pharmacy-Based HIV Interventions among IDUs: Ha Giang, Vietnam

Kumar, Anil -- University of Missouri, Kansas City
HIV, Drug Abuse and Neurotoxicity

Kuzhikandathil, Eldo V. -- University of Medicine/Dental of NJ, NJ Medical School
Regulation of D1 Dopamine Receptor Expression by ncRNA in Cocaine Addiction

Latimer, William W. -- Johns Hopkins University
Randomized Trial of IFCBT-HIVPI to Prevent HIV among Non-Injection Drug Users

Leve, Leslie Diane -- Oregon Social Learning Center, Inc.
Juvenile Justice Girls: Pathways to Adjustment and System Use in Young Adulthood

Licata, Stephanie C. -- McLean Hospital (Belmont, MA)
Neurochemical Substrates of Sedative/Hypnotic Action: Proton MRS Studies

Ling, Walter -- University of California, Los Angeles
Sustained-Release Methylphenidate for Management of Methamphetamine Use Disorders

Liu-Chen, Lee-Yuan -- Temple University
Cellular Pharmacology of Kappa Opiod Receptor

Lukas, Scott E. -- McLean Hospital (Belmont, MA)
Citicoline-Induced Modulation of Cannabis Effects: Imaging and Mechanism of Action

Mackenzie, Robert George -- Wayne State University
Inducible Regulation of Key Transcription Factors in Dopamine Neurons

Mahadevan, Anu -- Organix, Inc.
Development of CB2 Agonists for Treatment of Pain

Marks, Michael J. -- University of Colorado at Boulder
Genetics of Nicotine Tolerance: Role of Receptors

Mawhinney-Delson, Samantha M. -- University of Colorado, Denver
Consequences of Drug Use and Informative Dropout on HIV/AIDS Outcomes in the MACS

McCaffrey, Daniel F. -- Rand Corporation
The Causal Effect of Community-Based Treatment for Youths

McCaul, Mary E. -- Johns Hopkins University
Gender Effects on Amphetamine-Induced Dopamine Release and Subjective Responses

McClernon, Francis Joseph -- Duke University
Neuropharmacology of Response Inhibition in Comorbid ADHD and Nicotine Dependence

McMahon, Lance R. -- University of Texas Health Science Center, San Antonio
Nicotine Dependence: Neuropharmacology in Monkeys

Mehler, Ernest L. -- Weill Medical College of Cornell University
Functional Properties of Protein Segments in Receptors and Transporters

Merchant, Roland C. -- Rhode Island Hospital (Providence, RI)
Brief Intervention for Drug Misuse for the Emergency Department (BIDMED)

Montague, P. Read -- Baylor College of Medicine
Computational Substrates of Addiction and Reward

Moore, Richard D. -- Johns Hopkins University
HIV Disease Outcomes in Drug Users in Clinical Practice

Mutchler, Matt -- California State University, Dominguez Hills
Sex-Drugs and HIV: How Substances Became Associated with Sex among AA

Narendran, Rajesh -- University of Pittsburgh at Pittsburgh
Imaging Dopamine D2 Agonist Binding Sites in Cocaine Dependence with [11C] NPA

Nemoto, Tooru -- Public Health Institute
Substance Use and HIV Risk among Thai Women

Noel, Richard J. -- Ponce School of Medicine
Synergistic Neurotoxicity of Speedball and HIV Toxins

Nyamathi, Adeline M. -- University of California, Los Angeles
HBV Prevention for Homeless at Risk for HBV/HCV/HIV

Oncken, Cheryl -- University of Connecticut School of Medicine/Dental
Exercise in Smoking Cessation in Postmenopausal Women

Pan, Zhizhong Z. -- University of Texas, M.D. Anderson Cancer Center
Impact of Pain on Sensitivity to Opioid Reward

Patten, Christi A. -- Mayo Clinic College of Medicine, Rochester
Tobacco Cessation Treatment for Alaska Native Youth

Persidsky, Yuri -- Temple University
Mechanisms and Interventions for Methamphetamine and HIV-1 Induced CNS Injury

Peterson, Eric C. -- University of Arkansas Medical Sciences, Little Rock
Antibody-Nanoparticle Conjugates for the Treatment of Methamphetamine Abuse

Pickel, Virginia M. -- Weill Medical College of Cornell University
EM-Transmitter Interactions of Striatal Opioid Neurons

Prendergast, Michael L. -- University of California, Los Angeles
Pacific Coast Research Center of CJ-DATS 2

Rademacher, David J. -- Rosalind Franklin University of Medicine and Science
The Role of Activity-Regulated Cytoskeletal-Associated Protein in Amphetamine

Reggio, Patricia H. -- University of North Carolina, Greensboro
Molecular Determinants of Cannabinoid Activity

Richardson, Gale A. -- University of Pittsburgh at Pittsburgh
Effects of Prenatal Cocaine Use: 21-Year Follow-Up

Rosenman, Robert Edward -- Washington State University
Development of Econometric Models for Improved Estimation of Prevention Program

Rowlett, James K. -- Harvard University (Medical School)
Anxiolytic Effects and Abuse of BZ Receptor Ligands

Roy, Sabita -- University of Minnesota, Twin Cities
Opioid Abuse, Opportunistic Infection and NeuroAIDS

Ruiz-Velasco, Victor J. -- Pennsylvania State University, Hershey Medical Center
Coupling Mechanisms of NOP Receptors and Calcium Channels

Sacks, Stanley -- National Development and Research Institutes
NDRI Rocky Mountain Research Center for CJ-DATS 2

Salo, Ruth E. -- University of California, Davis
Neural and Cognitive Correlates of Methamphetamine Use in Schizophrenia

Schwartz, Seth J. -- University of Miami School of Medicine
The Role of Culture in Thriving and Risk Behavior in Hispanic Adolescents

Selley, Dana E. -- Virginia Commonwealth University
CB1 Receptor Regulation by Cannabinoid Receptor Interacting Protein Crip1a

Setlow, Barry -- Texas A&M University System
Neural Mechanism of Enduring Cocaine Effects on Impulsive Choice

Slesnick, Natasha -- Ohio State University
Stage 1 Treatment Development with Homeless Mothers and Their 2-6 Year Old Children

Spigelman, Igor -- University of California, Los Angeles
Development of Peripherally-Acting Cannabinoid 1 Receptor Ligands

Stein, Michael D. -- Butler Hospital (Providence, RI)
Linkage of Hospitalized Opioid Users to Buprenorphine

Sterk, Claire E. -- Emory University
Neighborhood Effects on Drug Use among African American Adults

Tracy, Elizabeth M. -- Case Western Reserve University
Role of Personal Social Networks in Post Treatment Functioning

Vandrey, Ryan G. -- Johns Hopkins University
Efficacy and Safety of Dronabinol (Oral THC) for Treating Cannabis Dependence

Visher, Christy A. -- University of Delaware
Implementing Effective HIV/Drug Treatment in Corrections-Midstates CJ-DATS Center

Vulchanova, Lyudmila H. -- University of Minnesota, Twin Cities
The Neurosecretory Protein VGF Contributions to Pain

Wakschlag, Lauren S. -- University of Illinois at Chicago
Prenatal Smoking and the Substrates of Disruptive Behavior in Early Life

Wang, Gene-Jack -- Brookhaven Science Associates, Brookhaven Laboratories
Studies in Cocaine Abuse

Winder, Danny G. -- Vanderbilt University
Physiology of Periaqueductal Gray Dopamine Neurons

Xu, Ming -- University of Chicago
Extinction of Cue-Elicited Cocaine Seeking

Zheng, Guangrong -- University of Kentucky
Development of Antagonists for M5 Muscarinic Acetylcholine Receptor

Zhu, Jun -- University of South Carolina at Columbia
Role of Dopamine Transporter: HIV-1 Tat Protein and Nicotine Sensitization

Zucker, Robert A. -- University of Michigan at Ann Arbor
Brain Endophenotypes Modulating Drug Abuse Risk

Zule, William A. -- Research Triangle Institute
The Role of Dead Space Syringes in HIV Epidemics Amount IDU's - Drug Abuse Aspect

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

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1106 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 883 applications.

OEA arranged and managed 18 grant review meetings in which 294 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 17 contract proposal review meetings.

NIDA's chartered committees consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). In addition to meetings of each of these committees, OEA staff held 14 Special Emphasis Panels to review grant applications for a variety of reasons:

Conflicts with the chartered committees
Program Project grant applications
Cutting-Edge Basic Research Awards (CEBRA)
Behavioral Science Track Award for Rapid Transition (B/START)
Imaging Science Track Award for Research Transition (I/START)
Conference Grants (R13)
Mechanism for Time-Sensitive Research Opportunities
Diversity-promoting Institutions Drug Abuse Research Program (DIDARP) (R24)
Requests for Applications (RFAs)

OEA managed the following RFA reviews:

- DA09-001 - Medications Development for Cannabis-Related Disorders (R01)
- DA09-002 - Medications Development Centers of Excellence (P50)
- DA09-003/004 - Functional Characterization of Genetic Variants and Interactions: The Genes, Environment and Health Initiative (R21 & R03)
- DA09-005 - Pilot Clinical Trials of Pharmacotherapies for Substance Related Disorders (R01)
- DA09-007 - The Interaction of HIV, Drug Use, and the Criminal Justice System (R01)

Completed contract-related review activity from the Contracts Review Branch since the last Council includes:

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R&D and non-R&D Contract Reviews

- N01DA-9-7770 - NIDA Center for Genetic Studies
- N01DA-9-8889 - Medication Discovery Using Rat Models of Relapse
- N01DA-9-8890 - Analytical Chemistry and Stability Testing of Treatment Drugs
- N01DA-9-1204 - National Hispanic Science Network
- N01DA-9-1140 - Educational Marketing
- N01DA-9-2217 - Data and Statistics Center for the CTN

Phase II SBIR Contract Reviews

- N44DA-9-2214 - Development of Web-Based Training
- N44DA-9-2215 - Just Ask: Web-Based SBIRT Support
- N44DA-9-2216 - Web-Based Skills Training for SBIRT
- N44DA-9-7764 - Use of I/M Cross-Section and m/z as a Unique Identifier of Lipids and Neuropeptides in Complex Biosamples
- N44DA-9-8874 - Novel Azetidine CB1 Antagonists
- N44DA-9-8869 - Long Acting Buprenorphine for Opiate Maintenance

Phase I SBIR Contract Reviews

- N43DA-9-7768 - Screening, Characterization and Validation Assays for Protein Capture Reagents
- N43DA-9-7769 - Tool Development for New or Improved Capture Reagents
- N43DA-9-5542 - Rapid Assessment Tools for Sexual and Drug Use Risk Behaviors
- N43DA-9-1138 - Development of Science Education Materials or Programs
- N43DA-9-5541 - Instrument Development

CTN Data and Safety Monitoring Board(s) Meetings

- January 21, 2009 to discuss the study proposal CTN 0037, Exercise as a Treatment for Substance Use Disorders.
- February 12, 2009 to discuss the study proposal CTN 0044 - Web-delivery of Evidence-Based, Psychosocial Treatment for Substance Use Disorders.
- March 27, 2009 to discuss the progress of study protocols CTN 0027: Starting Treatment with Agonist Replacement Therapies (START) and CTN 0031, Stimulant Abuser Groups to Engage in 12-Step (STAGE-12) and the final study results of study protocol CTN 0014 Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT).

Certificates of Confidentiality

Between December 5, 2008 and March 6 2009, OEA processed 68 Certificate applications, including 19 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 Enhancing Peer Review updates, Checklist training (type 5 review and approval process in IMPAC - PGM) and a talk on NIH/NSF collaborations.

Planned Meetings

Publications

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Grantee Honors

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

Congressional Affairs (Prepared May 1, 2009)

Appropriations/Funding

American Recovery and Reinvestment Act (ARRA)(text from Dr. Volkow's message on NIDA website)
On February 17, 2009, President Obama signed the American Recovery and Reinvestment Act of 2009 (ARRA). Among the goals of the ARRA are to preserve and create jobs, promote economic recovery, and provide investments to increase economic efficiency by spurring technological advances in science and health. NIH is grateful for the opportunity afforded by the ARRA to provide economic stimulus to the nation while furthering our mission to uncover new knowledge that will lead to better health for everyone. NIH will receive $10 billion through the ARRA for use over the next two years (2009 and 2010). Of this, $1 billion will be invested in extramural construction (administered through the National Center for Research Resources), $0.8 billion will be provided to the Office of the NIH Director for extending and developing appropriate programs, and $7.4 billion will be provided to the NIH institutes and centers (proportional to their appropriations). Staff throughout NIH, including those at NIDA, are working diligently to determine how to invest these resources. A major consideration is that these funds must be distributed over the next two years to meet the goals of the ARRA. We are aware of how interested you are in these programs and will be providing more details as they become available. Please visit https://archives.drugabuse.gov/Recovery/ for more information.

Appropriations
On March 11, 2009, the President signed into law H.R. 1105, the FY 2009 Omnibus Appropriations Act, as P.L. 111-8. NIH received $30.3 billion, $937,500,000 above the 2008 level the budget request. NIDA received $1.033 billion, as compared to $1.001 billion for FY 2008.

Transition - Executive Branch

Kathleen Sebelius, formerly the Governor of Kansas, was confirmed by the Senate as the Secretary of HHS.

Seattle Police Chief **Gil Kerlikowske** has been nominated by the President to be the Director of ONDCP. The Senate Judiciary Committee has approved the nomination, and it is awaiting a vote in the full Senate.

Treatment Research Institute CEO and long-time addiction researcher **A. Thomas McLellan, Ph.D.** has been nominated to be the Deputy Director of ONDCP. His nomination hearing is pending.

Events of Interest

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Friends of NIDA Bring Criminal Justice Substance Abuse Treatment Research to the Hill

In conjunction with the House Addiction, Treatment and Recovery Caucus, The Friends of NIDA coalition held another successful congressional briefing on March 27, 2009. The American Psychological Association took the organizational lead and 23 scientific societies and professional organizations cosponsored the event to educate congressional staff on the topic of "Implementing Effective Substance Abuse Treatment in the Criminal Justice System."

NIDA Director Nora Volkow, MD began the briefing with an overview of NIDA's criminal justice substance abuse treatment research portfolio. Temple University Professor Steven Belenko, PhD, followed with a presentation on the need to expand effective substance abuse treatment for offenders to enhance public safety. Linda Jalbert, a drug court graduate and former legislative assistant for Senator Susan Collins, concluded the briefing by sharing her story of addiction, prison, treatment, and recovery.

NIH Appropriations hearing in the House

On March 26, NIH Acting Director Dr. Raynard Kington testified before the House Appropriations Subcommittee on Labor, HHS, and Education. The topics for discussion were NIH implementation of the American Recovery and Reinvestment Act of 2009 and the status of the National Children's Study.

Legislation of Particular Interest

Parity Legislation enacted into law. In October 2008, after 12 years of effort, Congress passed and the President signed legislation designed to ensure parity for substance abuse and mental health in insurance coverage. The legislative language, the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008, was included in the economic recovery bill that moved through Congress last fall.

Additional parity-related legislation. In January 2009 the House and Senate introduced legislation to reauthorize the Children's Health Insurance Program, to amend Title XXI of the Social Security Act to extend and improve the Children's Health Insurance Program, and for other purposes. Section 502 of this bill included substance abuse and mental health parity for insurance coverage. Both bodies passed the legislation and it was signed by the President on February 4, 2009.

Tobacco. On April 2, 2009, the House passed H.R. 1256, the Family Smoking Prevention and Tobacco Control Act, a bill to protect the public health by providing the Food and Drug Administration with certain authority to regulate tobacco products. The bill was transmitted to the Senate, where action is pending.

Primate Safety. On February 24, 2009, the House passed H.R. 80, the Captive Primate Safety Act of 2009. The measure would amend section 3371 of the Lacey Act Amendments of 1981 to include in the list of prohibited wildlife species 'any non-human primate.' Among other provisions, the bill would further prohibit transport of primates by certain parties that are not specifically trained or certified for purposes of providing care for the primates or assisting handicapped persons who are unable to provide such veterinary and health care to primates. This measure would not amend or in any way change section 3372 of the Lacey Act, which includes a provision exempting Federal research agencies from such limitations on transportation of primates.

Bills of Interest

[For the full text and additional information about any bill, go to the Library of Congress website at http://thomas.loc.gov].

H.R. 18 - On January 6, 2009, Representative Roscoe Bartlett (R-MD) introduced the "Powder-Crack Cocaine Penalty Equalization Act of 2009," to amend the Controlled Substances Act and the Controlled Substances Import and Export Act with respect to penalties for powder cocaine and crack cocaine offenses. The bill was referred to the Judiciary and Energy and Commerce Committees.

H.R. 179 - On January 6, 2009, Representative Jose Serrano (D-NY) introduced the Community AIDS and Hepatitis Prevention Act, to permit the use of federal funds for syringe exchange programs for purposes of reducing the transmission of bloodborne pathogens, including HIV and viral hepatitis. The bill was referred to the House Committee on Energy and Commerce.

H.R. 193 - On January 6, 2009, Representative Pete Stark (D-CA) introduced the AmeriCare Health Care Act of 2009, to amend the Social Security Act and Internal Revenue Service Code of 1986 to provide for an AmeriCare that assures the provision of health insurance coverage to all residents, and for other purposes. Section 2221(h) of this Act would provide benefits for "mental health services and for substance abuse treatment in the same manner as such benefits are made available for medical and surgical services. The bill was referred to three committees: Energy and Commerce; Ways and Means; and Education and Labor.

H.R. 265 - On January 7, 2009, Representative Sheila Jackson-Lee (D-TX) introduced the Drug Sentencing Reform and Cocaine Kingpin Trafficking Act of 2009, to target cocaine kingpins and address sentencing disparity between crack and powder cocaine. The bill was referred to the Judiciary and Energy and Commerce Committees.

H.R. 439 - On January 9, 2009, Representative Dennis Rehberg (R-MT) introduced the Family-Based Meth Treatment Access Act of 2009, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other services. The bill was referred to the Committee on Energy and Commerce.

H.R. 554 - On February 11, 2009, the House passed the National Nanotechnology Initiative Amendments (NNI) of 2009. The measure was introduced by Representative Bart Gordon (D-TN) on January 15. In general, H.R. 554 would require all agencies participating in the NNI to support the setting of standards for nanotechnology. The bill was sent to the Senate where it is pending.

H.R. 756 - On March 30, 2009, the House passed the National Pain Care Policy Act. Relevant to NIH, the bill would (1) encourage the NIH Director, through the NIH Pain Consortium, to continue and expand an aggressive pain research program, (2) require the NIH Pain Consortium to submit annual recommendations on pain research initiatives that could be paid for by the Common Fund, and (3) require the HHS Secretary to establish an Interagency Pain Research Coordinating Committee, which would include NIH membership. The bill is pending in the Senate as S. 660.

H.R. 758 - On January 28, 2009, Representative Diana DeGette (D-CO) introduced the Pediatric Research Consortia Establishment Act to amend Title IV of the PHS Act to provide for the establishment of pediatric research consortia. The bill was referred to the House Committee on Energy and Commerce. See S.353

H.R. 836 - On February 3, 2009, Representative Earl Pomeroy (D-ND)

introduced the Brewers Excise and Economic Relief (BEER) Act, which if enacted would effectively return the federal beer excise tax to its pre-1991 levels. The bill was referred to the Committee on Ways and Means.

H.R. 872 - On February 4, 2009, Representative Diana DeGette (D-CO) introduced the Stem Cell Research Improvement Act of 2009. The bill would require the Secretary to conduct and support research that uses human embryonic stem cells, regardless of the date on which such cells were derived. The bill outlines certain ethical criteria, and would require that the Secretary, in consultation with the Director of NIH, issue guidelines to carry out the provisions of the legislation within 90 days of enactment. H.R. 872 also provides that the Secretary may issue guidelines on research involving other human stem cells, as determined to be scientifically warranted by the Director of NIH. The bill was referred to the House Committee on Energy and Commerce.

H.R. 873 - On February 4, 2009, Representative Diana DeGette (D-CO) introduced H.R. 873, the Stem Cell Research Enhancement Act of 2009. Like H.R. 872, the bill would require the Secretary to conduct and support research that uses human embryonic stem cells. The bill sets out certain ethical criteria, and would require that the Secretary, in consultation with the Director of NIH, issue final guidelines to carry out the provisions of the legislation within 60 days of enactment. H.R. 873 was referred to the House Committee on Energy and Commerce. See S. 487

H.R. 877 - On February 4, 2009, Representative Randy Forbes (R-VA) introduced H.R. 877, the Patients First Act of 2009. The bill would require the Secretary of HHS to conduct and support research using stem cells, including pluripotent stem cells that "have the flexibility of embryonic stem cells (whether or not such pluripotent stem cells have an embryonic source)." The Secretary, after consultation with Director of NIH, would be required to issue guidelines within 90 days that would prioritize research that has the "potential for near term clinical benefit in human patients." The bill also would add "stem cells" to the list of issues for which a summary of research activities is required as part of the NIH biennial report. H.R. 877 was referred to the House Committee on Energy and Commerce.

H.R. 1028 - On February 12, 2009, Representative Lucille Roybal-Allard (D-CA) introduced the Support 21 Act of 2009, to provide additional support for the efforts of community coalitions, health care providers, parents and others to prevent and reduce underage drinking, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

H.R. 1429 - On March 17, 2009, the House passed the Stop AIDS in Prison Act of 2009, to provide for an effective HIV/AIDS program in Federal prisons. The bill was transmitted to the Senate, where it is pending.

H.R. 1483 - On March 12, 2009, Representative Patrick Kennedy (D-RI) introduced the National Neurotechnology Initiative Act, to direct the Secretary of HHS to implement a National Neurotechnology Initiative, and for other purposes. The bill was referred to the Committee on Energy and Commerce. See S. 586

H.R. 1715 - On March 25, 2009, Representative Diana DeGette (D-CO) introduced H.R. 1715, the Protection for Participants in Research Act of 2009. The bill includes several modifications to the current system for protections of human research participants. H.R. 1715 was referred to the House Committee on Energy and Commerce.

H.R. 2138 - On April 28, 2009, Representative Patrick Kennedy (D-RI) introduced the Services, Education and Rehabilitation for Veterans (SERV) Act, to provide grants to establish veterans treatment courts. The bill was referred

to the Committee on the Judiciary. See S. 902

S. 77 - On January 6, 2009, Senator John Kerry (D-MA) introduced the Children's Mental Health Parity Act, to amend Title XXI of the Social Security Act to provide for equal coverage of mental health services under the State Children's Health Insurance Program. The bill was referred to the Committee on Finance. See H.R. 2 and S. 275.

S. 114 - On January 6, 2009, Senator Daniel Inouye (D-HI) introduced the National Center for Social Work Research Act, to amend the Public Health Service Act to provide for the establishment of a National Center for Social Work Research within the National Institutes of Health. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

S. 132 - On January 6, 2009, Senator Diane Feinstein (D-CA) introduced the Gang Abatement and Prevention Act of 2009, to increase and enhance law enforcement resources committed to investigation and prosecution of violent gangs, to deter and punish violent gang crime, to protect law-abiding citizens and communities from violent criminals, to revise and enhance criminal penalties for violent crimes, to expand and improve gang prevention programs, and for other purposes. Section 313 of the bill establishes a National Youth Anti-Heroin Media Campaign at the Office of National Drug Control Policy. The bill was referred to the Committee on the Judiciary.

S. 177 - On January 8, 2009, Senator Russ Feingold (D-WI) introduced S. 177, the Strengthening Our Economy Through Small Business Innovation Act of 2009. The measure would extend the SBIR program through 2022 and the STTR program through 2023. Additionally, S. 177 would increase SBIR set-aside allocations to 5 percent by 2010, 7.5 percent by 2011, and 10 percent by 2012. The set-aside levels for the STTR program would also double by 2010, and then increase to 0.8 percent by 2011 and to 1.0 percent by 2012. The measure also proposes to increase the SBIR and STTR award levels for phase 1 and 2 grants to $300,000 and $2.2 million, respectively. Finally, the bill would give greater priority consideration to research areas, including those related to energy, security, transportation, and water. S. 177 currently has no co-sponsors and was referred to the Senate Committee on Small Business and Entrepreneurship.

S. 353 - On January 29, 2009, Senator Sherrod Brown (D-OH) introduced the Pediatric Research Consortia Establishment Act to amend Title IV of the PHS Act to provide for the establishment of pediatric research consortia. The bill was referred to the House Committee on Energy and Commerce. See H.R. 758.

S. 487 - On February 26, 2009, Senator Tom Harkin (D-IA) introduced the Stem Cell Research Enhancement Act of 2009, which was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 873.

S. 459 - On February 24, 2009, Senator Claire McCaskill (D-MO) introduced the SUPPORT for Substance Use Disorders Act, to improve and enhance substance use disorder programs for members of the armed forces, and for other purposes. The bill was referred to the Committee on Armed Services.

S. 586 - On March 12, 2009, Senator Patty Murray (D-WA) introduced the National Neurotechnology Initiative Act, to direct the Secretary of HHS to implement a National Neurotechnology Initiative, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 1483

S. 660 - On March 19, 2009, Senator Orrin Hatch (R-UT), introduced S. 660, the National Pain Care Policy Act. The NIH provisions in S. 660 are identical to H.R. 756, described above. S. 660 was referred to the Senate Committee on Health, Education, Labor and Pensions.

S. 714 - On March 26, 2009, Senator James Webb (D-VA) introduced the National Criminal Justice Commission Act of 2009, a bill to establish the National Criminal Justice Commission. The bill was referred to the Committee on the Judiciary.

S. 754 - On March 31, 2009, Senator Jay Rockefeller (D-WV) introduced the Methadone Treatment and Protection Act of 2009, to provide for increased federal oversight of methadone treatment. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 902 - On April 27, 2009, Senator John Kerry (D-MA) introduced the Services, Education and Rehabilitation for Veterans (SERV) Act, to provide grants to establish veterans treatment courts. The bill was referred to the Committee on the Judiciary.

S. 914 - On April 28, 2009, Senator Arlen Specter (D-PA) introduced S. 914, the Cures Acceleration Network and National Institutes of Health Reauthorization Act of 2009. This legislation would (1) establish the Cures Acceleration Network, an independent agency that would make awards to accelerate the development of cures and treatment of diseases, (2) elevate NCMHD to institute status, (3) increase NIH's authorization of appropriations section to $40 billion for FY 2010 and such sums as may be necessary for each of the FYs 2011 to 2012, and (4) require the Director of NIH to develop and enforce conflict of interest policies. S. 914 was referred to the Senate Committee on Health, Education, Labor and Pensions (HELP).

111th Congress

As a result of the November 2008 elections, Democrats have strengthened their majorities in both the Senate and House of Representatives. The most relevant committee-related information for NIDA is listed below.

Senate

Committee on Appropriations, Subcommittee on Labor, Health and Human Services, and Education
Democrats: Tom Harkin (IA) (Chair), Daniel Inouye (HI), Arlen Specter (PA), Herb Kohl (WI), Patty Murray (WA), Mary Landrieu (LA), Richard Durbin (IL), Jack Reed (RI), Mark Pryor (AR)
Republicans: Thad Cochran (MS) (Ranking Member), Judd Gregg (NH), Kay Bailey Hutchison (TX), Richard Shelby (AL), Lamar Alexander (TN)

Committee on Appropriations, Subcommittee on Commerce, Justice, Science and Related Agencies
Democrats: Barbara Mikulski (MD) (Chair), Daniel Inouye (HI), Patrick Leahy (VT), Herb Kohl (WI), Byron Dorgan (ND), Dianne Feinstein (CA), Jack Reed (RI), Frank Lautenberg (NJ), Ben Nelson (NE), Mark Pryor (AR)
Republicans: Richard Shelby (AL) (Ranking Member), Judd Gregg (NH), Mitch McConnell (KY), Kay Bailey Hutchison (TX), Sam Brownback (KS), Lamar Alexander (TN), George Voinovich (OH), Lisa Murkowski (AK)

Committee on Appropriations, Subcommittee on Financial Services and General Government
Democrats: Richard Durbin (IL) (Chair), Mary Landrieu (LA), Frank Lautenberg (NJ), Ben Nelson (NE), Jon Tester (MT)
Republicans: Susan Collins (ME) (Ranking Member), Christopher Bond (MO), Lisa Murkowski (AK)

Committee on Health, Education, Labor, and Pensions (HELP)
Democrats: Edward Kennedy (MA) (Chair), Christopher Dodd (CT), Tom Harkin (IA), Barbara Mikulski (MD), Jeff Bingaman (NM), Patty Murray (WA), Jack Reed (RI), Bernard Sanders (I-VT), Sherrod Brown (OH), Robert Casey

(PA), Kay Hagan (NC), Jeff Merkley (OR)
Republicans: Michael Enzi (WY) (Ranking Member), Judd Gregg (NH), Lamar Alexander (TN), Richard Burr (NC), Johnny Isakson (GA), John McCain (AZ), Orrin Hatch (UT), Lisa Murkowski (AK), Tom Coburn (OK), Pat Roberts (KS)

Committee on the Judiciary, Subcommittee on Crime and Drugs
Democrats: Richard Durbin (IL) (Chair), Herb Kohl (WI), Dianne Feinstein (CA), Russell Feingold (WI), Charles Schumer (NY), Benjamin Cardin (MD), Amy Klobuchar (MN), Edward Kaufman (DE), Arlen Specter (PA)
Republicans: Lindsey Graham (SC) (Chair), Orrin Hatch (UT), Charles Grassley (IA), Jeff Sessions (AL), Tom Coburn (OK)

Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985)
Democrats: Diane Feinstein (CA), two vacant seats
Republicans: Charles Grassley (IA), Jeff Sessions (AL)

House

Committee on Appropriations, Subcommittee on Labor, Health and Human Services, Education, and Related Agencies
Democrats: David Obey (WI) (Chair), Nita Lowey (NY), Rosa DeLauro (CT), Jesse Jackson Jr. (IL), Patrick Kennedy (RI), Lucille Roybal-Allard (CA), Barbara Lee (CA), Michael Honda (CA), Betty McCollum (MN), Tim Ryan (OH), James Moran (VA)
Republicans: Todd Tiahrt (KS) (Ranking Member), Dennis Rehberg (MT), Rodney Alexander (LA), Jo Bonner (AL), Tom Cole (OK), Jerry Lewis (CA - ex officio)

Committee on Appropriations, Subcommittee on Financial Services
Democrats: Jose Serrano (NY), Debbie Wasserman Schultz (FL), Rosa DeLauro (CT), Chet Edwards (TX), Allen Boyd (FL), Chaka Fattah (PA), Barbara Lee (CA), Adam Schiff (CA), David Obey (WI - ex officio)
Republicans: Jo Ann Emerson (MO) (Ranking Member), John Abney Culberson (TX), Mark Steven Kirk (IL), Ander Crenshaw (FL), Jerry Lewis (CA - ex officio)

Committee on Appropriations, Subcommittee on Commerce, Justice, Science and Related Agencies
Democrats: Alan Mollohan (WV) (Chair), Patrick Kennedy (RI), Chaka Fattah (PA), Adam Schiff (CA), Michael Honda (CA), C.A. Ruppersberger (MD), Peter Visclosky (IN), Jose Serrano (NY), David Obey (WI - ex officio)
Republicans: Frank Wolf (VA) (Ranking Member), John Abney Culberson (TX), Robert Aderholt (AL), Jo Bonner (AL), Jerry Lewis (CA - ex officio)

Committee on Energy and Commerce, Subcommittee on Health
Democrats: Frank Pallone (NJ) (Chair), John Dingell (MI), Bart Gordon (TN), Anna Eshoo (CA), Eliot Engel (NY), Gene Green (TX), Diana DeGette (CO), Lois Capps (CA), Jan Schakowsky (IL), Tammy Baldwin (WI), Mike Ross (AR), Anthony Weiner (NY), Jim Matheson (UT), Jane Harman (CA), Charles Gonzalez (TX), John Barrow (GA), Donna Christensen (VI), Kathy Castor (FL), John Sarbanes (MD), Christopher Murphy (CT), Zachary Space (OH), Betty Sutton (OH), Bruce Braley (IA), Henry Waxman (CA - ex officio)
Republicans: Nathan Deal (GA) (Ranking Member), Ralph Hall (TX), Ed Whitfield (KY), John Shimkus (IL), John Shadegg (AZ), Roy Blunt (MO), Steve Buyer (IN), Joseph Pitts (PA), Mike Rogers (MI), Sue Wilkins Myrick (NC), Tim Murphy (PA), Michael Burgess (TX), Marsha Blackburn (TN), Phil Gingrey (GA), Joe Barton (TX - ex officio)

Committee on Oversight and Government Reform, Subcommittee on Domestic Policy
Democrats: Dennis Kucinich (OH) (Chair), Elijah Cummings (MD), John Tierney (MA), Diane Watson (CA), Jim Cooper (TN), Patrick Kennedy (RI),

Peter Welch (VT), Bill Foster (IL)
Republicans: Jim Jordan (OH) (Ranking Member), Mark Souder (IN), Dan Burton (IN), Michael Turner (OH), Jeff Fortenberry (NE), Aaron Schock (IL)

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

International Activities

Funding Initiatives

IAS and NIDA Establish a New HIV and Drug Abuse Fellowship
NIDA and the International AIDS Society (IAS) have established a fellowship program that focuses on HIV research related to drug abuse. 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. The fellowship program will offer two awards of $75,000 each: one to a junior HIV and drug abuse scientist for an 18-month post-doctoral fellowship at a leading research institute in the field; and one to a well-established HIV scientist, not currently active in the drug abuse field, for an 8-month period of professional development on HIV and drug abuse.

International Collaboration

Inhalant Working Group Publishes Call for Research in Addiction
Writing in the February 10, 2009, online edition of Addiction, a multidisciplinary group of NIDA-supported researchers discuss the strengths and weaknesses of various approaches to classification of inhalants and suggests areas for future research in the area. The authors conclude that classification of inhalants by form or product types is not useful for scientific purposes. They recommend that subclassification of inhalants should be based on a yet-to-be-determined combination of chemical and pharmacological similarity and shared patterns of abuse, and call for efforts to obtain more detailed information on individual products and chemicals, their patterns of use, and the geographical distribution of their use. The authors - Robert L. Balster, Virginia Commonwealth University; Silvia L. Cruz, Cinestav, Mexico; Matthew O. Howard, University of North Carolina; Colleen A. Dell, University of Saskatchewan, Canada; and Linda B. Cottler, Washington University - are part of the Inhalants Working Group, an ad hoc multi-national group of drug abuse researchers formed following the 2005 NIDA International Program meeting, Inhalant Abuse Among Children and Adolescents, whose 55 invited participants from 10 nations recommended that an international workgroup of pharmacologists and epidemiologists be created to classify substances and develop questions for use in screening instruments and surveys. The authors worked with Dr. Charles Sharp, DBNBR, and IP staff through the NIDA International Virtual Collaboratory (NIVC) to engage the international drug abuse research community as they drafted the paper. In addition to this paper, the group has planned workshops at the 2007, 2008, and 2009 NIDA International Forums and is working with other organizations to gather international data on inhalant abuse. [Addiction. 2009 Feb 10. (Epub ahead of print). Classification of abused inhalants. Balster RL, Cruz SL, Howard MO, Dell CA, Cottler LB. DOI: 10.1111/j.1360-0443.2008.02494.x]

DISCA Fellowship Leads to Publication and a New Technology Transfer Center
Octavio Campollo, Ph.D., of the University of Guadalajara, Mexico, finished his experience as a 2008 DISCA fellow with two published manuscripts and a

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collaborative effort to help other addiction professionals in his home country. Working with Fernando Wagner, Sc.D., Morgan State University, Dr. Campollo was involved in two research projects: risk factors for substance use in high school students in Jalisco, Mexico; and HIV and hepatitis in drug addicts in West Mexico. Two manuscripts prepared during Dr. Campollo's fellowship have been published in the international peer-review journal Anuario Investigaci—n en Adicciones (Volume 9, Number 1, 2008). One article, "Marijuana effects and medical consequences: a review," examines and draws conclusions about the most important medical and pathological effects of marijuana. The second article explores the "International ethos of addictions." After studying NIDA's Addiction Technology Transfer Centers in the continental United States and the Caribbean Basin during his fellowship, Dr. Campollo decided to start an independent technology transfer center with other faculty members to disseminate information and to train and support addiction professionals in Mexico.

NIDA Supported Researchers Give Notable Presentation

Two researchers initially supported by NIDA IP gave a presentation in Paris at the 2008 International Conference on Drugs and Cultures that was featured in the French newspaper *Le Monde*. Dr. Geoffrey P. Hunt of the Scientific Analysis Corporation, San Francisco, California, described findings from research comparing the social context of club drugs use by youth in San Francisco, California, and Mongkok, Hong Kong. Dr. Hunt and his colleague, Dr. Karen Joe-Laidler of the Hong Kong University Centre for Criminology, found that the drug of choice at rave parties in Mongkok was the anesthetic ketamine, rather than ecstasy, which is preferred at parties in many other international settings. Another difference was that drug-using youth in Mongkok were more likely than those in San Francisco to come from the working class. These and other research findings will increase understanding of the club drugs and techno dance culture as well as the influence of local context on behavior in party scenes.

International Collaboration Supported by NIDA Transfers Successful Model to the U.K.

Two programs that were recently endorsed by the United Kingdom's National Treatment Agency (NTA) for Substance Misuse have benefited from NIDA support for Dr. Dwayne Simpson, Director of the Institute of Behavioral Research (IBR) at Texas Christian University (TCU). NIDA grants awarded to IBR/TCU have supported the development of TCU drug treatment resources for 20 years. Under a NIDA administrative supplement, Dr. Simpson led international collaborations to determine whether applying the TCU approach to drug treatment, shown to be effective in the United States, would work in the U.K. context. Dr. Simpson helped two NTA-sponsored programs—the International Treatment Effectiveness Project (ITEP) and the Birmingham Treatment Effectiveness Initiative (BTEI)—translate and apply TCU-originated drug treatment resources to meet British service improvement needs. The programs adapted the TCU Treatment Process Model, which uses a psychosocial mapping intervention for discussing issues with clients, as well as a process for assessing and improving organizational functioning and service management that is advocated by the model. The ITEP and BTEI programs have shown that this intervention can be implemented effectively in the United Kingdom by following easy-to-use manuals and that this change can contribute to significant and lasting organizational improvements. Dr. Simpson recently received a NIDA IP Distinguished International Scientist Collaboration Award (USDISCA) to support his collaboration on efforts to broaden applications of this approach to treatment systems in the United Kingdom.

Fellowships

NIDA IP Presents New Web-Based Fellowship Map

NIDA is making it easier to find talented, NIDA-trained research partners from other countries by offering a new tool on the NIDA IP Website. The NIDA International Program Fellowship Map (online at http://www.international.drugabuse.gov/research/fellowships_worldwide_map.html) fosters collaboration among international researchers by allowing users to identify NIDA fellowship alumni from a particular country or fellowship program with just a

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click of a mouse. The mapping tool also links from individual fellows to their journal articles indexed in the NIH National Library of Medicine's PubMed database. Former fellows from the NIDA INVEST, INVEST-CTN, Hubert H. Humphrey, and DISCA/USDISCA programs are included on the map. NIDA IP is also developing new online tools due to be launched later this year that will allow users to find experts by research topic or to search the abstracts accepted for presentation at the past five NIDA International Forums.

HHH Fellowship Orientation

NIDA hosted 16 Humphrey, INVEST, and INVEST/CTN Fellows from 13 nations during an orientation program to introduce fellows to the Institute and its staff. International Program Director Dr. Steven W. Gust and Program Analyst Dale Weiss welcomed the fellows to NIDA headquarters and introduced them to NIDA-supported online collaboration tools. Drs. Krystyna Isaacs and Joseph Perpich demonstrated one of those tools, the NIDA International Virtual Collaboratory (NIVC), and discussed the Humphrey Fellowship Professional Affiliation Directory being created through NIVC. The fellows met individually or in small groups with NIDA project officers, and the INVEST/CTN Fellows presented their research projects to CTN staff and grantees. Fellows toured the Intramural Research Program (IRP) in Baltimore, meeting with the IRP Clinical Director, Captain Carlo Contoreggi, M.D., and the IRP Institutional Review Board Administrator, Ms. Anne E. Gupman, as well as attending a grand rounds presentation on therapeutic workplace interventions for addiction by Dr. Kenneth Silverman, Johns Hopkins University. The fellows toured the chemistry and drug metabolism laboratories with Dr. Marilyn Huestis; the magnetic resonance imaging suite with Dr. Eliot Stein; Archway Clinic with Dr. Kenzie Preston and Ms. Margaret Kroen; and the nicotine addiction and cognition outpatient testing rooms with Dr. Steve Heishman. Fellows also toured the National Library of Medicine and met with Dr. James Herrington at the Fogarty International Center. Ms. Mayaan Lawental Schori, an Israeli Ph.D. candidate at the University of Pennsylvania, also participated in the orientation.

NIDA Awards Three New INVEST/CTN Fellowships

NIDA has awarded NIDA INVEST/CTN Research Fellowships to researchers in the Philippines, Columbia, and Tanzania. Awardees will begin their 12-month Fellowship by June 30, 2009.

- **Leonardo R. Estacio, Jr.**, is an Associate Professor in the Department of Behavioral Sciences at the University of the Philippines Manila. He obtained his Ph.D. in anthropology/medical anthropology from that university in 2003 and a M.P.H from Johns Hopkins University (JHU) in 1999. He was an HHH Fellow at JHU in 1998 to 1999. Dr. Estacio also has served as an international consultant for the Vietnam and Bangkok offices of the United Nations Office on Drugs and Crime and as Executive Director of the Philippine Council of NGOs Against Drug and Substance Abuse. Dr. Estacio will spend his Fellowship year with Dr. Dennis M. Donovan of the Alcohol and Drug Abuse Institute at the University of Washington in Seattle, Washington, working to provide baseline evidence of the prevalence and incidence of amphetamine-type stimulant abuse and its associated risk and protective factors.
- **Mario A. Zapata** is a professor in epidemiology and mental health and a member of the Mental Health Research Group at CES University in Medellin, Columbia. He obtained his M.D. at Antioquia University in 1989 and a Master's degree in epidemiology at CES University in 2004. Dr. Zapata previously served as the Director and Coordinator of the Drug Prevention Committee of the CARISMA Mental Health and Addiction Center. Dr. Michael Robbins will mentor Dr. Zapata during his Fellowship year at the Miller School of Medicine, University of Miami, in Miami, Florida. Dr. Zapata will focus on gaining experience with the Brief Strategic Family Therapy model, particularly with adolescent drug users, to facilitate the implementation and evaluation of this approach in Columbia.
- **Stephen Nsimba** is a professor in the Department of Clinical Pharmacology at Muhimbili University of Health and Allied Sciences (MUHAS), Tanzania. He obtained his Doctor of Dental Surgery degree at the University of Dar-es-Salaam, Tanzania, in 1987, and his Ph.D. at the Karolinska Institute, Stockholm, Sweden, in 2003. Dr. Nsimba was an HHH Fellow at John Hopkins University from 2005 to

2006. Dr. Nsimba will be working with Kathleen Brady, M.D., Ph.D. at the Medical University of South Carolina on a CTN protocol that is comparing the relative effectiveness of three HIV testing strategies on increasing acceptance and receipt of test results among adult clients at community-based drug abuse treatment programs. Dr. Nsimba's intends to use this experience to implement and study substance abuse and HIV prevention interventions in urban and rural health clinics in four regions of Tanzania.

NIDA Selects Two New Distinguished International Scientists
NIDA has selected two senior scientists to work with their partners on binational collaborative research.

- **Carlos A. Zubaran, Jr., M.D., Ph.D.**, recipient of a DISCA award, will work with mentor Linda B. Cottler, Ph.D., M.P.H., at Washington University in St. Louis, Missouri, to compare illicit substance users from the United States and Australia to help identify substance use variables that are significantly influenced by geographical variations. This research will promote further understanding of the environmental factors that may promote or maintain substance use. Dr. Zubaran is an associate professor at the School of Medicine at the University of Western Sydney, Australia, and a consultant psychiatrist at Sydney West Area Health Service. He also has conducted drug abuse research in Brazil.
- **Dwayne Simpson, Ph.D.**, Director of the Institute of Behavioral Research (IBR) at Texas Christian University (TCU), is a new USDISCA recipient who will work with Dr. Ed Day at the University of Birmingham to address structural and systemic issues in sustaining the implementation of TCU-originated drug treatment resources in the United Kingdom. In this new stage of international collaboration, Dr. Simpson will provide strategic planning assistance to help teams of addiction treatment research scientists and clinical practitioners adapt concepts and tools from the TCU Treatment Process Model to treatment systems in the West Midlands and North West regions of the United Kingdom. Dr. Simpson has been a professor at TCU for more than 35 years and is the Director of TCU's IBR. He received a MERIT award from NIDA in 1999.

Travel Support

International Scientists Explore Role of Neuroimmunomodulation in Drug Abuse and HIV/AIDS
NIDA supported the International Symposium on Biotechnological Approaches to Neuroimmunomodulation and Infectious Diseases, held December 11-13, 2008, in Nagar, India. The meeting featured speakers from India, Germany, and the United States, including NIDA grantee Dr. Robert Donahoe, an expert in how abused drugs affect the progression of AIDS. The National Institute on Pharmaceuticals and Educational Research of India sponsored the conference, with support from NIDA, Roche Pharmaceuticals of India, and the University of Utah.

American Society of Addiction Medicine International Symposium
NIDA IP supported the participation of Dr. Evgeny M. Krupitsky of Pavlov Medical University, St. Peterburg, Russia, and Dr. John Strang of the National Addiction Centre in London, at a symposium on Unique Models for Comprehensive Substance Abuse Treatment. The American Society of Addiction Medicine (ASAM), in conjunction with NIDA and the International Society for Addiction Medicine (ISAM), conducted the symposium during ASAM's 40th Annual Medical-Scientific Conference, held in New Orleans, Louisiana, on April 30-May 3, 2009. During the symposium, international clinical researchers presented findings and clinically applicable experiences from other countries that shed light on problems being confronted in the United States, with the goal of broadening and extending competency in addiction treatment and research. Dr. Jag H. Khalsa, DPMCDDA, organized the symposium.

International Visitors

Visitors from the New Energy and Industrial Development Organization (NEDO)

visited NIDA and NIAAA on February 20, 2009. NEDO is Japan's largest public R&D management organization for promoting the development of advanced industrial, environmental, new energy and energy conservation technologies. The meeting was organized by the Fogarty International Center to enable the representatives of NEDO to learn more about the funding of international collaborations.

Other International Activities

Dr. Wilson M. Compton, Director, DESPR, chaired a panel and participated in a meeting on the WHO Schedules for Clinical Assessment of Neuropsychiatry (SCAN) at the International Federation of Psychiatric Epidemiology, Vienna, Austria, April 15-19, 2009.

Dr. Peter Hartsock, DESPR, worked with Fogarty to coordinate a special visit to NIH by the personal physician to the president of Madagascar and a team including the Malagasy Minister of Health, researchers, planners, and policy makers on January 8, 2009 held in Bethesda, MD. It was the first-ever delegation of Malagasy health researchers to an English-speaking country. Dr. Hartsock presented on NIDA's AIDS modeling program, including national policy changing research such as expanded HIV testing, circumcision, and multiple concurrent partnerships (the "HIV Superhighway"). Madagascar has applied approaches such as HIV testing and circumcision and has a highly successful national AIDS prevention program.

Dr. Peter Hartsock met with a visiting delegation to NIDA of Humphrey Fellows, January 23, 2009 in Bethesda, MD. Dr. Hartsock presented on NIDA's AIDS modeling and international research efforts.

Dr. Peter Hartsock participated in a special Center for Strategic and International Studies (CSIS) consultation on "HIV and Drug Use Prevention in Russia: The Challenge of Matching Science to Practice," heal on February 4, 2009 in Washington, D.C. Dr. Hartsock presented on NIDA's AIDS research efforts in the former Soviet Union.

Dr. Peter Hartsock participated in a special Center for Strategic and International Studies (CSIS) consultation on "Migration and Development in Russia's Northern and Arctic Regions," held in February 2009 in Washington, D.C. Dr. Hartsock presented on NIDA's Russian and Arctic research.

Dr. Peter Hartsock participated in a planning meeting for an international summit on the convergence of human medicine with veterinary medicine held on March 12, 2009 in Washington, D.C. The meeting was conducted by the One Health Academy and is important to NIDA's HIV and other infectious disease efforts because drug users who are at risk for AIDS are also at risk for increasing vector-borne diseases such as malaria and plague. Dr. Hartsock presented on NIDA's AIDS modeling efforts which have also been applied to anthrax and smallpox.

Dr. Peter Hartsock and NIDA grantee Dr. Martina Morris of the University of Washington met with the Institute of Medicine and National Research Council to present Dr. Morris's research on extremely rapid means by which HIV/AIDS spreads and applications of this research to global efforts to combat AIDS on March 20, 2009 in Washington, D.C.

Dr. John Satterlee played a key role in organizing a meeting entitled "Exploring International Coordination in Epigenomics" held on March 17-18, 2009 in Bethesda, Maryland. The goal of the meeting was to explore how NIH Roadmap Epigenomics Program efforts could be leveraged by other countries and research entities to further global epigenomics and disease research efforts. There were eleven presentations at the meeting most of which were on the topic of "International and US Epigenetics Programs: Progress and Opportunities." The participants included both scientists and funding agency representatives. Attendees were from Australia, Singapore, Korea, China, Japan, Canada, Switzerland, United Kingdom, United States, and the European Commission.

Dr. Allison Hoffman, DBNBR, organized a symposium for the 14th World Conference

on Tobacco OR Health on "Smoking and Co-Morbid Diseases". This conference took place in Mumbai, India on March 8-12, 2009.

Dr. Allison Hoffman organized a symposium for the 14th World Conference on Tobacco OR Health on "The Future of Smoking Cessation Treatment" 14th World Conference on Tobacco OR Health. This conference took place in Mumbai, India on March 8-12, 2009.

Dr. Allison Hoffman organized a symposium for the 2009 Joint conference of SRNT and RNT-Europe entitled "Nicotine and Information Processing". This conference took place in Dublin, Ireland on April 27-30, 2009.

Dr. Allison Hoffman organized a symposium for the 2009 Joint conference of SRNT and RNT-Europe entitled "Targets for treating nicotine addiction: not the usual suspects" This conference took place in Dublin, Ireland on April 27-30, 2009.

Dr. Ivan Montoya, DPMCDA, gave a plenary lecture at the 36th annual meeting of Socidrogalcohol (Drug and Alcohol Research Society of Spain) in Salamanca, Spain on March 27, 2009.

Dr. Eugene Kiyatkin from the Behavioral Neuroscience Section, IRP, was an invited speaker at the Second Joint Congress of GCNN and SSNN, Vienna, Austria, March 1-5, 2009.

There were three new international fellows selected for the INVEST/CTN fellowship that began in 2009. The Fellows will spend one year working with a mentor who is affiliated with one of the 16 NIDA Clinical Trials Network Regional Research and Training Centers.

- Mario A. Zapata, M.D., M.Sc., Public Health Professor and member of Mental Health Group Research, Faculty of Medicine-CES University, Medellin, Colombia, will be working with Michael Robbins, Ph.D., Center for Family Studies, University Miami.
- Leonardo R. Estacio, Ph.D., Associate Professor, Department of Behavioral Sciences, University of Philippines, Manila will be working with Dennis M. Donovan, Ph.D., University of Washington.
- Stephen Nsimba, E.D. (Dr.), Senior Lecturer/Assistant Professor, Department of Clinical Pharmacology, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, United Republic of Tanzania, East Africa, will be working with his mentor Kathleen Brady, M.D., Ph.D., Clinical Neuroscience Division, Institute of Psychiatry Medical University of South Carolina.

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Meetings/Conferences

On January 6-7, 2009 NIDA convened a two-day meeting to address the issue of **Substance Abuse and Comorbidities Among Military Personnel and Their Families**. There is growing concern that military personnel returning from Iraq and Afghanistan are experiencing a range of difficulties, including traumatic brain injury (TBI), post traumatic stress disorder (PTSD), depression, anxiety, and tobacco, alcohol and drug abuse. The goals of the meeting were to gain an understanding of the intervention needs of military personnel, veterans, and their families regarding substance abuse and associated difficulties; discuss current prevention and treatment approaches being used with these populations; review existing drug abuse prevention and treatment interventions that may be appropriate for adapting and testing for use with these audiences; understand how to successfully conduct research in military and veteran settings; and formulate a research agenda for conducting addiction prevention. The meeting was organized in collaboration with the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veterans Affairs, the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Heart, Lung, and Blood Institute (NHLBI), and the National Cancer Institute (NCI). As a result of the discussions held, a series of recommendations for new research directions and priorities will be produced.

A meeting to report on the progress of, and plan the next steps for, the **Centers of Excellence for Physician Information (CoE)** program was organized by Elisabeth Davis, OSPC and held on February 5, 2009. The purpose of the NIDA CoEs, established in 2007, is to advance addiction awareness, prevention, and treatment in primary care practices by educating medical students, residents, and faculty on drug abuse and addiction in patient populations. The meeting debuted findings from a formative assessment measuring medical student and resident physician attitudes, beliefs, and behaviors on screening and treatment of substance abusing patients. It also evaluated how students prefer to obtain their information and the sources they use to learn more about drug abuse and addiction subject matters. The meeting also introduced the 11 curriculum resources developed by the CoEs as well as the findings from an extensive review of these resources. For the second half of the meeting, participants brainstormed on the next steps for the implementation and dissemination of CoE curriculum resources, and dissemination plans are underway. The meeting was attended by representatives from each of the four Centers which are located at medical schools in North Dakota at the University of North Dakota; Nebraska at Creighton University; Pennsylvania, at the University of Pennsylvania and Drexel University; and a consortium of four schools in Massachusetts — including the University of Massachusetts, Boston University, Tufts University, and Harvard University. Also in attendance were representatives from the

American Medical Association and JBS, International.

NIDA's Office of Science Policy and Communications successfully hosted its first roundtable discussion for college journalism and communication majors, entitled **Covering Addiction: A Roundtable for College Journalists** on February 27, 2009. Fifteen students from universities around Washington D.C. participated in two question-and-answer sessions with NIDA scientists and some of the nation's top health journalists. The first topic of discussion, The Dope on Campus Drug Use, was led by NIDA Deputy Director Dr. Timothy P. Condon: Dr. Ruben Baler, Health Scientist Administrator, OSPC, Dr. Amelia Arria of the University of Maryland in College Park, and Dr. Carol J. Boyd of the University of Michigan also participated. The second topic, Reporting on the College High, included respectable journalists such as Lisa Stark of ABC News, Lauran Neergaard of Associated Press, and Jacqueline Duda, a freelancer who contributes to The Washington Post. The second panel also included John Burklow of the NIH Office of Communications. The roundtable received positive feedback from the students, and OSPC is considering more roundtables in the other parts of the country.

Dr. Yu (Woody) Lin, DCNBR, organized a meeting on **Healthier Life Choices and Wellness through Tai-Chi/Qi-Gong Exercise: Implications for Substance Abuse** which was held on May 6, 2009 at NIDA. The meeting was sponsored jointly by the Division of Clinical Neuroscience and Behavioral Research (DCNBR) and the Center for the Clinical Trials Network (CCTN). A major purpose was to introduce Tai-Chi/Qi-Gong exercise as a milder challenge and resource-free practice for physical and mental wellness, review its association to self-awareness, self-efficacy and attention/focus, and discuss its implications for stress release/tranquility, sleep disorder and substance abuse.

Dr. Yu (Woody) Lin of DCNBR, chaired a meeting on **HIV & Substance Abuse: from Genes to Therapy** that was jointly sponsored by the Department of Psychiatry, John A. Burns School of Medicine, University of Hawaii, National Institute on Drug Abuse (NIDA) Special Populations Office and the International Office and National Institute of Mental Health (NIMH). It was held on May 11-12, 2009 in Honolulu, Hawaii. The meeting was a session of the 2009 Hawaii Addictions Conference / AAPI Work Group Scientific Conference entitled **Addiction and Related-Issues: Focusing on Recent Research and Culturally Relevant Treatments among Asian Americans and Pacific Islanders**. It was organized jointly by the planning committees of the 10th Hawaii Addictions Conference and the 2nd National Institute of Health Asian Americans and Pacific Islanders Scientific Conference. The purpose of this conference was to: 1) identify findings from addiction research and science which translate to treatment modalities that improve clinical outcomes; and 2) integrate knowledge of Asian and Pacific Islanders cultural, psycho-social, and co-morbid characteristics into addiction research and treatment alternatives for special populations of those who are chemically dependent.

Drs. Bethany G. Deeds and Yonette F. Thomas, DESPR, convened a meeting of NIDA grantees to discuss their findings on **"After Hurricane Katrina: Alcohol and Drug Abuse Research."** The meeting was held on October 29, 2008 in Rockville, MD. Participants described their research findings on drug abuse and related risk behaviors among persons living in New Orleans and nearby areas most affected by the hurricane.

On February 23, 2009, Dr. Aria Crump, PRB, DESPR and Dr. Jeffrey Schulden, ERB, DESPR organized a joint NIDA/NIDCR meeting entitled **"Opioid Prescribing to Adolescents in Dental Settings."** This roundtable meeting with a small group of invited researchers and clinicians was held to discuss a potential research agenda around the prescribing of opioid analgesics to adolescents in dental settings. In the spirit of understanding patient and clinician perceptions and behaviors related to the prevention of opioid misuse and abuse among adolescents, the agenda included topical presentations by

Planned Meetings

Publications

Staff Highlights

Grantee Honors

participants, discussant remarks, and moderated group discussion. Presenters discussed 1) current research on standard practices for dentists for prescribing opioid analgesics, 2) dentists' perceptions of the risk and safety of opioid analgesics, 3) current knowledge regarding opioid misuse and abuse among adolescents, and 4) the potential for prevention practices to decrease opioid misuse and diversion among adolescents.

On February 2-3, 2009, NIDA convened the second meeting of the **Prevention Research Review Work Group** in Bethesda, Maryland. This meeting was chaired by Dr. Mark Greenberg, who served as a recent member of the National Advisory Council on Drug Abuse and was coordinated by Dr. Denise Pintello. The purpose for this Work Group is to conduct a comprehensive review of NIDA's prevention research portfolio and to provide recommendations to effectively address the future direction of prevention research at NIDA. The Work Group members will prepare a written report for the National Advisory Council on Drug Abuse in May of 2009.

The annual DPMCDA **P50 Medications Development Centers Meeting** was held on March 30 and 31, 2009, in San Francisco, CA.

The **National CTN Steering Committee Meetings** were held March 24-26, 2009 in Rockville, MD. The following meetings/committees convened:

CTP and PI Caucuses
TEAM Task Force
Young Adult BUP Treatment
Steering Committee
Executive Committee
Research Utilization Committee
Research Development Committee
Node Coordinator Workgroup
Pharmacotherapy Special Interest Group
Health Services Research Interest Group
SBIRT Group
CTN 0030 POATS Long-term Follow-up Team
CTN 0031 STAGE-12 Study Team

Two workshops were held during the CTN Steering Committee Meetings: **Practical Approaches for Valid Subgroup Analysis in the CTN** The purpose of this workshop was to facilitate valid analyses of ethnic/racial minorities, gender and other subpopulations in the CTN. Speakers presented and discussed issues and strategies for planning and executing subgroup analyses during study design and data analysis, as well as when combining data sets from multiple studies.

Research Utilization in the CTN: Methods for Disseminating Evidence-based Treatments from the Frontlines of Community Treatment Programs This workshop highlighted different methods CTPs have used to disseminate evidence-based treatment into their practice settings. Representatives from CTPs presented five dissemination methods that have resulted in successful implementation of evidence-based treatment. These methods included: 1) strategies to adapt treatments to best fit clinical practice; 2) use of opinion leaders; 3) quality improvement initiatives; 4) organizational change efforts; and 5) beyond journals: the use of popular professional magazines. In addition, there was a live demonstration of the CTN Dissemination Library website showing how this resource could support the adoption of evidence-based treatment. Workshop participants learned about approaches they might use to promote similar practices within their programs.

Dr. Timothy P. Condon, Deputy Director, NIDA, moderated "Addressing Substance Abuse and Comorbidities Among Military, Veterans and their

Families: A Research Agenda" in Bethesda, Maryland on January 6, 2009.

Dr. Timothy P. Condon presented "Research on Addiction: What Have We Learned?" at the New York Society of Addiction Medicine (NYSAM) 5th Annual Medical Scientific Conference in New York, New York on January 24, 2009.

Dr. Timothy P. Condon presented "National Institute on Drug Abuse: Progress, Priorities & Plans for the Future" at the Community Anti-Drug Coalitions of America (CADCA) 19th National Leadership Forum in National Harbor, Maryland on February 11, 2009.

Dr. Timothy P. Condon presented "What Research Tells Us About Treatment" at Neurobiologia de l'addiccio in Barcelona, Spain on February 19, 2009.

Dr. Timothy P. Condon presented "Understanding Drug Abuse & Addiction Through Research" at the Roundtable for College Journalists in Bethesda, Maryland on February 27, 2009.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt - The Neuroscience of Addiction" at the Supreme Court of Ohio Judicial College, Addictions: What Every Judge Should Know in Cincinnati, Ohio on March 5, 2009.

Dr. Timothy P. Condon presented "National Institute on Drug Abuse: Progress, Priorities & Plans for the Future" at the 2009 Annual Meeting of the Academic Consortium, in Washington, D.C. on March 12, 2009.

Dr. Timothy P. Condon spoke at National Inhalant Prevention Coalition Inhalants Press Briefing at the National Press Club, Washington, DC, March 16, 2009.

Dr. Cindy Miner, Deputy Director, OSPC participated in a pre-conference session entitled "Social Work Research Career Development at the National Institutes of Health" at the Society for Social Work and Research Conference on January 15, 2009, in New Orleans, LA.

Dr. Cindy Miner, Dr. Gaya Dowling, OSPC, and Ms. Carol Krause, OSPC Co-Presented a workshop entitled "The Real Inside Scoop on What Teens Want to Know About Drug Abuse" at CADCA's 19th Annual Leadership Forum on February 12, 2009, in Baltimore, MD.

Dr. Cindy Miner presented "Accessing Information on Addiction: An Update on NIDA's Research Dissemination Efforts" at the NIMH Outreach Partnership Program on March 18, 2009, in Charlotte, NC.

Dr. Ruben Baler, OSPC, presented a Keynote address on the Science of Addiction, at the 2009 Wyoming Methamphetamine and Substance Abuse, on January 8, 2009, in Casper, WY.

Dr. Ruben Baler lectured on the Science of Addiction for the George Washington University's Drug Awareness Freshman Course, on February 10, 2009, in Washington, DC.

Dr. Ruben Baler delivered a brief presentation on Brain Development and Decision making at the First NIDA's College Journalists Roundtable, on February 27, 2009, at the Natcher Conference Center, NIH campus, Bethesda, MD.

Dr. Ruben Baler presented a lecture entitled: "Navigating Around the Dangers of Abuse and Addiction" to the Youth National Leadership Forum at the CADCA Conference, on February 11, 2009, in Washington, DC.

Dr. Lula Beatty, Chief, Special Populations Office (SPO), chaired a session at a symposium titled "Addressing Social Justice through Health Research and

Intervention" and made a presentation titled "Changing the Drug Abuse Research Agenda to Benefit Racial/Ethnic Minority Populations" at the National Multicultural Conference and Summit, January 16, 2009 in New Orleans.

Dr. Lula Beatty attended the Third National Leadership Summit on Eliminating Racial and Ethnic Disparities in Health: A Blueprint for Change on February 25-27, 2009 in National Harbor, Maryland.

Dr. Lula Beatty attended a conference titled "Black Women Academics in the Ivory Tower" at Rutgers University on March 5-6, 2009 in New Brunswick, New Jersey.

Dr. Lula Beatty attended a meeting convened by the Office of Minority Health, HHS, to discuss interest in efforts to address marginalized males on March 19, 2009 in Washington, DC. She agreed to chair a research interest group on this topic.

Dr. Lula Beatty participated as a faculty member in the Leadership Institute for Women in Psychology sponsored by the Women's Office, American Psychological Association, March 19, 2009 in Washington, DC.

Ana Anders, SPO, attended the "NIH Summit: The Science of Eliminating Health Disparities," December 15-18, 2008, in National Harbor, MD. In addition, she served as a review team leader and session moderator.

Ana Anders participated at the National Hispanic Science Network Steering Committee meeting February 27-28, 2009 in Miami, Florida.

Dr. Teri Levitin, Director, OEA, helped organize a workshop on mentoring the next generation of researchers for the biennial meeting of the Society for Research on Child Development in Denver, Colorado, April 2-4, 2009. Her specific presentation was on training mechanisms and the NIH review process.

Dr. Jerry McLaughlin, OEA, provided invited talks/reviews for the NIH Biocomputing Interest Group (BCIG) and the Washington Evolution Society on Reis's "The Synaptic Self: How Our Brains Become Who We Are"; Norbert Weiner's "The Human Use of Human Beings", and Ernst Myer's "What Makes Biology Unique."

Dr. Jerry McLaughlin coordinated and presented a talk as an expert panel member for the Scientific Program and Review Interest Group (SPRIG) on a session entitled "Innovation in Peer Review", February 6, 2009.

Dr. Jerry McLaughlin participated in the Addiction Interest Group's group discussion at the Gerontology Society's annual meeting in Washington DC.

Dr. Meenaxi Hiremath, OEA, participated in a Mock review at the Special Populations Research Development Seminar Series workshop on April 23 2009, at the Bethesda Doubletree Hotel in Bethesda, Maryland.

On January 22, 2009, Dr. Betty Tai, Director, CCTN, presented an overview of the CTN and the resources it has available, to the awardees of the Hubert H. Humphrey Drug Abuse fellowships.

On February 10, 2009, Dr. Betty Tai presented "How the National Institute on Drug Abuse (NIDA) Initiatives Promote Understanding of Prescription Opiates" at an FDA sponsored meeting titled "FDA Regulatory Processes and Standards for Review and Approval of Opioid Analgesics: An Educational Primer."

Dr. Roger Sorensen, DBNBR, and Dr. Diane Lawrence, ARP, organized a colloquium titled: "Neurotoxicity or Neuroprotection: The Two Sides of Drug Abuse Action" that was held on March 7, 2009 in conjunction with the 40th Annual Meeting of the American Society for Neurochemistry (ASN) , Charleston, SC. The purpose of this colloquium was to disseminate current

research findings on the biological mechanisms underlying neurotoxicity or neuroprotection produced by drugs of abuse, including the role of glia in these processes. The presenters were: M. Kerry O'Banion (University of Rochester Medical Center); Katherine Conant (Johns Hopkins University Medical Center); Jean-Christopher Rochet (Purdue University); and Stanley Thayer (University of Minnesota Medical School).

Dr. Cora Lee Wetherington, Coordinator, Women and Sex/Gender Differences Research Program and DBNBR, was an invited participant and represented NIDA at the NIH Office of Research on Women's Health (ORWH) strategic planning workshop held at Washington University, March 4-6, 2009. This workshop was the first of four regional scientific workshops to explore new dimension for the NIH women's health research agenda for the next decade. Dr. Wetherington was a member of the workgroup, "Brain and Psychiatric Disorders." The next regional workshop will be convened May 27-28, 2009 at the University of California, San Francisco. These workshops are open to the public and ORWH invites both oral and written testimony.

Drs. Cora Lee Wetherington and Samia Noursi, DBNBR, chaired a symposium, "Biobehavioral Mechanisms of Sex Differences in Nicotine Addiction: A Translational Perspective," at the joint meeting of the Society for Research on Nicotine and Tobacco (SRNT) and SRNT-Europe in Dublin, Ireland, April 27-30, 2009. Presenters were Sakire Pogun, Ph.D. (Ege University Center for Brain Research, Department of Physiology, Bornova, Izmir, Turkey), Ken Perkins, Ph.D. (University of Pittsburgh), Caryn Lerman, Ph.D. (University of Pennsylvania), Julie Staley, PhD. (Yale University School of Medicine), and Stephanie O'Malley Ph.D. (Yale University School of Medicine).

Dr. Samia Noursi, Deputy Coordinator, Women and Sex/Gender Differences Research Program, represented NIDA at the "National Partnership to End Interpersonal Violence across the Lifespan (NPEIV), held in January 13, 2009 in New Orleans, LA. 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. Allison Hoffman, DBNBR, organized a seminar entitled "FDA Tobacco Product Regulation: Regulatory History and Overview of Pending Legislation", presented by Mitch Zeller. This event was hosted by the NIH Tobacco and Nicotine Research Interest Group (TANRIG) on February 25, 2009.

Dr. Allison Hoffman organized a Cutting Edge seminar entitled "Nicotine and Neuropeptides", sponsored by the NIDA Neuroscience Consortium and held on March 10, 2009. Presenters were Drs. Jim Fadel and Glen Hanson.

Dr. Allison Hoffman organized a webinar entitled "Novel Tobacco Products", presented by Dorothy Hatsukami on April 7, 2009. This event was hosted by the NIDA Nicotine and Tobacco Interest Group.

Dr. Allison Hoffman was invited to serve on the Healthy People 2020 Tobacco Workgroup, organized by the Centers for Disease Control and Prevention.

Dr. John Satterlee, DBNBR, played a key role in organizing a Roadmap Epigenomics Program-sponsored symposium entitled "Emerging Evidence for Epigenomic Changes in Human Disease" held in Natcher Conference Center in Bethesda, MD on March 16-17, 2009. This meeting consisted of 23 speakers who presented their cutting edge research on the role of epigenomic changes in the broad array of diseases of interest to NIH. Scientific sessions included "Epigenomic Mapping in Normal and Diseased Cells", "Epigenetics, Environmental Exposures, and Contributions to Disease", "Epigenetics and Disease", "The Potential for Epigenetic Diagnosis and Therapy", and "Integrating Epigenomics with Genetic and Epidemiological Studies". There were 48 poster presentations and a total of 700 registered attendees. Dr.

Satterlee gave a presentation entitled: "The Roadmap Epigenomics Program: Why and How?"

Dr. John Satterlee presented an update on "The Roadmap Epigenomics Program" to the trans-NIH Genomics Workgroup on February 2, 2009.

Dr. Da-Yu Wu, DBNBR, represented NIDA at the NIH Neuroscience Blueprint workgroup for non-invasive human brain imaging for dynamics of neurotransmission and brain connectome. The imaging for dynamics of neurotransmission is now a Blueprint NIH Grand Challenge Grant Topic in both the Omnibus NIH RFA, jointly sponsored by NIDA. The Connectome project has been adopted as a Blueprint Grand Challenge beginning in FY10. Da-Yu Wu will work with the project team for this initiative.

Dr. Jonathan Pollock, DBNBR, has organized a weekly webinar series entitled, "Genetics of Nicotine Addiction and Lung Cancer." The purpose of this meeting is to foster collaboration of investigators studying smoking and smoking related phenotypes in the hopes that a meta-analysis can be conducted.

Drs. Diane Lawrence and David Shurtleff, DBNBR, presented a symposium entitled " HIV/AIDS and International Research Opportunities at the National Institute on Drug Abuse, National Institutes of Health" at Hong Kong University, Hong Kong, P.R. China, on April 17, 2009.

Drs. Diane Lawrence and David Shurtleff presented at a symposium entitled "Research and Funding opportunities at NIDA" at the 15th annual meeting of the Society for Neuroimmune Pharmacology, Wuhan, P.R. China on April 23, 2009.

Dr. Joseph Frascella, Director, DCNBR, gave two presentations at Hamilton College on the neurobiology of addiction and on the common neurobiological mechanisms between drug addiction and obesity in Clinton, NY, April 21-22, 2009. He also spoke with faculty and grants office staff on funding opportunities in the ARRA era.

Dr. Joseph Frascella attended the 2009 Summit on Food Addiction that discussed the latest scientific evidence for "food addiction" and its connection to the worldwide obesity epidemic. The Summit was held in Bainbridge Island, Washington, April 24 - 26, 2009.

Dr. Steven Grant, DCNBR, served on the organizing committee and co-chaired the session of "Addiction and Mental Health Disorders" during the Brain Blueprint Workshop on Harnessing Brain Plasticity for Human Applications held in Rockville, MD on April 21-22, 2009.

Dr. Steven Grant gave a presentation entitled "Advances in the Neuronal Basis of Addiction" for Grand Rounds at the Department of Psychiatry, University of California, Davis on March 20, 2009.

Dr. Steven Grant conducted a "Grant Writing Workshop" at the annual meeting of the Cognitive Neuroscience Society in San Francisco on March 23, 2009.

Dr. James M. Bjork, DCNBR, gave a lecture: "Rewards, Risk, and the Teenage Brain: Insights from brain imaging research conducted at the NIH Clinical Center" at Natcher Auditorium at the NIH main campus on March 30, 2009.

Dr. James Bjork is participating in the Common Data Elements (CDE) workgroup for establishing recommended measures for substance abuse surveillance and assessment among veterans. The CDE initiative was organized by the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (Department of Defense).

Dr. Cecelia Spitznas and Dr. Lisa Onken, DCNBR, participated in launch of NIDA MED SBIRT website and Principles of Treatment 2nd Edition at the Washington

Press Club on April 20, 2009.

Dr. Nicolette Borek, DCNBR, presented a grant-writing workshop at the Pediatric Academic Societies Southern Regional Meeting, February 12, 2009 in New Orleans.

Drs. Nicolette Borek and Karen Sirocco, DCNBR, organized and presented talks at the workshop "Grants 201 for Mid-Career and Senior Level Scientists: Supporting Thyself and Mentoring the Next Generation of Researchers" at the 2009 Society for Research on Child Development Biennial Meeting, April 1-4, 2009 in Denver, CO. Drs. Kathy Etz, Teresa Levitin, and Belinda Sims from NIDA and colleagues from NIMH and NICHD also participated in the session. Dr. Borek also presented a talk on consulting with NIH program staff at the session "NIH Transdisciplinary & Translational Research Priorities in Drug Abuse and Mental Health."

Dr. Shoshana Kahana, DCNBR, served as the Discussant on an Invited Panel discussion, "Contingency Management Strategies for Improving HIV Treatment Adherence", at the 4th International Conference on HIV Treatment Adherence, April 5-7, 2009, at the InterContinental Miami, sponsored by the International Association of Physicians in AIDS Care and the National Institute of Mental Health (NIMH).

Dr. Shoshana Kahana, DCNBR, moderated a panel discussion "Alcohol and Drug Use: Adherence Implications" at the 4th International Conference on HIV Treatment Adherence, April 5-7, 2009, at the InterContinental Miami, sponsored by the International Association of Physicians in AIDS Care and the National Institute of Mental Health (NIMH).

Dr. Wilson M. Compton, Director, DESPR, participated in meetings of the DSM-V Task Force and the Substance Use Disorders Workgroup, Arlington, Virginia, February 24 and March 24-25, 2009.

Dr. Wilson M. Compton chaired a plenary session on dimensional approaches to psychiatric diagnosis at the American Psychopathological Association (APPA) meeting New York, New York, March 5, 2009.

Dr. Wilson Compton participated in a webcast by the Substance Abuse Mental Health Services Administration (SAMHSA) to support National Alcohol and Drug Addiction Recovery Month. The webcast, entitled "Treatment 101 — Recovery Today," available on April 1 on SAMHSA's website at www.recoverymonth.gov. Other panelists included Dr. H. Westley Clark, Director of the Center for Substance Abuse at SAMHSA and Dr. Mark Willenbring, M.D., Director of Treatment and Recovery Research at NIAAA.

Dr. Wilson M. Compton presented a keynote address to the Federal District Court Reentry Conference, Portland, Oregon, April 2, 2009.

On February 9-10, 2009, Drs. Aleta Meyer, Aria Crump, and Belinda Sims, DESPR participated in the Federal Meeting on Prevention of Violence in Educational Settings. This meeting was convened by the National Institute of Justice and brought together federal partners from multiple agencies and institutes (i.e., CDC; SAMHSA; Office of Juvenile Justice and Delinquency; Federal Bureau of Investigation; Alcohol, Tobacco, and Fire Arms; Bureau of Justice Statistics; NIMH; NICHD; NIDA). The purpose of the meeting was to provide an update on current research related to violence prevention in educational settings, as well as to discuss ways to collaborate on activities to fill gaps in programming, data collection, research/evaluation, and communication toward the goal of violence prevention. Dr. Meyer highlighted NIDA-funded prevention and prevention services research portfolio with a presentation titled "Guiding Principles for Substance Use Prevention that Link to School-Based Violence Prevention."

Drs. Aleta Meyer, Augusto Diana, and Marsha Lopez, DESPR, presented at the "Physical Activity as Intervention" Scholar-in-Residence Workshop for the Southeast Connecticut Child and Family Agency on March 9, 2009, in Hartford, CT. Dr. Lopez's presentation was titled "Physical Activity and its Association with Depression, Obesity, and Drug Use across the Lifespan." Dr. Diana presented "Physical Activity as Drug Use Prevention and Treatment" with Dr. Dorothy Pekmezi of Brown University; he also led a break-out session titled "What Types and Characteristics of Activities Provide Benefits, and How?" Dr. Meyer served as a primary organizer for the day, providing opening and closing comments, as well as leading a break-out session titled "Physical Activity as a Strategy to Prevent Problem Behavior and Promote Positive Youth Development."

Dr. Marsha Lopez organized a field visit to NIDA's DESPR for predoctoral and postdoctoral trainees participating in the Johns Hopkins Drug Epidemiology T32 on November 4, 2008. The visit provided an opportunity for the T32 trainees to meet individually with DESPR Program Officials about their research interests and career goals, and to identify grant application mechanisms that might be most appropriate for them.

On March 18 and 19, 2009, Dr. Aleta Meyer gave two presentations at the 5th Annual Research and Evaluation of Adventure Programs Symposium in Atlanta, GA. Dr. Meyer gave the opening plenary, titled "Experiential Education and Public Health: The Potential to MOVE America Toward Health," as well as led a workshop titled "Seeking Funding Through a Small Business Approach."

On April 1, 2009 Dr. Belinda Sims and Dr. Molly Oliveri of NIMH Co-chaired a Preconference session at the Society for Research in Child Development meeting in Denver, CO titled "NIH Transdisciplinary and Translational Research Priorities in Drug Abuse and Mental Health." The purpose of this panel, co-sponsored by the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH), was twofold: (1) to highlight funding priorities, strategic plans, and new initiatives; and (2) to discuss framing innovative translational research within NIH funding priorities. Panelists included Drs. Elizabeth Ginexi, PRB, DESPR, Allan Reiss of Stanford University, Philip Fisher of the Oregon Social Learning Center, and Nicolette Borek, DCNBR.

On April 3, 2009 Dr. Aria Crump presented on the NIH budget, major initiatives, & the public access policy as a part of a panel entitled "NIH Update on Policy Issues, Scientific Review, and Research Priorities" at the Society for Research in Child Development meeting in Denver, CO. The panel was organized by Dr. LeShawndra Price, ERB, DESPR.

Dr. Elizabeth Ginexi, DESPR, served as the Discussant for a Paper Symposium at the biannual meeting for the Society for Research in Child Development in Denver, CO on April 3, 2009 titled "Impact of Adverse Experiences in Childhood and Adolescence on Brain Development and Functioning: Results From Neuroimaging Studies." Drs. Jacqueline Bruce of the Oregon Social Learning Center, Deborah Yurgelun-Todd of Harvard Medical School, and Dr. Martin Teacher of McLean Hospital, Harvard Medical School presented papers.

Dr. Elizabeth Ginexi served as the Discussant for a Paper Symposium at the biannual meeting for the Society for Research in Child Development in Denver, CO on April 4, 2009 titled "Sitting Still and Learning to Read: Inhibitory Control and School Readiness in At-Risk Populations." Drs. Megan McClelland of Oregon State University, Erika Lunkenheimer of the University of Oregon, and Katherine Pears of the Oregon Social Learning Center presented papers.

Dr. Dionne Jones, DESPR, presented "NIDA Initiatives, Collaborations and Research Activities relating to Substance Abuse and HIV/AIDS" at the SAMHSA/CSAT Annual TCE/HIV and HIV Outreach Grantee Meeting:

Maintaining Treatment Excellence, February 19, 2009.

Dr. Dionne Jones presented "Tips on Granstmanship for Early Career Investigators" at a NIDA-sponsored meeting "Integrating Services, Integrating Research for Co-occurring Conditions: A need for New Views and Action, Bethesda, MD, March 2, 2009.

Dr. Ivan Montoya, DPMCDA, presented a lecture entitled "Treatment of Drug Abuse in the Criminal Justice System" at the Latin American Conference of Therapeutic Justice and Drug Courts in San Juan, Puerto Rico, on April 17, 2009.

The 30th Annual Meeting of the Society for Clinical Trials took place May 3-6, 2009, in Atlanta, GA. CCTN staff participated in the following sessions: 1) Dr. Paul Wakim organized and will chair an invited session titled, "Is a Null Result a Failure? Can Anything Good Come out of Null Results?." The three invited speakers were Drs. Gail Neely (Washington University School of Medicine), Maria Mori Brooks (University of Pittsburgh Graduate School of Public Health) and Lawrence M. Friedman (NIH Consultant). 2) Joint work by Ms. Carmen Rosa and Dr. Paul Wakim on "Participation in Substance Abuse Clinical Trials: Comparing Gender and Racial/Ethnic Groups" was presented as part of a Contributed Paper Session titled, "Patient Recruitment, Enrollment and Retention".

Dr. Amy Newman, IRP, was invited to give a seminar at Duquesne University, School of Pharmacy, Pittsburgh, PA, entitled "Atypical Dopamine Uptake Inhibitors: A Strategy Toward Cocaine-Abuse Medication Discovery" in January 2009.

Dr. Amy Newman chaired a panel at the 42nd Annual Winter Conference on Brain Research entitled "Stop yawning and "see what's new at D2," in Copper Mountain, CO in January 2009.

Dr. Amy Newman participated in the 1st Behavior, Biology and Chemistry Translational Research in Addiction Meeting in San Antonio, TX and served on the Travel Award Committee and as a Poster/Oral Presentation Judge in February 2009. Several IRP scientists presented at the Winter Conference on Brain Research, Copper Mountain, CO, January 24-31, 2009. Dr. Satoshi Ikemoto attended while Dr. Bruce Hope was chair of a panel entitled "Bighorn C1 Neuronal Ensembles in the Nucleus Accumbens."

Danielle Guez presented a poster entitled "Fluorescence Activated Cell Sorting: A Novel Method to Study Neurons Selectively Activated During Context-specific Cocaine Sensitization." Dr. Eisuke Koya presented a poster entitled "Daun02 Lesions Neuronal Ensembles that Encode Learned Associations between Cocaine and its Administration Environment." Sam Golden presented a poster entitled "Investigating the Role of Drug Administration Context in Haloperidol-Induced Striatal and Prefrontal Cortex Fos Expression after Repeated Haloperidol Injections."

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

Media and Education Activities

Press Releases

February 2, 2009 - **NIDA Study Shows That Methylphenidate (Ritalin) Causes Neuronal Changes in Brain Reward Areas.** Investigators funded by NIDA have shown that the medication methylphenidate (Ritalin), which is commonly prescribed to treat attention-deficit hyperactivity disorder (ADHD), can cause physical changes in neurons in reward regions of mouse brains - in some cases, these effects overlapped with those of cocaine. Both methylphenidate and cocaine are in the class of drugs known as psychostimulants. While methylphenidate is widely prescribed, this study highlights the need for more research into its long-term effects on the brain. These research findings were published February 3, 2009 in the Proceedings of the National Academy of Sciences.

March 4, 2009 - **Combination of Genes and Prenatal Exposure to Smoking Increases Teens' Risk of Disruptive Behavior.** A study funded by NIDA shows that prenatal exposure to smoking combined with a specific genetic variant places children at greatest risk for behavioral problems. Many studies have established that there is an increased risk of aggressive behavior in children exposed to cigarette smoke before birth, a significant problem given that many women still smoke during pregnancies. According to the National Survey on Drug Use and Health, in 2006-2007 slightly more than 16 percent of pregnant women aged 15-44 (426,000) were current cigarette smokers.

March 16, 2009 - **Study Helps Unravel Mysteries of Brain's Endocannabinoid System.** New research funded by NIDA has identified a new mechanism for the processing of endocannabinoids, natural brain compounds similar to THC, the active ingredient in marijuana. The results of this study, led by researchers from Stony Brook University, were published March 16, 2009 in the Proceedings of the National Academy of Sciences.

Research News

Full NewsScans can be seen at http://www.nida.nih.gov/NIDANews.html#newsscan.

January 12, 2009 - **NIDA NewsScan #58** - Research News

- Contingency Management Helps Pregnant Women Abstain From Smoking
- Higher Prevalence of Sexual Risk Behavior Found in Teens Not Attending College
- Lofexidine Reduces Opioid Withdrawal Symptoms
- Dopamine Helps Balance Striatal Synaptic Plasticity

Substance Abusers' Brains Hypersensitive to Normal Rewards

- Increased Hormone Processing in the Brain May Result in Transition From Drug Use to Drug Abuse
- Defects in Dopamine-Regulating Mechanisms Found in Obese Rats
- Cocaine-Induced Cellular Stress Inhibits Neural Development

February 27, 2009 - **NIDA NewsScan #59** - Research News

- First-Year College Students Show High Rate of Cannabis Use Disorders
- Nonmedical Use of Prescription Stimulants Among First-Year College Students
- Graphic Warnings Change Viewers' Perception of Tobacco Advertisements
- Parental Monitoring Reduces High School Drinking, Leading to Reduced College Drinking
- Higher Prevalence of Sexual Risk Behavior Found in Teens Not Attending College

March 24, 2009 - **NIDA NewsScan #60** - Research News

- Hepatitis C Virus Can Be Transmitted by Drug Use Through the Nose
- Smoking Cessation More Difficult for African-Americans, Hispanics
- Adolescent Mouse Brains More Sensitive to Oxycodone Than Adult Brains
  Brain Activity Prior to Drug Treatment May Predict Treatment Outcomes for Cocaine Addiction
- Family-Based Intervention Improves Children's Early Problem Behavior
- Social Contexts of College Drinking Explored
- HealthWise Program Tested for Reduction of Substance Use and Risky Sexual Behavior in South African Schools
- DNA Variation Influences Neural Response to Negative Stimuli

Interviews & Articles of Interest

December 15, 2008, *Marie Claire* -- Interview with Dr. Gaya Dowling, OSPC, about the effects of illicit drugs on dopamine levels.

January 5, 2009, *Reuters/Thomson* -- Interview with Dr. Nora Volkow about NIDA military meeting.

January 13 and 21, 2009, *Scientific American* -- Two interviews with Dr. Nora Volkow, one about study regarding obesity and gender and the other about a JAMA paper and addiction treatment in the criminal justice system.

January 13, 2009, *Nature* -- Interview with Dr. Nora Volkow about the science of addiction.

January 16, 2009, *Maxim* -- Interview with Dr. Richard Denisco, DESPR, about adolescents and prescription drug abuse.

January 28, 2009, *Associated Press* -- Interview with Dr. Wilson Compton, DESPR, about NESARC data used in paper published in the Archives of General Psychiatry.

January 28, 2009, *Radio Health Journal* -- Interview with Dr. Wilson Compton, DESPR, about article in Nature on cognitive-enhancing drugs.

February 3, 2009, *National Public Radio "On Point"* -- Interview with Dr. Nora Volkow about cognitive-enhancing drugs.

February 3, 2009, *Reuters - Chicago bureau* -- Interview with Dr. Nora Volkow

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about news release on Methylphenidate.

February 4, 2009, *New York Times* -- Interview with Dr. Wilson Compton, DESPR, about new RAND study on the economic cost of methamphetamine use in the U.S.

February 19, 2009, *AARP Bulletin* -- Interview with Dr. Timothy Condon about rising prescription drug abuse and risk factors among seniors.

February 24, 2009, *Glamour* -- Interview with Dr. Nora Volkow about the growing acceptance and use of prescription medications among young women without a prescription.

March 3, 2009, *Science Magazine* -- Interview with Dr. Steven Grant, DCNBR, about deep brain stimulation as a treatment for addiction and other neuropsychiatric disorders.

February 2009, Dr. Steven R. Goldberg, IRP, was interviewed by the BBC in the documentary *Horizon* broadcast in Europe.

Outreach Activities

Brain Awareness Week

NIDA once again participated in Brain Awareness Week activities at the National Museum of Health and Medicine on March 18-19, 2009. This year marked the 10th anniversary of Brain Awareness Week as well as NIDA's participation in the activities. NIDA played "NIDA Brain Derby," an interactive game, with students from middle school through high school. Students were divided into two teams that then competed by answering quiz questions on a variety of topics related to how drugs act in the brain. The students had a great time and seemed to learn as they played. NIDA participants included Dave Thomas, Dave White, Allison Hoffman, Roger Sorenson, Jane Acri, Denise Pintello, and Cathrine Sasek.

NIDA Goes Back to School Presentation

March 21, 2009 — To encourage teachers to use NIDA youth education materials, Brian Marquis of NIDA's Public Information and Liaison Branch presented a "NIDA Goes Back to School" (NGBTS) workshop at the National Science Teachers Association annual conference in New Orleans, LA. More than 70 teachers attended the workshop, and each participant received a copy of the powerpoint presentation detailing the NGBTS materials and how they can be used as supplements to the curriculum the teachers are using.

NIDAMED To Be Launched

NIDA is set to unveil NIDAMED, an initiative to give medical professionals tools and resources to screen their patients for substance use, in conjunction with NIDA's recently updated *Principles of Drug Abuse Treatment: A Research Based Guide.* The products, including an online screening tool and resource guide, will be unveiled during a morning press conference and an afternoon state-of-the-science meeting entitled "The Science of Recognizing and Treating Substance Abuse and Addiction." The event took place April 20, 2009. Additional information will appear in the next Director's Report.

New NIDA Videos are Available

To help make the NIDA Teen Website more fun, and to make NIDA's science more accessible to youth, the Office of Science Policy and Communications produced three creative videos in which some of NIDA's scientists speak directly to teens. The videos feature Drs. Ruben Baler, Joseph Frascella, Gaya Dowling, and Redonna Chandler discussing the latest scientific understanding of the risks of using steroids, marijuana, and nicotine in an entertaining and educational style. The videos will be offered to other sites, such as The Research Channel and NIH's YouTube site. To view the videos, go to the links

below.

http://teens.drugabuse.gov/facts/facts_mj3.php

http://teens.drugabuse.gov/facts/facts_ster3.php

http://teens.drugabuse.gov/facts/facts_nicotine3.php

Additional Highlights

On January 8, 2009, Dr. Gregory Farber, Senior Health Scientist Administrator in the Division of Biomedical Technology, NCRR, presented the CCTN Classroom seminar on "BIRN: A Solution for your Data Sharing Problems." NIH has created two significant data sharing infrastructures: BIRN (the Biomedical Informatics Research Network) and caBIG. In this talk, the two infrastructures were briefly described. Uses of the BIRN infrastructure for sharing data of relevance to biomedical researchers were discussed. Finally, the relationship of the BIRN to other informatics initiatives supported by the Neuroscience Blueprint (the Neuroscience Information Framework, NIF and NITRC, the Neuroimaging Informatics Tools and Resources Clearinghouse) was described.

On March 12, 2009, Richard A. Elion, M.D., Director of Research at Whitman Walker Clinic, Washington, DC and Associate Clinical Professor of Medicine at George Washington University School of Medicine presented the CTN Classroom seminar. His presentation titled "Treatment as Prevention: A time for change" gave a description of his experience with treatment of HIV positive patients from the HIV clinic perspective.

Awards

NIDA's MTV-style video of Director Dr. Nora Volkow's conversation about the science of addiction with high school students in Harlem, New York has won a national Aegis Award. The Aegis Awards is one of the few video competitions that features true peer judging by fellow producers, directors, cameramen, editors, and other professionals who work in the video/film industry. The video, produced by the Office of Science Policy and Communications, can be viewed at http://www.drugabuse.gov/chat/.

Recent and Upcoming Conference Exhibits

American Medical Student Association (AMSA) 59th Annual Convention
March 12-15, 2009 -- Arlington, VA

National Science Teachers Association (NSTA) 57th Annual Conference
March 19-21, 2009 -- New Orleans, LA

American Counseling Association (ACA)
March 19-23, 2009 -- Charlotte, NC

American Alliance for Health, Physical Education, Recreation and Dance (AAHPERD)
March 31 - April 4, 2009 -- Tampa, FL

The Society for Research and Child Development (SCRD) Biennial Meeting
April 2-4, 2009 -- Denver, CO

39th National Council Conference
April 5-8, 2009 -- San Antonio, TX

American Association for the Treatment of Opioid Dependence (AATOD) National Conference
April 25-29, 2009 -- New York, NY

American Society of Addiction Medicine (ASAM) 40th Annual Medical-Scientific Conference
April 30 - May 3, 2009 -- New Orleans, LA

American Psychiatric Association (APA) 162nd Annual Meeting
May 16-21, 2009 -- San Francisco, CA

National Association of Drug Court Professionals 15th Annual Training Conference
June 10-13, 2009 -- Anaheim, CA

National Conference on Tobacco or Health (NCTOH)
June 10-12, 2009 -- Phoenix, AZ

National Association of School Nurses (NASN) 41st Annual Conference
June 25-29, 2009 -- Boston, MA

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

Planned Meetings

The National Institute on Drug Abuse (NIDA) is organizing a program at the **American Psychiatric Association (APA) Annual Meeting in San Francisco, May 16-21, 2009.** A number of NIDA staff and NIDA researchers will participate in several symposia and workshops at the upcoming meeting on a wide range of topics such as, *Diversion of Prescription Stimulants; Imaging Insight: Basic Definitions, Measures, and Relevance to Psychopathology; Older Adults and the Neurobiology of Substance Abuse; Clinical Challenges Identifying and Treating Unpresented Co-morbidity; Integrating Treatment for Substance Use and Post-Traumatic Stress Disorders in Patients with Co-Occurring Conditions; and, Genetic Vulnerabilities for Drug Abuse and Co-Morbid Mental Health Disorders.* This program will build on previous tracks NIDA has been conducting at the APA Annual meeting since 1998.

The National Institute on Drug Abuse (NIDA) is organizing a program at this year's **American Psychological Association (APA) Annual Meeting in Toronto, Canada, August 6-9, 2009.** A number of NIDA staff throughout the Institute are involved in organizing symposia on a wide range of 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.

Dr. Harold Gordon, DCNBR, will chair a symposium entitled, **Sleep Disturbances and Circadian Disruptions Affecting, and Affected by, Addiction to Drugs** at the American Psychiatric Association annual meeting in San Francisco, May 16-21, 2009. The purpose is to present NIDA-funded research on sleep physiology and how it is altered by abused drugs, how to identify signs and symptoms of drug-abuse-related insomnia and cognitive deficits, what are the disruptions in the circadian clock related to cocaine, what are the reciprocal interactions between sleep and the immune system in substance dependence, and what are the treatment issues related to sleep disturbances in cocaine and opiate dependent individuals.

Dr. Steven Grant, DCNBR, will co-chair a workshop entitled, **Imaging Insight: Basic Definitions, Measures, and Relevance To Psychopathology** at the American Psychiatric Association annual meeting in San Francisco, May 16-21, 2009. The workshop will focus on evidence that dysregulation of specific brain systems may impair the ability of substance abusers to have accurate insight into their behavior.

Cora Lee Wetherington, DBNBR, and Wendy Lynch (University of Virginia) will co-chair the symposium, **"Biological Basis of Sex Differences in Drug Abuse: A Translational Perspective,"** at the annual meeting to the American Psychiatric Association, May 16-21, 2009 in San Francisco, CA. Presenters will be Wendy Lynch, Ph.D. (University of Virginia), Jill Becker, Ph.D. (University of Michigan), Karen Berman, M.D. (NIMH), Marc Potenza,

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M.D., Ph.D. (Yale University School of Medicine), and Larry Cahill, Ph.D. (UC Irvine).

Minda Lynch and Joni Rutter, DBNBR are co-chairing a symposium at this year's American Psychiatric Association Convention entitled **"Genetic Vulnerabilities for Drug Abuse and Co-Morbid Mental Health Disorders".** Participants in this session, scheduled for May 21, 2009, include: Harriet de Wit, Ph.D. - Subjective Drug Effects as Endophenotypes for Vulnerability, Teresa Franklin, Ph.D. - The Influence of Genetic Variance in the Dopamine Transporter on Brain and Behavioral Responses to Smoking Cues, Caryn Lerman, Ph.D. - Interacting Effects of COMT Genotype and Nicotine Withdrawal on Brain Function and Cognition, Joel Gelernter, M.D., Yale University - Approaching Comorbidity in Addiction Genetics, and Howard Edenberg, Ph.D., Indiana University School of Medicine - Genetics of Alcoholism and Related Endophenotypes.

A NIDA-OSPC supported symposium entitled **Integrating Treatment for Substance Use and Post-Traumatic Stress Disorders in Patients with Co-occurring Conditions** has been accepted for presentation at the 2009 American Psychiatric Association Annual Meeting May 16-21, 2009. Dr. Udi Ghitza, CCTN, will chair this event. At the conclusion of this symposium, participants should have increased knowledge of: (1) prevalence of co-occurring post-traumatic stress disorder (PTSD) and substance use disorders (SUD) in both civilian and returning veteran populations, (2) psychotherapy treatment programs developed for patients with co-occurring SUD and PTSD, (3) pharmacotherapy treatment programs for these patients, and (4) challenges and opportunities for advancing an integrated medical care approach concurrently treating functional impairments associated with both SUD and PTSD.

Dr. Petra Jacobs will co-chair with Dr. Richard Denisco, DESPR, the NIDA/Prescription Opioid and Pain Workgroup-sponsored workshop entitled **"Opioid Agonist Medications Effects on Cardiovascular System."** This workshop will be held on June 16, 2009.

The College on Problems of Drug Dependence (CPDD) will hold its 71st annual meeting June 20-25, 2009, in Reno/Sparks, Nevada. CCTN staff will participate in the following:

1. Dr. Raul Mandler will chair a mini symposium entitled, "HIV Risk Prevention in the CTN."
2. A poster presentation by Ms. Carmen Rosa and Dr. Paul Wakim on "Participation in Substance Abuse Clinical Trials: Comparing Gender and Racial/Ethnic Groups" will be presented on June 25, 2009.
3. A poster presentation by Drs. Steven Sparenborg, Udi Ghitza, and Betty Tai on "Comparative effectiveness research in the National Drug Abuse Treatment Clinical Trials Network (CTN)" will be presented on June 25, 2009.

A NIDA-OSPC supported meeting entitled **Narrowing the Research-Practice Divide in Evidence-Based Medicine with Adoption of Electronic Medical Record Systems: Present and Future Directions** will be held in Rockville, Maryland on July 13-14, 2009. Dr. Udi Ghitza, CCTN, will co-chair this event. An aim of this two-day meeting is to explore the prospects and challenges of utilizing interoperable electronic medical record systems to bridge the gap between specialized substance abuse treatment and mainstream medical care. To do so, this meeting will examine the ethical, policy, privacy, logistical, regulatory, technical, and financial challenges of developing and implementing integrated compatible electronic medical record systems in evidence-based behavioral research and healthcare settings with a special focus on substance abuse screening, treatment, and follow-up.

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NIDA will host the eighth **Blending Conference** at the Albuquerque Convention Center in Albuquerque, New Mexico on April 22-23, 2010. This 2-day conference is designed to bring clinicians and researchers together to examine the most up-to-date scientific drug abuse and addiction findings and their application to clinical practice. NIDA's Deputy Director, Dr. Timothy Condon, is overseeing all conference planning activities, Dr. Cindy Miner (OSPC) conducted the site visit and is working with Dr. Denise Pintello (OD), who is coordinating meetings with the two CTN Nodes co-hosting the Blending Conference.

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NIDA Publications

Screening for Drug Use in General Medical Settings: Quick Reference Guide
(Publication Date: April 2009)
NIH Pub. No.: 09-7384
This pocket guide briefly summarizes the questions from the NIDA Modified WHO Assist (Alcohol, Smoking, and Substance Involvement Screening Test), how to score the test, and the steps involved in discussing screening results and providing a brief intervention based on assessed level of risk. It is a complement to NIDA's online screening tool, as part of the NIDAMED initiative.

Epidemiologic Trends in Drug Abuse, Volume I: Executive Summary June 2008 (Publication Date: May 2009)
NIH Pub. No. 09-6421
This report provides descriptive information on the most recent significant trends, 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, Volume II: Meeting Proceedings June 2008 (Publication Date: May 2009)
NIH Pub. No. 09-6422
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.

National Survey Results From the Monitoring the Future Study 1975-2008: Overview of Key Findings 2008
(Publication Date: May 2009)
This publication provides a summary of drug use trends from a survey of 8th-, 10th-, and 12th-grade students nationwide. It also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.

National Survey Results From the Monitoring the Future Study 1975-2008: Secondary Schools, Volume I
(Publication Date: June 2009)
This publication presents detailed results and data tables from the 2008 MTF survey of secondary school students regarding drug use and related attitudes.

National Survey Results From the Monitoring the Future Study 1975-

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2008: College and Adults Ages 19-50, Volume II
(Publication Date: July 2009)
This publication contains findings from the MTF survey of American college students, their age peers not in college, young adult high school graduates through age 30, and high school graduates ages 35, 40, 45, and 50.

Mentoring Guide for Drug Abuse Research: Tips for Mentors and Mentees
(Publication Date: July 2009)
NIH Pub. No.: 09-5770
This publication will describe "best practices" for recruiting, training, mentoring, and advancing the careers of highly talented scientists focused upon drug abuse epidemiological, services, and prevention research.

Mind Over Matter: The Brain's Response to Prescription Drugs
(Publication Date: June 2009)
This brochure will contain scientific information on how various prescription drugs act in the body and brain to elicit their effects. It will be designed to provide this information in a format that will use drug information to teach science and engender student interest in science, while also providing messages of the harmful effects associated with the abuse of prescription drugs.

NIDA's Addiction Science & Clinical Practice
Volume 5, Number 1 - April 2009
This issue features three articles on drug abuse and criminal justice. In the first, Dr. Michael Prendergast describes how correctional drug treatment can improve outcomes for offenders upon release and stresses the importance of community aftercare for reducing relapse and recidivism. In the second, Dr. Carl Leukefeld and colleagues describe two projects for drug-abusing offenders re-entering the community after incarceration: the development of a set of re-entry guidelines through a Delphi process and an intervention to reduce post-release HIV risk in women offenders. Concluding the criminal justice feature, Ms. Melody Heaps and her colleagues at Treatment Alternatives for Safe Communities (TASC) of Illinois posit a recovery-oriented system of care for drug-abusing criminal offenders that exists outside of the justice system, comanages offender treatment, and provides other services to promote successful outcomes as well as public health and safety. Finally, addressing some of the medical complications of illicit drug use, Drs. Kristy Hendricks and Sherwood Gorbach describe the nutrition issues of chronic drug users living with HIV.

NIDA's Addiction Science & Clinical Practice
Volume 5, Number 2 - Fall 2009
Two articles in this issue of *Addiction Science & Clinical Practice* describe the challenging process of implementing evidence-based practices in treatment settings. Dr. Michael S. Robbins and colleagues describe their implementation of Brief Strategic Family Therapy in community treatment centers, and Ms. Laurie Davidson and colleagues discuss the development and implementation of BASICS, an alcohol-abuse prevention program targeting college students, a population at high risk for substance abuse. Dr. Patricia E. Molina presents an overview of endocrine system physiology and reviews how drugs of abuse alter healthy endocrine function. Ms. Margaret Mroziewicz and Dr. Rachel F. Tyndale describe pharmacogenetics, the study of genetic influences on drug response, and how this field can impact addiction research and treatment. Finally, Dr. Sonia Minnes reviews the effects of prenatal drug exposure.

NIDA NOTES

***NIDA NOTES,* Vol. 22, No. 3**
The lead story explores how cocaine impairs ability to avoid detrimental

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outcomes. Research with rats shows that brain circuits that guide behavior by registering consequences become less flexible after drug exposure. Also included in the issue are features reporting that methamphetamine abusers show increased distractibility that corresponds to brain cell impairment; patients with injury to the insula brain region immediately lose the urge to smoke; prenatal nicotine exposure damages receptors that influence auditory processing; and cocaine influences receptors in the brain's reward system, thereby heightening the reinforcing effects of cocaine. The Director's Perspective announces NIDA's plans for stimulus funds from the American Recovery and Reinvestment Act of 2009.

***NIDA NOTES,* Vol. 22, No. 4**
The lead story reports that treating bipolar disorder and substance dependence together can reduce drug abuse. It tells how an integrated group counseling program improved outcomes in a difficult-to-treat dual-disorder population. 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; data identifying chromosome sites linked with nicotine addiction in two racial groups; 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**
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 abuse and 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, positioned beneath patches, that 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 examines the potential of physical exercise to prevent substance abuse.

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 18 CTN trials are now available on the CTN Data Sharing Web Site. Nearly 300 research scientists have downloaded one or more data sets. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap.

International Program-Related Publications

NIDA International Program E-News Letter
April 2008 - This issue reported on the new IAS/NIDA fellowship program that focuses on HIV and drug abuse research; expanded efforts to promote Humphrey Fellowship recruitment; and a NIDA orientation program for 16 Humphrey, INVEST, and INVEST/CTN Fellows. The issue also introduced the new, Web-based NIDA International Program Fellowship Map and the NIH RePORT (Research Portfolio Online Reporting Tool) Web site, announced

awards for new INVEST/CTN and DISCA Fellowships, and related the recent achievements of NIDA Fellows or alumni.

Other Publications

Chandler R, Fletcher B, Volkow N. Treating drug abuse and addiction in the criminal justice system: improving public health and safety. JAMA. 301(2):183-90.

Compton WM, Saha TD, Conway KP, Grant BF. The role of cannabis use within a dimensional approach to cannabis use disorders. Drug and Alcohol Dependence. 2009;100:221-7.

Merikangas KR, Conway KP, Swendsen J, Febo V, Dierker L, Brunetto W, Stolar M, Canino G. Substance use and behavior disorders in Puerto Rican youth: A migrant family study. Journal of Epidemiology and Community Health. 2009 Jan 15. [Epub ahead of print].

Booth B, Shields J, Chandler R. Recent achievements in alcohol and drug abuse health services research. Journal of Beh Health Service and Research. 36(1):5-10.

Mejia R, Jenkins RA, Carey JW, Amaro H, Morrill AC, Krech L, Logan JA, Cranston K. Longitudinal observation of an HIV prevention Community Planning Group (CPG). Health Promotion Practice. 2009;10:136-43.

Dr. Tom Hilton, SRB, DESPR, coauthored an article with Paul Spector, Tammy Allen, Lois Tetrick, and Nick Warren which was published in the January 2009 Society for Occupational Health Psychology Newsletter. The article was titled "The Future of OHP: The Experts Speak (Part I)" in which they commented on various aspects of the field of Occupational Health Psychology.

Vocci FJ, Montoya ID. Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. Curr Opin Psychiatry. 2009;Mar 20. [Epub ahead of print]

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Bjork JM, Momenan R, Hommer DW. Delay discounting correlates with proportional lateral frontal cortex volumes. Biol Psychiatry. 2008; Dec 31; (Epub ahead of print).

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Addiction: From Molecules to Neural Functions - the molecular and cellular mechanisms in the development of addiction. Eds. Da-Yu Wu, Jonathan D. Pollock and David Shurtleff. In Seminars in Cell and Developmental Biology (special issue) ELS Elsevier April 2009.

Pollock JD, Ramaswami M The Genetics and Epigenetics of Addiction J Neurogenet. 2009 Feb 4:1. [Epub ahead of print].

Collins GT, Truccone A, Haji-Abdi F, Newman AH, Grundt P, Rice KC, Husbands SM, Greedy BM, Enguehard-Gueiffier C, Gueiffier A, Chen J, Wang S, Sunahara RK, Katz JL, Grandy DK, Woods JH. Pro-erectile effects ofdopamine D2-like agonists are mediated by the D3 receptor in rats and mice. J Pharmacol Exp Ther. 2009; e-pub January 9, 2009.

Vahabzadeh M, Lin JL, Mezghanni M, Epstein DH, Preston KL. Automation in an addiction treatment research clinic: Computerised contingency management, ecological momentary assessment and a protocol workflow system. Drug

Alcohol Rev. 2009;28(1):3-11.

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Staff Honors and Awards

Richard A. Jenkins, Ph.D., DESPR, received the 2008 Award for Distinguished Contributions to Practice in Community Psychology from the Society for Community Research & Action (Division 27 of the American Psychological Association).

Dr. Stefanie Geisler, IRP, from the Behavioral Neuroscience Section won the NIDA Fellow Award from the Women Scientists Advisor Achievement Award.

Dr. Amy Newman, IRP, was the first recipient of the NIDA/NIH Women in Science Achievement Award in March 2009.

In January 2009, **Dr. Mary Kautz,** DCNBR, was appointed as Co-Chair of the NIDA Neuroscience Consortium Workgroup and as Co-Chair, along with Dr. Minda Lynch, DBNBR, of the newly formed NIDA Behavioral Science Interest Group.

Staff Changes

Dr. Cheryl Anne Boyce joined NIDA as Chief of the Behavioral and Brain Developmental Branch within DCNBR on March 1, 2009. She will also serve as the Institute's Associate Director for Child and Adolescent Research. Previously, Dr. Boyce served for over ten years as a program officer and most recently as Associate Director for Research Training and Career Development, and Chief of the Trauma Program, within the Division of Developmental Translational Research at NIMH. Dr. Boyce serves as a member of the scientific technical working group for the National Survey of Child and Adolescent Well-Being (NASCAW) and a member of the CTSA Consortium Child Health Oversight Committee. Dr. Boyce also co-chairs the NIH Child Abuse and Neglect Working Group. She has received numerous awards including the 2008 Lifetime Award for Distinguished Contributions to Diversity in Clinical Psychology, Science and Practice in the Public Interest. In 2007, she received the NIH Office of the Director Merit Award in recognition for administrative management of leadership initiatives. Her doctoral studies were completed in clinical psychology at the University of North Carolina at Chapel Hill as an American Psychological Association (APA) Minority Fellow. Building upon clinical and research training and fellowships at the Children's National Medical Center and the University of Maryland Department of Psychiatry, she began her Federal career as a Society for Research in Child Development (SRCD) Executive Branch Policy Fellow and American Association for the Advancement of Science (AAAS) Fellow. Her research interests include child maltreatment, stress and trauma, early childhood influences on drug use vulnerability, health disparities, developmental psychopathology, HIV/AIDS and pediatric health risk behaviors.

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To facilitate cross-cutting collaborations, she will assume the role as chair of the Child and Adolescent Workgroup (CAWG) and Dr. Denise Pintello, OSPC, will serve as co-chair. Dr. Nicolette Borek who took on additional duties to lead the CAWG during the interim and worked tirelessly as Acting Chief of the Behavioral and Brain Developmental Branch (BBDB), DCNBR has resumed her role as Deputy Branch Chief for BBDB.

Dr. Kejun Cheng joined IRP's Drug Design and Synthesis Section in CBRB as a Staff Scientist in December, 2008. He received his Ph.D. in Organic Chemistry from Fudan University, Shanghai, China, in 1997, and was selected for a highly competitive fellowship sponsored by the Japanese Society for the Promotion of Science. This fellowship allowed him to work on asymmetric drug synthesis with the 2001 Nobel Laureate in chemistry, Professor Ryoji Noyori. He has also studied also with the internationally known Professor H-J. Gaiss in Aachen, Germany, and Professor S.M. Hecht, at the University of Virginia, and joined NIDA as a Research Fellow in 2005. Dr. Cheng is an expert in the asymmetric synthesis and chirality of complex organic chemical entities as drugs and has published his work in renowned scientific journals such as the Journal of the American Chemical Society (JACS), Tetrahedron Asymmetry, Organic and Biomolecular Chemistry, and the Journal of Medicinal Chemistry.

Dr. Ron Edgar joined NIDA on May 11, 2009 as the new Director for the Office of Computational Biology and Bioinformatics. Dr. Edgar comes to us from the National Center for Biotechnology Information (NCBI) at the National Library of Medicine where he headed NCBI's Reference Collections Section. Dr. Edgar's research has been focused on the creation and continued development of the Gene Expression Omnibus (GEO) resource for functional genomics data and the newly released resource for mass spectrometry data. Dr. Edgar earned his Bachelor of Science from the Department of Chemistry from the Tel-Aviv University in Israel, his Master of Science in Organic Chemistry, and his Ph.D. in Physical Chemistry from the Weizmann Institute of Science, Israel. At NIDA, Dr. Edgar will provide scientific and executive-level management, leadership, and direction for the scientific computational biology and bioinformatics Office.

Michele M. Straus, R.Ph., M.S. became a member of the CCTN team on February 17, 2009. Before joining NIDA, Ms. Straus served as principal investigator for the Clinical Coordinating Center of NIDA's NDAT CTN. In this capacity she also served on the Steering and Executive Committees of the CTN and was integral to the development and implementation of CTN clinical trials. Ms. Straus has over 20 years of experience coordinating and directing clinical research and regulatory affairs-related projects in a variety of settings and organizations. She holds a B.S.P. in Pharmacy from the University of Florida and an M.S. from the University of Maryland UC in Technology Management.

Brenda Fogel, OSPC, accepted a new position in the Office of Human Resources, NIH as a Human Resource Specialist. Ms. Fogel served as a Program Analyst in OSPC for 10 years.

Sheryl Massaro, OSPC, retired at the end of February 2009 after 21 years at NIDA, ending 35 years of Government service. She began at NIDA in late 1988, writing speeches for then director Dr. Charles Schuster. In 1994 she became deputy press officer and in 1999 she assumed responsibility for developing communications programs for targeted audiences such as special populations, students, and physicians. She spearheaded NIDA's marketing program using promotional postcards to drive audiences to NIDA's web site and created annual calendars highlighting drug abuse and geared toward Native Americans and Asian Americans. Most recently she oversaw NIDA's active collaboration with Scholastic magazines and our Physician Outreach activities including the Centers of Excellence for Physician Information. Before joining NIDA, Sheryl served briefly as a review team writer/editor at the General Accountability Office and for many years as a managing editor and technical writer at the U.S. Nuclear Regulatory Commission.

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Grantee Honors

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

Grantee Honors

NIDA Grantee **Dr. Margaret Brandeau** of Stanford University was presented with the President's Award during the national conference of INFORMS (Institute for Operations Research and Management Sciences), October 13, 2008, in Washington, D.C. Dr. Brandeau has played a central role in advanced HIV/AIDS modeling research, including expanded HIV testing. Her work has led to important HIV/AIDS policy changes in the U.S.

On January 28, 2009, **Lynn Kunkel**, CTN Oregon/Hawaii Node, received a Golden Rose Award from Oregon Health and Science University for service of excellence. Each month the University selects five individuals for recognition of services that exceed expectations on one or more of five Pillars of Excellence: People, Service, Quality, Finance and Growth. The award included an engraved plaque and an Apple iPod. Dennis McCarty, OR/HI Node PI, nominated Lynn for her perseverance during a trip to Hartford, CT in December to complete a Simulated Patient (SP) walkthrough for CTN-0032 at the Wheeler Clinic. Lynn's commitment to the Clinical Trials Network and the research protocol being implemented exceeded expectations. Despite the setbacks, the site visit received rave reviews from the Wheeler Clinic staff and provided them with an invaluable opportunity to practice study procedures prior to the start of the CTN-0032 trial. She provided excellent service and strengthened OHSU's contributions to the National Drug Abuse Treatment Clinical Trials Network.

Jennifer Prah Ruger, Ph.D., was promoted to Associate Professor at the Yale School of Public Health.

On February 5, 2009, **Dr. George Woody**, CTN Delaware Valley Node (Node PI), received a memorial award in honor of Alexei Alexeevich Likhachev, the founder of the Pharmacology Department of the Women's Medical Institute of St. Petersburg, Russia (later renamed Pavlov State Medical University). Dr. Woody gave a presentation entitled "Naltrexone treatment and HIV risk reduction for heroin addiction: 10-years Penn-Pavlov experience". The occasion was a meeting celebrating the 110th year of the Department of Pharmacology at Pavlov State Medical University.

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