Director's Report to the National Advisory Council on Drug Abuse - September, 2006

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Research Findings - Basic Neurosciences Research

Phosphorylation of WAVE1 Regulates Actin Polymerization and Dendritic Spine Morphology

The connectionist theory posits that behavioral changes such as those produced by learning and addiction occur by strengthening the connections between neurons called synapses. A neuron sending a signal to a neighboring neuron releases a chemical neurotransmitter into the synapse, which then diffuses across the synapse and binds to receptors located on the adjacent neuron. The receptors in most cases are located on specialized processes or protrusions called dendritic spines. Drugs of abuse such as cocaine, nicotine, and opiates produce long term changes in the length of dendrites, the number of spines, and the shape of spines. An important molecule implicated by the Greengard laboratory in regulating the morphology of dendritic spines is cdk5, a kinase that phosphorylates proteins, i.e., adds a high energy phosphate to proteins. Nobel Laureate Paul Greengard and his colleagues show that WAVE1 (the Wiskott-Aldrich syndrome protein (WASP)-family verprolin homologous protein 1) forms a complex with cdk5 and is phosphorylated by cdk5. Phosphorylation of WAVE1 or the loss of WAVE 1 prevents actin, a major cytoskeletal protein from polymerizing and leads to a loss of dendritic spines. Dopamine, a neurotransmitter implicated in reward, decreases WAVE1 phosphorylation by cdk5 through a cAMP dependent dephosphorylation. The decrease in WAVE1 phosphorylation leads an increase in actin polymerization resulting in an increase in the number of spines. Thus, phosphorylation and dephosphorylation of WAVE1 regulates actin polymerization and dendritic spines. Future research will determine the mechanism by which WAVE1 is dephosphorylated by cAMP. Kim, Y., Sung, J.Y., Ceglia, I., Lee, K-W., Ahn, J-H., Halford, J.M., Kim, A.M., Kwak, S.P., Park, J.B., Ryu, S.H., Schenck, A., Bardoni, B., Scott, J.D., Nairn, A.C., and Greengard, P. Phosphorylation of WAVE1 Regulates Actin Polymerization and Dendritic Spine Morphology. Nature, 442, pp. 814-817, 2006.

Synaptopodin Regulates Cytoskeleton Through RhoA

The initiation and regulation of protruding subcellular structures, such as lamellipodia, filopodia formed during cell migration, and dendritic spines formed during neuronal synaptic growth, involves Rho family of small GTPases, including RhoA, Rac1 and Cdc42. It is through reorganization of the cytoskeleton that cells can move and make connections with other neurons. How these molecules each function differently in regulating cytoskeletons, which support the subcellular structures is not clear. Dr. Mundel and colleagues report that RhoA functions in stress fiber formation by interacting with a novel protein called synaptopodin. First, using wild type podocytes as a model system, they found that knock-down of synaptopodin suppresses RhoA initiated

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stress fibers, and overexpression of RhoA increases stress fibers in these cells. However, when they looked at podocytes lacking synaptopodin, the mRNA for RhoA does not change. Additional search enabled them to discover that synaptopodin does not affect RhoA transcription, but blocks the targeting of RhoA for degradation by Smurf1, a molecule which mediates ubiquitin induced protein degradation. The researchers further noticed that simply overexpressing RhoA in synaptopodin silenced podocytes does not initiate more stress fibers, since synaptopodin also plays roles in activating RhoA when stress fiber forms. Since RhoA is downstream of many G-protein coupled receptors in memory and reward pathways, this work provides important insights about how such pathways can be activated or manipulated during drug abuse. Asanuma, K., Yanagida-Asanuma, E., Faul, C., Tomino, Y.,Kim, K. and Mundel, P. Synaptopodin Orchestrates Actin Organization and Cell Motility Via Regulation of RhoA Signalling. Nature Cell Biology, 8(5) pp. 485-491, 2006.

Distinct Modes of Regulated Receptor Insertion to the Somatodendritic Plasma Membrane

One of the most critical factors in determining whether or not two molecules with the potential to interact in a biological system will in fact interact is whether or not they ever "see" each other. It is, of course, essential for interaction between two molecules that the molecules be present in the same place at the same time so they might have the opportunity to interact. Even such co-localization is no guarantee of interaction, but it is guaranteed that they will not interact if they never co-localize. A critical step in ensuring the potential for interaction with other biologically relevant components is delivery of proteins and other cellular component to their site of action. In this study, the researchers have observed just such a delivery. Using cutting edge technology that allowed them to monitor molecular movement at the cell surface using a microscope, they report the observation of a member of the G-protein coupled receptor family inserting into the cell membrane of a primary cultured neuron upon exposure to an agonist of the receptor. They see not only delivery or receptor to the cell membrane at the outer surface of the cell, but have also learned about lateral movement of the receptors once at the surface. One of the intriguing aspects of their observations is that there appear to be two types of insertion events for this receptor. They have named these two events "transient" and "persistent" insertion referring to the length of time a cluster of receptors will remain clustered at the surface once delivered there before spreading out throughout the cell membrane. While both transient and persistent insertion events are observed at the surface of a given cell, continued exposure of the cell to receptor agonist causes a decrease in the frequency of the transient events while causing an increase in persistent events when compared to agonist washout conditions. It is important to note that these studies are consistent with the recycling of already existing receptors to the cell surface rather than delivery of newly synthesized receptors to the cell surface. The opioid receptors are from the same receptor family as the receptor studied here and recycling events of those receptors are believed to be closely linked to drug tolerance. Future studies looking specifically looking at the opioid receptors using this system will be valuable in trying to develop strategies to manage drug tolerance. Yudowski, G.A., Puthenveedu, M.A., and von Zastrow, M. Distinct Modes of Regulated Receptor Insertion to the Somatodendritic Plasma Membrane. Nature Neuroscience, 9(5), pp. 622-627, 2006.

Regulation of DeltaFosB Stability by Phosphorylation

Addiction is a chronic relapsing disease characterized by drug seeking behavior even in the face of adverse consequences. One mechanism thought to mediate addiction is long term changes in gene expression in which genes that encode proteins, the major regulators of cell function, are turned on or off. Addictive drugs acting through receptors on the surface of neuronal cells send signals to

the cell nucleus that leads to the activation or inactivation of transcription factors. These transcription factors are proteins that bind to a gene to act as a molecular switch. This in turn leads to increased or decreased transcription of the gene into mRNA. Increases in mRNA lead to increased protein synthesis for a gene encoding a particular protein while decreases in mRNA lead to decreased protein synthesis for a particular protein. In neurons changes in gene expression can lead to changes in neuronal excitability and changes in the strength of connections between neurons. One such transcription factor implicated in addiction is deltaFosB. Once induced, this transcription factor is highly stable and is not degraded for weeks or months. A key question is what mechanism prevents deltaFosB from becoming degraded. In the May 10, 2006 issue of the Journal Neuroscience, Dr. Eric Nestler and his colleagues at the University of Texas Southwestern Medical center provide an answer. They show that phosphorylation of deltaFosB on a serine at position 27 (this serine is the 27th amino acid of deltaFosB) by casein kinase 2 promotes the stability of deltaFOSB. This observation supports the theory that deltaFOSB acts as sustained molecular switch in the brain to promote and maintain long lasting changes in nervous system function. Ulery, P.G., Rudenko, G., and Nestler, E.J. Regulation of _FosB Stability by Phosphorylation. Journal of Neuroscience, 26(19), pp. 5131-5142, 2006.

In Vivo Experience Changes Synaptic Strength and Glutamate Receptor Composition

Sensory experiences such as touch are processed by neuronal circuits within our brains. The neurons in these circuits signal to one another using synaptic connections between the neurons, and these connections can become stronger or weaker depending on the strength and frequency of the sensory experience. This "synaptic plasticity" is critical for learning and remembering sensory experiences, and importantly plays a significant role in the development of addiction to drugs of abuse. Although the molecular mechanisms underlying synaptic plasticity are partially understood, investigating these processes in vivo (in intact organisms) is difficult. Dr. Barth is investigating the molecular mechanisms mediating synaptic plasticity in response to touch experience. She uses mice which have all but one whisker removed, since removal of these touch sensory structures alters the touch experience of the animals, and evokes changes in synaptic plasticity in the neural circuits which can be monitored experimentally. These mice express a piece of DNA containing the promoter of the c-fos transcription factor fused to Green Fluorescent Protein (GFP). After all but one whisker is removed, GFP turns on and green light is emitted in neurons undergoing functional changes in response to the altered sensory experience. These green neurons can then be characterized in a variety of electrophysiological and pharmacological ways to see how their properties have changed as the result of altered sensory experience. Dr. Barth found that GFP neurons in the single whisker animals have stronger synaptic connections. At the molecular level, she found that this is due to the presence of AMPA glutamate receptors (which lack a GluR2 subunit) at the input synapses. Dr. Barth's work expands our understanding of the molecular mechanisms underlying synaptic plasticity, which is critical for gaining a complete understanding of the neuronal basis of addiction. It is hoped that in the future, pharmaceuticals that modulate synaptic plasticity in specific brain regions could be used as therapeutic agents to treat addiction. Clem, R.L. and Barth, A. Pathway-Specific Trafficking of Native AMPARs by In Vivo Experience. Neuron, 49, pp. 663-670, 2006.

Reduced Nicotine Reward in Obesity: Cross-Comparison in Human and Mouse

Recent estimates suggest that 20% of current smokers are obese, and there are no studies that have examined differences in nicotine reward between

obese and non-obese smokers. Dr. Julie Blendy and her colleagues investigated factors that maintain smoking behavior in obese individuals and to explore the underlying molecular mechanisms in a mouse/human cross-validation model of nicotine reward in lean and obese subjects. In humans, a cigarette choice paradigm was used to examine the relative reinforcing value of nicotine in obese and non-obese smokers. Conditional place preference (CPP) for nicotine was assessed in mice fed standard low fat rodent chow and mice rendered obese by a high fat diet. This study showed that in humans, obese smokers self-administered nicotine via cigarettes significantly less often than non-obese smokers and showed attenuated hedonic effects of nicotine-containing cigarettes compared to denicotinized cigarettes. Similarly, mice exposed to a high fat diet did not exhibit nicotine CPP, compared to control mice. mRNA levels for the m-opioid receptor and the leptin receptor were also downregulated in the ventral tegmental, a key brain reward region, of these mice. Together, these studies provide the first evidence for reduced nicotine reward in obese subjects and suggest that this may be mediated by dietary influences on the endogenous opioid system. Blendy, J.A., Strasser, A., Walters, C.L., Perkins, K.A., Patterson, F., Berkowitz, R., and Lerman, C. Reduced Nicotine Reward in Obesity: Cross-Comparison in Human and Mouse. Psychopharmacology, 180, pp. 306-315, 2005.

Cannabinoids Directly Inhibit Peripheral Capsaicin-Sensitive Nociceptive Neurons

Cannabinoids can reduce pain at a peripheral site of action. However, the signaling pathway mediating this effect is not clearly understood. NIDA grantee Kenneth Hargreaves (University of Texas Health Science Center, San Antonio) and his colleagues tested the hypothesis that certain cannabinoids directly inhibit peripheral capsaicin-sensitive nociceptive neurons by desensitizing the transient receptor potential vanilloid 1 (TRPV1) receptor. Application of the cannabinoid WIN 55,212-2 (WIN) to cultured trigeminal (TG) neurons or isolated skin biopsies rapidly and significantly inhibited capsaicin activated inward currents. The inhibitory effect did not involve the activation of G protein-coupled cannabinoid receptors. Rather, the application of WIN produced a dephosphorylation of the TRPV1 receptors. These data demonstrate that cannabinoids such as WIN directly inhibit TRPV1 functional activities and represents a mechanism of cannabinoid actions at peripheral sites. Patwardhan, A.M., Jeske, N.A., Price, T.J., Gamper, N., Akopian, A.N., and Hargreaves, K.M. The Cannabinoids WIN 55,212-2 Inhibits Transient Receptor Potential Vanilloid 1 (TRPV1) and Evokes Peripheral Antihyperalgesia Via Calcineurin. Proceedings of the National Academy of Science, NAS, 103(30), pp. 11393-11398, 2006.

N-Substituted cis-4a-(3-Hydroxyphenyl)-8a-methyloctahydroisoquinolines are Opioid Receptor Pure Antagonists

In continuation of their studies to develop new opioid receptor antagonists as possible treatment drugs for substance abuse, Dr. Carroll and associates have reported that N-substituted cis-4a-(3-hydroxyphenyl)-8a-methyloctahydroquinolines are potent opioid antagonists in the [35S]GTP-(-S functional assay with several analogues showing preferences for the 6 opioid receptor. In this presentation, N-substituted cis-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines were designed and synthesized as conformationally constrained analogues of the trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine class of opioid receptor pure antagonists. The methyl octahydroisoquinolines can exist in conformations where the 3-hydroxyphenyl substituent was either axial or equatorial similar to the 3-hydroxyphenylpiperidines. The 3-hydroxyphenyl equatorial conformation was responsible for the antagonist activity observed in the (3-hydroxyphenyl)

piperidine antagonists. Single crystal X-ray analysis of N-methyl cis-4a-(3-hydroxyphenyl)-8a-methyl-octahydroisoquinoline showed that the 3-hydroxyphenyl equatorial conformation was favored in the solid state. Molecular modeling also suggested that the equatorial conformation had lower potential energy relative to that of the axial conformation. Evaluation of N-substituted cis-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines in the [35S]GTP-g-S in vitro functional assay showed that they were opioid receptor pure antagonists. N-[4a-(3-hydroxyphenyl)-8a-methyl-2-(3-phenylpropyl) octahydro-isoquinoline-6-yl]-3-(piperidin-1-yl) propionamide with a Ke of 0.27 nM at the k opioid receptor with 154- and 46- fold selectivity relative to those of the m and d receptors, respectively, possessed the best combination of the k potency and selectivity. Carroll, F.I., Chaudhari, S., Thomas, J.B., Mascarella, S.W., Gigstad, K.M., Deschamps, J., and Navarro, H.A. N-substituted cis-4a-(3-Hydroxyphenyl)-8a-methyloctahydroisoquinolines Are Opioid Receptor Pure Antagonists. Journal of Medicinal Chemistry, 48, pp. 8182-8193, 2005.

Multiple Mechanisms for the Biosysnthesis of Endocannabinoids

N-Acyl ethanolamines (NAEs) constitute a large and diverse class of signaling lipids that includes the endogenous cannabinoid, anandamide. Like other lipid transmitters, NAEs are thought to be biosynthesized and degraded on-demand rather than being stored in vesicles prior to signaling. The identification of enzymes involved in NAE metabolism is therefore imperative to achieve a complete understanding of this lipid signaling system and control it for potential therapeutic gain. Recently, an N-acyl phosphatidylethanol-amine phospholipase D (NAPE-PLD) was identified as a candidate enzyme involved in the biosynthesis of NAEs. Here, Cravatt's group describes the generation and characterization of mice with a targeted disruption in the NAPE-PLD gene [NAPE-PLD(-/-) mice]. Brain tissue from NAPE-PLD(-/-) mice showed more than a 5-fold reduction in the calcium-dependent conversion of NAPEs to NAEs bearing both saturated and polyunsaturated N-acyl chains. However, only the former group of NAEs was decreased in level in NAPE-PLD(-/-) brains, and these reductions were most dramatic for NAEs bearing very long acyl chains. Further studies identified a calcium-independent PLD activity in brains from NAPE-PLD(-/-) mice that accepted multiple NAPEs as substrates, including the anandamide precursor C20:4 NAPE. The illumination of distinct enzymatic pathways for the biosynthesis of long chain saturated and polyunsaturated NAEs suggests a strategy to control the activity of specific subsets of these lipids without globally affecting the function of the NAE family as a whole. This is a first step toward understanding and controlling this system for therapeutic gain. Leung, D., Saghatelian, A., Simon G.M., and Cravatt, B.F., Inactivation of N-acyl Phosphatidylethanolamine Phospholipase D Reveals Multiple Mechanisms for the Biosynthesis of Endocannabinoids, Biochemistry, 45(15), pp. 4720-4726, 2006.

Uterine Anandamide Levels and Pregnancy

Anandamide, an endogenous cannabinoid, plays an important role in implantation of the fertilized ovum. Uterine implantation requires a reciprocal interaction between a blastocyst and a receptive uterus. NIDA supported research in mice has illuminated anandamide's role in mediating this interaction. During early pregnancy, anandamide is at lower levels in both the receptive uterus and at the implantation site. However, the mechanism by which differential uterine anandamide gradients are established is not clearly understood. NIDA researchers Dr. Dey and his associates have recently demonstrated that uterine anandamide levels are primarily regulated by Nape-Pld, the gene encoding N-acylphosphatidyl-ethanolamine-hydrolyzing phospholipase D (NAPE-PLD) that generates anandamide. This suggests that aberrant uterine NAPE-PLD activity may cause implantation failure or defective implantation. These findings may be relevant to human abuse of cannabinoids,

since elevated anandamide is associated with spontaneous pregnancy failure. Guo, Y., Wang, H., Okamoto, Y., Ueda, N., Kingsley, P.J., Marnett, L.J., Schmid, H.H.O., Das, S.K., and Dey S.K., N-Acylphosphatidylethanolamine-hydrolyzing Phospholipase D Is an Important Determinant of Uterine Anandamide Levels during Implantation, Journal of Biological Chemistry, 280, pp. 23429-23432, 2005.

Opiates and Apoptosis (Programmed Cell Death)

Opiates have been shown to inhibit cell growth and trigger apoptosis, but the underlying molecular mechanisms remain unclear. Other research has reported that morphine induces Fos expression and promotes Fos-mediated apoptosis. In a recent study, NIDA-supported researchers, Dr. Deling Yin and his associates investigated the mechanisms by which morphine modulates apoptosis in human Jurkat cells, a human T-cell leukemia line. Their study revealed that morphine induced Jurkat cell apoptosis through FADD/p53, anti-apoptotic Pl3K/Akt and NF-kB pathways. They came to these conclusions because they observed that morphine-induced apoptosis was inhibited by transfection with a dominant negative Fos-associated death domain (FADD) plasmid. This suggests that morphine-induced apoptosis is dependent on FADD. Furthermore, suppression of endogenous p53 expression attenuated the morphine-induced apoptosis. In addition, morphine-induced apoptosis appeared to be dependent on the activation of phosphatidylinositol 3-kinase (Pl3K), as Pl3K inhibition significantly enhanced morphine-induced apoptosis. They also noted inhibition of Akt or nuclear factor-kappaB (NF-kB) expression dramatically increased morphine-induced apoptosis. These findings are important as they further our insight in the regulation of morphine-induced immunosuppression. Yin, D.L., Woodruff, M., Zhang, Y., Whaley, S., Miao J.Y., Ferslew, K., Zhao, J., and Stuart, C., Morphine Promotes Jurkat Cell Apoptosis through Pro-apoptotic FADD/P53 and Anti-apoptotic Pl3K/Akt/NF-kB Pathways, Journal of Immunology, 174, pp. 101-107, 2006.

The Properties of in vivo Salvinorin A

Salvinorin A is a non-nitrogenous diterpene produced in the leaves of the sage, Salvia divinorum, along with related salvinorins B-F, and is a potent kappa opioid receptor (KOR) agonist in terms of in vitro binding, despite being structurally unrelated to other known nitrogenous kappa ligands. Its in vivo effects in mice include sedation and antinociception. In the rhesus monkey, intravenous injection of salvinorin A produces sedative effects. In humans, smoking of the leaves and leaf extracts induces hallucinations. Drs. Roth, Pintar, and Rothman, have identified some in vivo properties of salvinorin A based on the development of a KOR knockout mouse model. In brief, wild type mice receiving an intracerebroventricular injection of salvinorin A showed a dose-dependent analgesic response. This effect was absent in the KOR knockout mice. Salvinorin-2-propionate (a chemical derivative of salvinorin A) also produced analgesia, but the salvinorin B did not. Salvinorin A and salvinorin-2-propionate, but not salvinorin B, produced hypothermia in wild type mice. Again the effect was not seen in the knockout mice. Radioligand binding showed that salvinorin A and salvinorin-2-propionate could displace U69,593 at the kappa1 binding site, but not bremazocine, from the kappa 2a/2b binding sites. Binding was not detected in the KOR knockout mice. The data support the idea that most of the behavioral effects of salvinorin A are due to agonist activation of the KOR at the kappa1 binding site. Ansonoff, M.A., Zhang, J., Czyzyk T., Rothman R.B., Stewart J., Xu, H., Zjwiony J., Siebert, D.J., Yang, F., Roth, B.L., and Pintar, J.E., Antinociceptive and Hypothermic Effects of Salvinorin A are Abolished in a Novel Strain of Kappa-Opioid Receptor-1 Knockout Mice, Journal of Pharmacology and Experimental Therapeutics, 318(2), pp, 641-648, 2006.

Cocaine Increases Actin Cycling

Cocaine addiction, like other forms of memory, is associated with persistent changes in synaptic function. Peter Kalivas and his colleagues are investigating the response of actin to cocaine. Actin cycling regulates dendritic spine morphology and protein insertion into the postsynaptic density. Kalivas and his colleagues recently reported an increase in filopodia-like actin formation in the nucleus accumbens after cocaine. Following acute cocaine, the increase is short-lived and depends primarily on changes in actin assembly, while after 3 weeks withdrawal from chronic cocaine, the increase is enduring, consistent with filopodia formation, and results primarily from a change in actin cycling. The increased cycling is produced by a reduction in LIM-kinase and a corresponding decreased inactivation (phosphorylation) of cofilin. Further, when increased actin cycling was reversed by intra-accumbens injection of either a Tat-peptide LIM-kinase antagonist (promotes actin de-polymerization and branching) or latrunculin A (inhibits actin polymerization), the reinstatement of cocaine-seeking in rats was augmented. This argues that the increase in actin cycling produced by chronic cocaine is compensatory. Toda, S., Shen, H.-W., Peters, J., Cagle, S. and Kalivas, P.W. Cocaine Increases Actin Cycling: Effects in the Reinstatement Model of Drug Seeking. J. Neurosci., 26, pp. 1579-1587, 2006.

Plasma Concentrations of MDMA that Produce Serotonergic Neurotoxicity in Monkeys Overlap those Reported in Human "Ecstasy" Abusers

George Ricaurte's group examined the pharmacokinetic profile of MDMA in squirrel monkeys after different routes of administration, and examined the relationship between acute plasma MDMA concentrations and subsequent brain serotonin deficits. Oral MDMA administration engendered a plasma profile of MDMA in the monkeys similar to that seen in humans, though the half-life of MDMA in monkeys is shorter (3-4 hr vs. 6-9 hr). As in humans, MDMA was N-demethylated to MDA, and the plasma ratio of MDA to MDMA was 3-5/100, similar to that in humans. MDMA accumulation in the monkeys was non-linear, and plasma levels were highly correlated with regional brain serotonin deficits observed two weeks later. Plasma concentrations of MDMA that produced serotonergic neurotoxic effects in the monkeys overlapped those reported in human "ecstasy" abusers, though their studies did not allow for possible development of tolerance in humans. Their results also indicate that neurotoxic plasma MDMA levels in monkeys are only two to three times higher than those that develop in humans after a single 100-150 mg dose of MDMA in a controlled setting. Since "ecstasy" abusers often use sequential doses hours apart, the findings in the monkeys may be most relevant to such individuals. Mechan, A., Yuan, J., Hatzidimitriou, G., Irvine, R.J., McCann, U.D. and Ricaurte, G.A. Pharmacokinetic Profile of Single and Repeated Oral Doses of MDMA in Squirrel Monkeys: Relationship to Lasting Effects on Brain Serotonin Neurons, Neuropsychopharmacology, 31, pp. 339-350, 2006.

Alpha3beta4 Nicotinic Antagonists, Administered into the Medial Habenula or Interpeduncular Nucleus, Attenuate the Self-Administration of Morphine in Rats

The novel iboga alkaloid congener 18-methoxycoronaridine (18-MC) is a putative anti-addictive agent that has been shown, in rats, to decrease the self-administration of morphine and other drugs of abuse. Previous work established that 18-MC is a potent antagonist at alpha3beta4 nicotinic receptors. Because alpha3beta4 nicotinic receptors in the brain are preferentially located in the medial habenula (MHb) and the interpeduncular nucleus (IPN), a study was conducted to determine if 18-MC could act in these

brain areas to modulate morphine iv self-administration in rats. Local administration of 18-MC into either the MHb or the IPN decreased morphine self-administration while having no effect on responding for a non-drug reinforcer (sucrose). Similar results were produced by local administration into the same brain areas of two other alpha3beta4 nicotinic antagonists, mecamylamine and alpha-conotoxin AuIB. Local administration of 18-MC into the ventral tegmental area had no effect on morphine self-administration. These data are consistent with the hypothesis that 18-MC decreases morphine self-administration by blocking alpha3beta4 nicotinic receptors in the habenulo-interpeduncular pathway. Glick, S.D., Ramirez, R.L., Livi, J.M. and Maisonneuve, I.M. 18-Methoxycoronaridine Acts in the Medial Habenula and/or Interpeduncular Nucleus to Decrease Morphine Self-Administration in Rats. Eur J Pharmacol, 537, pp. 94-98, 2006.

D1 and D2 Dopamine Receptors Form Heterooligomers and Cointernalize Following Selective Activation of Either Receptor

Earlier Dr. Susan George and her research team at the University of Toronto showed that a novel phospholipase C-mediated calcium signal arose from coactivation of D1 and D2 dopamine receptors. In the present study, robust fluorescence resonance energy transfer showed that these receptors exist in close proximity, indicative of D1-D2 receptor heterooligomerization. The closeness of these receptors within the heterooligomer allowed for cross-phosphorylation of the D2 receptor by selective activation of the D1 receptor. D1-D2 receptor heterooligomers were internalized when the receptors were coactivated by dopamine or either receptor was singly activated by the D1-selective agonist (+/-)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (SKF 81297) or the D2-selective agonist quinpirole. The D2 receptor expressed alone did not internalize after activation by quinpirole except when coexpressed with the D1 receptor. D1-D2 receptor heterooligomerization resulted in an altered level of steady-state cell surface expression compared with D1 and D2 homooligomers, with increased D2 and decreased D1 receptor cell surface density. Together, these results demonstrated that D1 and D2 receptors formed heterooligomeric units with unique cell surface localization, internalization, and transactivation properties that are distinct from that of D1 and D2 receptor homooligomers. So, C.H., Varghese, G., Curley, K.J., Kong, M.M.C., Alijaniaram, M., Ji, X., Nguyen, T., O'Dowd, B.F., and George, S.R. D1 and D2 Dopamine Receptors Form Heterooligomers and Cointernalize after Selective Activation of Either Receptor. Molecular Pharmacology, pp. 568-578, 2005.

GABA Inhibits NAC Neurons After Intracranial Self-stimulation

Intracranial self-stimulation (ICS) of the median forebrain bundle (MFB) is a motivated behavior that results from contingent activation of the brain reward system. Neurons that course through this pathway elaborate a variety of neurotransmitters including dopamine and GABA. The specific roles each transmitter subserves remain unclear. Cheer, et al., used extracellular electrophysiology and cyclic voltammetry at the same electrode in awake rats to simultaneously examine cell firing and dopamine release in the nucleus accumbens (NAc) during ICS and noncontingent stimulation of the MFB. ICS elicited dopamine release in the NAc and produced coincident time-locked changes (predominantly inhibitions) in the activity of a subset of NAc neurons. Similar responses were elicited with noncontingent stimulations. The changes in firing rate induced by noncontingent stimulations were reversed by the GABAA receptor antagonist bicuculline. Thus, neurons in the NAc are preferentially inhibited by GABAA receptors after MFB stimulation, a mechanism that may also be important in ICS. After inhibition of dopamine release, bicuculline reversed the time-locked inhibitory responses evoked by noncontingent stimulations. GABAergic neurons from the VTA project to the

NAc along with the ascending dopamine systems. Thus, their activation by the noncontingent stimulation or during ICS could lead to inhibitions similar to those found in the prefrontal cortex and NAc during electrical stimulation of the VTA. Overall, these findings bolster the view that GABA release occurs during ICS-like stimulations, and suggests that ICS is a behavior involving extensive neuronal circuitry, not solely involving dopamine. Cheer, J.F., Heien, M.L.A.V., Garris, P.A., Carelli, R.M., and Wightman, R.M. Simultaneous Dopamine and Single-unit Recordings Reveal Accumbens GABAergic Responses: Implications for Intracranial Self-stimulation. Proceedings of the National Academy of Science, 102, pp. 19150-19155, 2005.

Dopamine Neurons of the VTA Differ with Respect to the Class of Opiate Receptors They Express and this is Reflected in their Terminal Destinations

The mesolimbic dopamine system, which mediates the rewarding properties of nearly all drugs of abuse, originates in the ventral tegmental area (VTA) and projects to both the nucleus accumbens (NAc) and the basolateral amygdala (BLA). Dr. John Williams' lab distinguished dopamine (DA) neurons within VTA that projected to the BLA from those projected to the NAc based on their expression of kappa and mu opiate receptors. DA neurons originating in the anterolateral VTA project to the BLA and neurons that terminate in the NAc originate in the posteromedial VTA and differed from each other in three important ways. First, differential postsynaptic inhibition by opioids was evident at VTA, where DA neurons that projected to the NAc were sensitive to a kappa-opioid agonist but not the mu/delta opioid agonist [Met5] enkephalin. The opposite action of the opioids was observed in neurons that projected to the BLA. Second, the presynaptic mechanisms mediating GABAergic transmission were also differently affected by the kappa opioid receptor activation. The presynaptic GABAA inputs onto BLA-projecting neurons were more sensitively disinhibited while GABAB input onto NAc-projecting neurons were more sensitively disinhibited. In contrast, activation of the mu/delta receptor equally disinhibited the GABAergic transmission (either GABAA or GABAB) on BLA-projecting neurons and NAc-projecting neurons. Third, the kappa receptor activation disinhibited D2 receptor mediated synaptic activity on these two groups of neurons, while mu/delta receptor activation showed no effect. The DA uptake transporter-mediated properties were identical between these two groups of VTA neurons. These results suggest that the properties of mesolimbic dopamine neurons of the VTA are not homogenous but vary according to terminal location. Behavioral effects of opioids may therefore be the result of inhibition of distinct subpopulations of mesolimbic neurons. Identifying the properties of mesolimbic VTA dopamine projecting neurons is critical to understanding the action of drugs of abuse. These findings warrant further mechanistic investigation of specific signaling between different brain regions. Ford, C.P., Mark, G.P., and Williams J.T. Properties and Opioid Inhibition of Mesolimbic Dopamine Neurons Vary According to Target Location. Journal of Neuroscience, 26(10), pp. 2788-2797, 2006.

Glial Activation Resulting from Combined Morphine and HIV-1 Tat Protein Exposure is Mediated by Inflammatory Chemokine Receptor CCR2 Activation in the Brain

Opiate abuse is believed to exacerbate the neuropathogenesis associated with HIV/AIDS. Laboratory studies have provided compelling evidence for additive or synergistic effects of opioid compounds and neurotoxic HIV proteins such as Tat on glial activation and neuronal dysfunction. In addition, opioid receptor activation can greatly increase the expression (and function) of inflammatory chemokines and their receptors in neural cells (neurons, microglia and astrocytes) as well as leukocytes (lymphocytes, monocytes and macrophages).

Glial activation and increased chemokine production in the brain, particularly CCL2 (monocyte chemoattractant protein-1, or MCP-1), are associated with increased neuropathology in multiple diseases including HIV encephalitis, and CCL2 levels are markedly increased by substance abuse in HIV-1 infected individuals. Therefore, this study asked whether increased CCL2 signaling (via the CCR2 receptor) mediated increased astrocyte, macrophage and microglial activation resulting from combined morphine and Tat exposure in mice. The mice received intracerebral injections of HIV-1 Tat into the striatum, or saline/sham injection as controls. Two days following injection, mice received subcutaneous implants of time-release morphine and/or naltrexone pellets, with placebo pellets as controls, to deliver drugs for 5 days. Brains from these mice were examined for expression of the astrocyte marker GFAP, the macrophage/microglia marker F4/80, mu opioid receptor, CCL2 and CCR2. Astrocytes were the predominant contributors of increased CCL2 production following morphine and/or Tat exposure. Systemic morphine increased the proportion of CCL2+ astrocytes at the site of Tat injection, and to a lesser degree saline injection, suggesting that opiates aggravate both focal and Tat-induced inflammatory responses. This increase was completely blocked by naltrexone, and there were no effects of morphine or Tat in the contralateral striatum. Glial changes induced by Tat or morphine + Tat were completely abolished in CCR2(-/-) mice, suggesting that signaling from activation of this chemokine receptor is the principal mechanism involved in this aspect of HIV neuropathogenesis. El-Hage, N., Wu, G., Ambati, J., Bruce-Keller, A.J., Knapp P.E., and Hauser K.F. CCR2 Mediates Increases in Glial Activation Caused by Exposure to HIV-1 Tat and Opiates. Journal of Neuroimmunology, (epub), 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Basic Behavioral Research

An Experimental Paradigm for Reinstatement of Nicotine-Seeking Behavior with Drug-Associated Stimuli

In typical drug self-administration procedures, animals are first taught to respond for food on an active lever (while a second inactive lever serves as a control) until responding is stable, whereupon food is replaced by drug. To test for possible response bias in this procedure, Drs. Lui, Caggiula and colleagues, trained one group of rats to respond for nicotine on the same lever that had been active for food, and another group to respond for nicotine by responding on the formerly inactive lever. During the nicotine self-administration sessions, an illuminated light above the active lever was associated with nicotine delivery. Following acquisition of bar pressing for nicotine, the behavior was extinguished by substituting saline for nicotine and omitting the light following active lever presses. Following extinction, presentation of the light was sufficient to reinstate nicotine-seeking (i.e., lever pressing on the lever formerly associated with nicotine). Pretreatment with mecamylamine, a nicotinic antagonist attenuated the visual stimulus' effectiveness in producing reinstatement. Although there were initial differences in response rates depending upon which lever was used to train nicotine self-administration, no overall response biases were found. Since the observed differences were found in early stages of training for nicotine self-administration, this lever-switch paradigm may be useful for studying the addictive properties of nicotine in short duration experiments. Lui, X., Caggiula, A.R., Yee, S.K., Nobuta, H., Poland, R.E. and Pechnick, R.N. Reinstatement of Nicotine-Seeking Behavior by Drug-Associated Stimuli after Extinction in Rats. Psychopharmacology, 184, pp. 417-425, 2006.

Rats Given Prolonged Access to Nicotine Display Age, But Not Gender, Differences

In a recent study by NIDA grantee Dr. B. M. Sharp, adolescent rats were housed in operant chambers allowing 23 hr access to self-administered nicotine via lever-pressing on one of two available levers (one active, one inactive). During acquisition of self-administration behavior, males displayed greater variation in responding on the active lever, but there were no significant gender differences in acquisition. Thus, both genders rapidly learned to self-administer nicotine and there were no gender differences in sensitivity to dose. However, adult female rats acquired nicotine self-administration at a slower rate than adolescent females and the adult females self-administered significantly less drug than their adolescent counterparts. (Adult male rats were not tested in this phase of the study). The procedure used by Dr. Sharp and his colleagues differs from those previously employed to establish nicotine self-administration in that animals were not food restricted (which may affect

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growth, especially in animals that are continuing to develop). This experimental paradigm more closely mimics the conditions under which humans self-administer nicotine. Additionally, since the "adolescent" phase of development is short in rats, this model allows for rapid acquisition of the self-administration behavior for study. Chen, H., Matta, S.G. and Sharp, B.M. Acquisition of Nicotine Self-Administration in Adolescent Rats Given Prolonged Access to the Drug. Neuropsychopharmacology, (e-pub): 1-10, 2006.

Hedonic Response to an Initial Lapse Predicts Progression to Second Lapse (Relapse), but Aversive Ratings or High Dose NRT Do Not

In a NIDA supported investigation, Dr. Chad Gwaltney, asked smokers to use electronic diaries to record their smoking and subjective responses to smoking during baseline and test periods. Following baseline assessments (2 weeks prior to a previously set quit date), subjects were treated with either a high dose nicotine patch (35 mg), or a placebo patch. Initial abstinence was defined as 24 consecutive hours without smoking. Subjects continued to record observations in the electronic diaries for 6 weeks following the quit date. These data were used to assess (1) the pleasantness and satisfaction ("hedonic rating"), and aversive effects, of smoking lapse and relapse; (2) the relationship between the hedonic effects of first and second lapses, amount smoked, and likelihood of future lapses; and (3) the effect of a high dose nicotine patch (35 mg) on the hedonic effects of initial lapse. Dr. Gwaltney found that the likelihood of a second lapse was increased when a larger amount of the initial lapse cigarette was smoked, and if the subject reported greater 'liking' the cigarette. By contrast, aversive rating did not affect likelihood for a second lapse. Moreover, the high dose nicotine patch did not affect time to first or second lapse, and did not affect hedonic or aversive ratings. Programs examining the affective variables that affect lapse and relapse in smoking behavior have translational potential for interventions that may lead to smoking cessation. Shiffman, S., Ferguson, S.G. and Gwaltney, C.J. Immediate Hedonic Response to Smoking Lapses: Relationship To Smoking Relapse, and Effects of Nicotine Replacement Therapy. Psychopharmacology, 184, pp. 608-618, 2006.

Effects of Early Drug Exposure on the Transition to Addiction

The development of sensitization is believed to contribute to the emergence of addiction, and may underlie the rapid progression to drug dependence seen in some individuals. Animal models have been developed to study escalated, compulsive drug intake, and these excessive patterns of intake have been associated with sensitization. For example, using progressive ratio (PR) operant schedules, Dr. David Roberts and colleagues have demonstrated sensitization to the reinforcing strength of cocaine in animals allowed to self-administer in a binge pattern over two weeks. These animals show increased break points for self-administered cocaine, often making hundreds of responses over sessions to receive a single drug infusion. In the present study, the investigators assessed break points and determined dose-response curves for cocaine self-administration in animals with varied initial exposures to cocaine self-administration. Initially, all rats in these studies were trained to self-administer cocaine on a FR1 schedule over 1-5 days. Total intake during this training ranged from 60-150 mg/kg/day. As soon as animals acquired the self-administration behavior, they were switched to a PR schedule for 14 days. Other groups of animals received additional self-administration sessions for five more days before being switched to a PR schedule. Animals in these extended exposure groups self-administered 13, 40 or 67 injections of cocaine per day prior to PR testing; thus, 20, 60 or 100 mg/kg/day. Then, in a final study, rats with extensive initial cocaine exposures, (100 mg/kg/day x 5 days), were tested to determine a cocaine dose-response curve for self-administration

following the 14 days of testing on a PR schedule. The investigators found that in animals with only one day of FR training, break points successively increased over 14 days of PR testing, suggesting a progressive increase in reinforcer strength of the drug. Then, to investigate a threshold for initial exposure in this sensitization process, animals undergoing previous FR self-administration to receive 20, 60 or 100 mg/kg/day were compared on 14 days of PR testing for cocaine. Only animals in the 20 mg/kg group showed this same progressive increase in break points and the sensitization effect was masked by high levels of drug intake in the other groups. In fact, a significant change in break point emerged by day four of testing in this low dose group, so low levels of cocaine exposure may be optimal for inducing a rapid, escalated pattern of drug intake. The authors argue that this low dose exposure leads to a sensitization of cocaine's reinforcing effects and contributes to the transition to addiction, whereas higher drug exposures produce a different outcome - for example, a deterioration of behavioral regulation as has been reported in earlier studies. Morgan, D., Liu, Y. and Roberts, D.C.S. Rapid and Persistent Sensitization to the Reinforcing Effects of Cocaine. Neuropsychopharmacology, 31, pp. 121-128, 2006.

Cocaine Self Administration, but Not Passive Cocaine Exposure, Selectively Abolishes Long-Term Depression in the Nucleus Accumbens Core

Dr. Antonello Bonci and his colleagues have discovered a mechanism that may underlie two phenomena that are important for understanding the neural basis of drug addiction. One of these is the differential roles of the core versus the shell of the nucleus accumbens (NAcc) in drug-related behaviors. The core is thought to regulate the control of behavior by salient stimuli, such as cue- and stress-induced reinstatement of drug seeking. The role of the shell is less well understood, but it appears to be involved in the primary reinforcing effects of drugs of abuse. A second subject of interest is the differential behavioral and neurobiological effects of drugs when they are obtained by self administration versus when they are passively received. In this study, the ability of cells in the NAcc to develop long-term depression (LTD) was investigated in four groups of animals: [1] rats trained to self administer cocaine ('cocaine rats') or [2] food ('food rats') for 14-19 days; [3] rats that received cocaine passively whenever their paired cocaine rat pressed the bar for cocaine ('yoked rats'); and [4] sham-naïve controls, which were exposed to the operant chamber, but not trained or exposed to cocaine. LTD was evaluated by whole-cell patch clamp recordings from brain slices. LTD is a form of synaptic plasticity, revealed as a reduction in synaptic currents, after a cell has been stimulated with a train of pulses at a low rate. This form of synaptic plasticity is, essentially, the opposite of long-term potentiation and is believed to be necessary for forgetting and new learning. One day after the training period, LTD was measured in brain slices from half of the rats in each group. NAcc neurons in sham-naïve animals showed robust LTD in both the core and shell, while LTD failed in both areas in cocaine rats. In the yoked and food rats, levels of LTD were similar to those in the sham-naïve animals. These results indicate that cocaine self administration blocks LTD, and that this loss cannot be attributed to either cocaine exposure alone (yoked rats) or operant training alone (food rats). The investigators then measured LTD in the other half of the rats after 21 days of abstinence. At this time, LTD could be induced in NAcc shell in all groups of rats, but it continued to be blocked in the NAcc core of the cocaine rats. These results indicate that voluntary cocaine self-administration selectively induces long-lasting neuroadaptations in the NAcc core. This loss of LTD may occlude further learning and thus contribute to the reduced behavioral flexibility often observed in drug addicts. It may also reflect ongoing memory consolidation of stimuli related to drug self-administration and thereby facilitate reactivity to relapse-inducing stimuli. Martin, M., Chen, B.T., Hopf, F.W., Bowers, M.S., and Bonci, A. Cocaine Self-Administration Selectively Abolishes LTD in the Core of the

Nucleus Accumbens. Nature Neuroscience, 9, pp. 868-869, 2006.

Prior Cocaine Exposure Disrupts Extinction of Fear Conditioning

Exposure to drugs of abuse is known to disrupt, or in some cases, to enhance, various sorts of learning and memory. In this study Dr. Schoenbaum and his colleagues tested the effect of cocaine exposure on extinction of fear conditioning. Recent research in animal models of this type of learning and extinction indicate that fear conditioning is initially established by circuits in the amygdala, but its extinction requires new learning (i.e., learning not to respond to stimuli previously associated with shock) that involves the medial prefrontal cortex (mPFC) -- an area critical for the suppression of inappropriate responses. Because psychostimulant exposure has been shown to cause molecular and cellular changes in prefrontal cortex, it has been hypothesized that these changes might affect the operation of prefrontal-limbic circuits and disrupt their normal role in controlling behavior, thereby contributing to compulsive drug-seeking. The investigator reasoned that, if this hypothesis is correct, cocaine exposure should interfere with extinction learning. They found that rats that had been exposed to a sensitizing regimen of cocaine for two weeks showed similar rates of fear conditioning as saline controls when a shock was paired with a tone stimulus, but their extinction learning rate was slower. Extinction was tested in two different ways when the animals were exposed to the tone cue in the absence of shock - by a reduction in freezing behavior, and by reductions in the ability of the tone to suppress bar-pressing for sucrose pellets (conditioned suppression). In another part of the experiment, half the rats were exposed to an "inflation" procedure after fear conditioning. In this procedure, animals are given several shocks of greater magnitude than those used for fear conditioning, but un-paired with the tone stimulus. This treatment increased the freezing response to the tone, particularly at the beginning of the extinction trials, but inflation did not differ between the cocaine- and saline-treated rats. The authors argue that because inflation involves enhancement of associations in the amygdala, whereas extinction learning depends on mPFC, these results support the hypothesis that control processes in the mPFC are impaired by cocaine exposure. Dr. Schoenbaum's group and other laboratories have previously shown that drugs of abuse impair behaviors that depend on the orbitofrontal cortex, such as adjustments of behavior in response to devaluation of reinforcers and reversal learning. This new study, which implicates deficits in mPFC function after drug exposure, further highlights the importance of neural changes in frontal areas for understanding long-term consequences of drug abuse. Burke, K.A., Franz, T.M., Gugsa, N., Schoenbaum, G. Prior Cocaine Exposure Disrupts Extinction of Fear Conditioning. Learning and Memory, 13, pp. 416-421, 2006.

Sex Difference in Visual Cue Enhancement of Nicotine Reinforcement

Human laboratory studies have shown that sensitivity to nicotine is lower in females than in males but that sensitivity to nonpharmacological stimuli associated with cigarette use is higher in females than in males. The importance of stimuli associated with nicotine to the reinforcing effects of nicotine has been established by researchers at the University of Pittsburg. That research was conducted previously in male rats and the researchers have now extended this work to female rats and have observed sex differences in this effect. Following acquisition of i.v. self-administration of either 0.03, 0.06, or 0.15 mg/kg nicotine and stable responding, nicotine deliveries were subsequently paired with a visual cue. In the absence of the visual cue, nicotine alone functioned as a reinforcer in both males and females at the .06 and 0.15 mg/kg doses, but not the 0.03 mg/kg dose. Addition of the visual cue produced a robust enhancement of nicotine reinforcement (response rate, infusions earned, and nicotine intake) in both males and females at the lower

doses, and this enhancement at the 0.06 mg/kg dose was greater in females than males. The authors suggest possible explanations for this greater enhancement in females, including a greater synergistic interaction between nicotine and the visual cue and sex differences in limbic responses to nicotine and nicotine cues. This sex difference in visual cue enhancement of nicotine reinforcement could have implications for the use of pharmacologic versus non-pharmacologic strategies for nicotine cessation in males versus females. Chaudhri, N., Cagguila, A.R., Donny, E.C., Booth, S., Gharib, M.A., Craven, L.A., Shannon, S.A., Alan, F.S., and Perkins, K.A. Sex Differences in the Contribution of Nicotine and Nonpharmacological Stimuli to Nicotine Self-Administration in Rats. Psychopharmacology, 180, pp. 258-266, 2005.

THC Produces More Impairment in Learning in Adolescent Versus Adult Male Rats

In rats, levels of CB1 receptors for THC, the major psychoactive constituent in marijuana, are maximal in early adolescence, and then decrease into adulthood, thus suggesting that THC would have greater effects on the adolescent than adult brain. Dr. Scott Swartzwelder and colleagues at Duke University compared the effects of an acute dose THC (2.5, 5.0, and 10.0mg/kg) in a water maze learning task in adolescent and adult male rats. The water maze task had both a spatial and a non-spatial variation. In the spatial task, the rats had to learn the fixed location of a platform submerged slightly below the water surface within the water tank. In the non-spatial variation of the task, the platform was raised above the surface of the water and its location within the water tank was changed from trial to trial. At all dose levels, THC disrupted both spatial and non-spatial learning more powerfully in adolescent animals than in adults as measured by the distance rats swam to reach the goal platform. In a study of the chronic effects of THC in adolescents and adults, both groups received 21 daily injections of 5.0 mg/kg THC and following the last injection were tested 28 days later at which time the adolescents had reached adult age. In this chronic THC study, THC had no effect on subsequent maze learning either in the adolescents or the adults. The authors caution, however, that the results from this chronic study do not rule out the possibility of persisting effects on maze learning which possibly could have been unmasked by various experimental challenges, and they further note that the findings may not extend to other learning tasks. Importantly, the authors conclude that the data from the acute study suggest that "adolescence is a period of heightened sensitivity to the neurobehavioral effects of THC." Cha, Y.M., White, A.M., Kuhn, C.M., Wilson, W.A., and Swartzwelder, H.S. Differential Effects of Delta9-THC on Learning in Adolescent and Adult Rats. Pharmacology, Biochemistry and Behavior, 83, pp. 448-455, 2006.

PET Imaging of Dopamine D2 Receptors Before, During and After Cocaine Self-Administration in Rhesus Monkeys

Research with both human and non-human primates has demonstrated an association between susceptibility to the reinforcing and positive subjective effects of psychostimulants and D2 receptor availability. Further, among cocaine users, D2 receptor availability has been found to be lower than that seen in age-matched non-cocaine users. Dr. Mike Nader and his colleagues at Wake Forest University School of Medicine recently sought to determine whether D2 receptor availability is a trait variable that confers vulnerability to cocaine, whether cocaine use alters D2 receptor availability, and whether D2 receptor availability changes during cocaine abstinence. Twelve experimentally naïve adult male rhesus monkeys underwent PET scans to determine baseline D2 receptor availability and were then exposed to a schedule of response-contingent food and cocaine availability. Data indicated that from weeks 4 to10 the rate of cocaine self-administration was negatively associated with baseline

D2 receptor availability. Over 12 months of cocaine self-administration, the number of cocaine injections did not change, but D2 receptor availability declined approximately 22% and the decline was independent of the baseline levels. Following the one year of cocaine self-administration, five of the 12 monkeys were studied in abstinence. Within three months, three of the monkeys exhibited recovery of baseline D2 receptor availability, whereas after 12 months, the remaining two monkeys failed to exhibit recovery. These data suggest that D2 receptor availability is both a predisposing trait for cocaine abuse and a consequence of cocaine exposure and that there are individual differences in whether there is recovery of D2 receptor availability during abstinence. Nader, M.A., Morgan, D., Gage, H.D., Nader, S.H., Calhoun, T.L., Buchheimer, N., Ehrenkaufer, R., and Mach, R.H. PET Imaging of Dopamine D2 Receptors During Cocaine Self-Administration in Monkeys. Nature Neuroscience, 9, pp. 1050-1056, 2006.

Hyperthermic Effects of (+/-)3,4-Methylenedioxymethamphetamine, (+/-)3,4-Methylenedioxyamphetamine and Methamphetamine in Rhesus Monkeys

Severe hyperthermia leading to death has been reported in human recreational users of 3,4-methylene-dioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), and methamphetamine (METH). In rodents, the degree of hyperthermia produced by these compounds has also been associated with the extent of amphetamine-induced neurotoxicity. Dr. Michael Taffe and his associates at The Scripps Research Institute sought to systematically determine the thermoregulatory risks of recreational doses of these compounds in nonhuman primates. Six rhesus monkeys were given a range of doses of each drug via intramuscular injection and then monitored for body temperature and locomotor activity in their home cages via telemetry. All three compounds significantly raised body temperature in the animals, although in a manner unrelated to dose and with varying time courses. The effects of METH lasted hours longer than MDMA or MDA and disrupted nighttime circadian cooling for as long as 18 hours as well. In general, activity levels were not affected by the doses tested. These findings demonstrate that this paradigm can serve as a reliable primate model for studying the thermoregulatory effects of drugs of abuse, and found that three commonly identified constituents of ecstasy produce hyperthermia in monkeys under ambient temperatures. R.D. Crean, S.A. Davis, S.N. Von Huben, C.C. Lay, S.N. Katner, and M.A. Taffe. Effects of (+/-)3,4-Methylenedioxymethamphetamine, (+/-)3,4-Methylenedioxyamphetamine and Methamphetamine on Temperature and Activity in Rhesus Macaques. Neuroscience, advance online publication, July 27, 2006.

Cognitive Performance During Simulated Shift Work

Individuals who are required to work irregular or rotating shifts (e.g., healthcare workers and military personnel) frequently adjust their sleep-wake cycles and report sleep disruptions and increased sleepiness while working. These conditions may contribute to diminished performance and work-related accidents. One strategy used to offset shift change-related disruptions is the administration of psychostimulants. Psychostimulants such as the amphetamines, however, pose a risk of dependence. An alternative to psychostimulants is the alerting agent Modafinil. The purpose of this double-blind, within-participant study was to examine the effects of Modafinil on cognitive/psychomotor performance, mood, and measures of sleep during simulated shift work. In all, 11 participants completed this 23-day residential laboratory study. They received a single oral Modafinil dose (0, 200, 400 mg) 1 h after waking for three consecutive days under two shift conditions: day shift and night shift. Shifts alternated three times during the study, and shift

conditions were separated by an 'off' day. When participants received placebo, cognitive performance and subjective ratings of mood were disrupted during the night shift, relative to the day shift. Objective and subjective measures of sleep were also disrupted, but to a lesser extent. Modafinil reversed disruptions in cognitive performance and mood during the night shift. While Modafinil produced few effects on sleep measures during the night shift, the largest dose produced several sleep alterations during the day shift. These data demonstrate that abrupt shift changes produce cognitive performance impairments and mood disruptions during night shift work. Therapeutic doses of Modafinil attenuated night-shift-associated disruptions, but the larger dose produced some sleep impairments when administered during day-shift work. Hart, C.L., Haney, M., Vosburg, S.K., Comer, S.D., Gunderson, E., and Foltin, R.W. Modafinil Attenuates Disruptions in Cognitive Performance During Simulated Night-Shift Work. Neuropsychopharmacology, 31, pp. 1526-1536, 2006.

Mechanism of the Immunomodulatory Effects of Opioids

It has been known for a long time that opiate abusers are at high risk for infectious diseases. Although the high incidence of infections among opioid users is due in part to increased exposure to germs from needle sharing or non-sterile iv drug use, opioids themselves contribute to increased infection by direct effects on the immune system. However, there is little known about the mechanism of the immunomodulatory effects of opioids. Whereas, there is evidence that opioids such as morphine modulate the immune system via activation of CNS _-opioid receptors, the neural pathways involved in these immunomodulatory effects have not been well-characterized. In a recent study, NIDA grantee Donald Lysle and colleagues showed that the dopaminergic system was critical for the induction of morphine-induced suppression of natural killer (NK) cell activity by demonstrating that the administration of the dopamine D1 receptor antagonist SCH-23390 into the nucleus accumbens shell, but not the core, dose dependently blocked the suppressive effect of morphine on splenic NK cell activity, while injection of the D2 receptor antagonist raclopride did not. In support of these findings, morphine-induced reductions of NK activity were also prevented in animals that received intra-accumbens microinfusions of the dopaminergic immunotoxin anti-DAT-saporin. Furthermore, administration of the D1 agonist SKF-38393 into the nucleus accumbens produced reductions in splenic NK activity comparable to morphine, suggesting a critical role for accumbens D1 receptors in the modulation of splenic NK activity. These findings demonstrate that dopaminergic inputs to the nucleus accumbens are critically involved in opioid-induced immunosuppression and suggest that acute increases in dopamine signaling may have adverse consequences on the immune system. Saurer, T.B., Carrigan, K.A., Ijames, S.G., and Lysle, D.T. Suppression of Natural Killer Cell Activity by Morphine is Mediated by the Nucleus Accumbens Shell. Journal of Neuroimmunology, 173, pp. 3-11, 2006. In a follow-up study, the role of the sympathetic transmitter neuropeptide Y (NPY) in mediating morphine-induced immune alterations was investigated. The results showed that administration of the selective NPY Y1 receptor antagonist BIBP3226 blocked morphine's effect on splenic NK activity. The results showed that microinjection of the D1 receptor agonist SKF-38393 into the nucleus accumbens shell induced a suppression of NK activity that was reversed by BIBP3226. Collectively, these findings demonstrate that NPY Y1 receptors mediate morphine's suppressive effect on NK activity and further suggest that opioid induced increases in nucleus accumbens D1 receptor activation inhibit splenic NK activity via increased NPY release from the sympathetic nervous system Saurer, T.B., Ijames, S.G., and Lysle, D.T.. Neuropeptide Y Y(1) Receptors Mediate Morphine-Induced Reductions of Natural Killer Cell Activity. Journal of Neuroimmunology, June 9, 2006 [Epub ahead of print].

Negative Consequences of Nicotine Withdrawal are Less in Adolescent Compared to Adult Rats

There is now general agreement that adolescence is a period marked by enhanced vulnerability to the effects of nicotine, and that nicotine addiction is more common among smokers who initially started smoking at a young age. A number of studies have indicated that the reinforcing effects of nicotine are greater in adolescent animals and contribute significantly to the rapid development of dependence in this group. Although nicotine addiction has been hypothesized to be influenced by both positive reinforcing effects of the drug and negative effects of withdrawal, little research has focused on the severity of the withdrawal symptoms in adolescents. Drs. Athina Markou and George Koob and colleagues at the Scripps Research Institute compared the motivational (changes in intracranial self-stimulation thresholds) and somatic (e.g. writhing, tremors, headshakes) signs of mecamylamine-precipitated nicotine withdrawal in adult and adolescent rats that had been chronically exposed to nicotine via implanted minipumps. They reported that adolescents displayed fewer symptoms of withdrawal than did adults, and that these differences did not appear to be due to differences in metabolism. The authors hypothesized that the positive effects of nicotine are enhanced and the negative effects of withdrawal are diminished in adolescence, which in turn could help explain the enhanced vulnerability to addiction seen during this developmental period. O'Dell, L.E., Bruijnzeel, A.W., Smith, R.T., Parsons, L.H., Merves, M.L., Goldberger, B.A., Richardson, H.A., Koob, G.F., and Markou, A. Diminished Nicotine Withdrawal in Adolescent Rats: Implications for Vulnerability to Addiction. Psychopharmacology 186, pp. 612-619, 2006.

Cue-Conditioned Withdrawal Responses Motivate Escalated Drug Taking in an Animal Model

A great deal of anecdotal evidence suggests that continued drug taking behavior is motivated, in part, by relief from affective, negative states in withdrawal. However, empirical evidence to support a role for withdrawal states in motivating drug consumption is lacking. In animal models using intracranial self-stimulation (ICSS) to quantify central motivational state, withdrawal from addictive drugs shifts thresholds for responding to higher values, indicating a suppression of brain reward systems. Since it is known that reward deficits seen in withdrawal can be conditioned to environmental cues paired with reward, investigators at The Scripps Research Institute sought to determine if withdrawal-associated cues can motivate continued drug taking behavior. Rats were trained on unlimited heroin self-administration (i.v.), available for nose-poke responses over 23 h per day to induce physical dependence, while control animals self-administered for only 1 h each day. All rats were also trained to response for ICSS and tested until their individual thresholds were stable. Then, thresholds were determined every day after heroin self-administration. The 1 h group showed decreased thresholds over 24 days of testing, presumably a direct pharmacological effect of the opiate on central reward systems. However, 23 h (dependent) rats had a steady rise in ICSS threshold over the 24 days, suggesting a progressive blunting of central reward circuits due to neuroadapative changes produced by this dependence-inducing regimen. In a second experiment, withdrawal was precipitated in these two groups with naloxone injections over 4 days of self-administration. Both 1 h and 23 h groups increased their heroin intake following each naloxone injection, presumably in an attempt to counteract the opioid receptor blockade. However, only in the 23 h group did investigators see evidence that this shifted threshold became conditioned to environmental cues present when the naloxone was administered. Thus, during a test on day five, saline was injected prior to heroin self-administration, rather than naloxone, and a significant increase in heroin intake was seen only in the 23 h animals. Lastly, when ICSS thresholds were examined over the four days of naloxone pre-session

injections, naloxone reversed heroin's threshold lowering effects in the 1 h rats but this effect was not conditioned to cues in the environment. In 23 h rats, naloxone injections prior to heroin self-administration raised threshold above their already elevated level (produced by heroin alone), and this effect was conditioned to the test environment. These findings show that self-administered heroin, in a regimen previously demonstrated to induce dependence, induces persistent alterations in the sensitivity of central reward systems. The authors argue that their results also indicate that attenuated central reward sensitivity can drive increased heroin intake to counter this deficit, resulting in the escalation seen in addiction. Furthermore, the negative, affective state induced by precipitated withdrawal can be conditioned to the environment, under conditions of high drug intake and dependence, and the authors argue that this conditioned affect can also motivate greater heroin intake. Kenny, P.J., Chen, S.A., Kitamura, O., Markou, A. and Koob, G.F. Conditioned Withdrawal Drives Heroin Consumption and Decreases Reward Sensitivity. The Journal of Neuroscience, 26, pp. 5894-5900, 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Behavioral and Brain Development Research

Prenatal Smoking and Disruptive Behavior in Early Development

An association between prenatal smoking and disruptive behaviors in children has been documented in the research literature, but little is known about the possible emergence of these behaviors in early development. Dr. Lauren Wakschlag and colleagues investigated very early precursors to disruptive behavior problems, examining behaviors of prenatally-exposed children and non-exposed children at 12, 18, and 24 months of age. Maternal reports were recorded at 12, 18, and 24 months, and behavioral observations were carried out at 24 months. Analyses took into account multiple covariates (e.g., other substances used during pregnancy, parenting practices, and cumulative family risk, which included demographic, psychiatric, and psychosocial factors). The investigators report that exposed toddlers exhibited higher levels of behavior problems from 12 to 24 months, and that virtually all of the toddlers with clinically significant problems at age 2 years had been exposed. They also report that exposure was associated with social, rather than emotional aspects of early problem behaviors. Those exposed were more likely to exhibit stubbornly defiant and aggressive behavior, and lower social engagement. The two groups did not differ on difficulty regulating negative emotion. While pointing out that the data do not prove a causal relationship, the researchers do note that the findings allow generating ideas concerning which areas of the brain may be affected by exposure, and highlight a potential window of opportunity for early interventions aimed at altering disruptive behavior pathways before they become serious clinical patterns. Wakschlag, L.S., Leventhal, B.L., Pine, D.S., Pickett, K.E., and Carter, A.S. Elucidating Early Mechanisms of Developmental Psychopathology: The Case of Prenatal Smoking and Disruptive Behavior. Child Development, 77, pp. 893-906, 2006.

Postnatal Cocaine Use and Parental Behavior During Mother-Infant Interactions

Within a broader conceptual model for maternal behavior among polydrug cocaine-using mothers, this study investigated the relationship between maternal cocaine use (prenatal and postnatal) and maternal behavior during mother-infant interactions. Specifically, behaviors were observed in a feeding context between 4 and 8 weeks of infant age. The categories of maternal behaviors analyzed were maternal insensitivity (e.g., position without support, misses infant cues) and maternal warmth (e.g., talks to infant, pleasure toward infant). The conceptual model used by Dr. Eiden and her colleagues included prenatal and postnatal polydrug use, maternal psychopathology, maternal childhood history, and infant birth weight. There were no group differences in maternal warmth or between maternal psychological functioning and maternal

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warmth. Results of conceptual model testing indicated that only postnatal cocaine use was a significant and unique predictor of maternal insensitivity during feeding. Maternal depression/anxiety was marginally associated with maternal insensitivity. The investigators point out that the results add to a growing body of evidence that indicates the importance of examining postnatal caregiving as a predictor of child outcome among children exposed to substances in the prenatal period. Eiden, R.D., Stevens, A., Schuetze, P., and Dombkowski, L.E. A Conceptual Model for Maternal Behavior Among Polydrug Cocaine-Using Mothers: The Role of Postnatal Cocaine Use and Maternal Depression. Psychology of Addictive Behaviors, 20, pp. 1-10, 2006.

Prediction of Parenting Stress and Perception of Infant Temperament

This investigation was conducted from the perspective that prenatal cocaine exposure is a marker of developmental risk, and the risk may involve a range of social, environmental, and biological factors. The researchers note that two factors likely to mark heightened risk are the degree to which mothers perceive their parental role as highly stressful and the degree to which they perceive their infant as temperamentally difficult. Therefore, the goal of this study was to understand processes that may heighten or attenuate levels of parenting stress and perceptions of infant temperament for infants prenatally-exposed to cocaine. Neonatal behavior, infant temperament, parenting stress, and maternal psychopathology were assessed in a large sample of mother-infant dyads (394 prenatally-exposed infants and 590 comparison infants). The sample was drawn from the multi-site longitudinal Maternal Lifestyle Study, and infants were selected for inclusion if they were in the care of their biological mother. Neonatal behavior was observed at 1 month corrected age, and other assessments were carried out at 4 months corrected age. Results indicated that neonatal behavioral characteristics and certain maternal psychological characteristics interacted to predict maternal ratings of infant temperament, and maternal self-reports of parenting stress. Results were not related to drug exposure history. The researchers conclude that for mothers of at risk infants, with or without prenatal cocaine exposure, psychological distress affects the degree to which infant behavioral characteristics are experienced as stressful or difficult. The researchers also discuss implications of the findings for interventions. Sheinkopf, S.J., Lester, B.M., LaGasse. L.L., et al. Interactions Between Maternal Characteristics and Neonatal Behavior in the Prediction of Parenting Stress and Perception of Infant Temperament. Journal of Pediatric Psychology, 31, pp. 27-40, 2006.

Predicting Caregiver-Reported Behavior Problems in Cocaine-Exposed Children

The purpose of this study was to investigate predictors of caregiver-reported behavior problems in a sample of 3-year-old children. The children were either in a group exposed to cocaine prenatally, or in a comparison group. Two measures of behavior problems were used: the Conners' Parent Report Scale, and the Eyberg Child Behavior Inventory. The Conners' Scale has scales assessing conduct problems and impulsive/hyperactive behaviors. The Eyberg Inventory was designed to assess disruptive behaviors, especially those associated with oppositional-defiant and conduct disorders. Concurrent maternal/caregiver depression as measured by the Center for Epidemiologic Studies-Depression (CES-D) Scale was the only significant predictor of reported child behavior problems in a model that included prenatal drug exposure, child sex, and the quality of the child's environment. Comparisons involving maternal and non-maternal caregivers relative to depression scores and child behavior ratings are also provided in the report. The researchers discuss implications of the findings for clinical care and for future research on behavioral functioning of prenatally exposed children. Warner, T.D., Behnke,

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M., Hou, W., et al. Predicting Caregiver-Reported Behavior Problems in Cocaine-Exposed Children at 3 Years. Journal of Developmental and Behavioral Pediatrics, 27, pp. 83-92, 2006.

Behavioral Reactivity and Regulation in Preschoolers Prenatally-Exposed to Cocaine

Based on concerns in the literature that prenatal exposure to cocaine may increase risk for problems related to reactivity and regulation in infancy and childhood, this study examined whether cocaine-exposed children show such difficulties during the preschool period, a time of increased social and cognitive demands, and a time of rapid changes in reactivity and regulation. The procedure involved observing reactivity and regulation during a frustrating problem-solving task at 4.5 years of age. Frustration reactivity was measured by latency to show frustration and number of disruptive behaviors. Regulation was measured by latency to approach and attempt the problem-solving task and by the number of problem-solving behaviors. Results indicated that cocaine-exposed children took longer to engage in the problem-solving task, and that cocaine-exposed boys showed the most difficulties. The cocaine-exposed boys expressed frustration more rapidly and had a larger number of disruptive behaviors compared to non-exposed children and cocaine-exposed girls. The researchers make note that the effect sizes were relatively small, and feel that the results indicate both resilience and vulnerabilities. They also comment on implications for intervention and prevention. Dennis, T., Bendersky, M., Ramsay, D., and Lewis, M. Reactivity and Regulation in Children Prenatally Exposed to Cocaine. Developmental Psychology, 42, pp. 688-697, 2006.

Prenatal Cocaine Exposure and Childhood Externalizing and Internalizing Behavior Problems at Age 7 Years

In this longitudinal study on the neurodevelopmental consequences of in utero exposure to cocaine Dr. Emalee Bandstra and her colleagues at the University of Miami examined the relationship between prenatal cocaine exposure and parent-reported child behavior problems at age 7 years in a birth cohort of 407 African-American children (210 cocaine-exposed, 197 non-cocaine-exposed). The Achenbach Child Behavior Checklist (CBCL), a measure of childhood externalizing and internalizing behavior problems, was completed by the child's current primary caregiver during an assessment visit scheduled when the child was seven years old. Structural equation and GLM/GEE models disclosed no association linking prenatal cocaine exposure status or level of cocaine exposure to child behavior (CBCL Externalizing and Internalizing scores or the eight CBCL subscale scores) with this caregiver report. A next step in this line of research is to secure standardized ratings from other informants including teachers as well as youth self-report given previous research findings indicate that discordance between child, parent, and teacher reports of symptoms is common. Accornero, V.H., Anthony, J.C., Morrow, C. E., Xue, L., and Bandstra, E.S. Prenatal Cocaine Exposure: An Examination of Childhood Externalizing and Internalizing Behavior Problems at Age 7 Years. Epidemiol Psychiatric Society, 15 (1), pp. 20-29, 2006.

Predicting Cognitive Control from Preschool to Late Adolescence and Young Adulthood

The purpose of this study was to investigate whether cognitive control in early life predicts cognitive control later in life. At approximately 4 years of age, children participated in a delay-of gratification assessment which measures the ability to control attention in the face of temptation. These same children performed the go/no-go task (a well-studied measure of cognitive control) 10

years later at a mean age of 18 years 2 months. The delay-of-gratification and go/no-go tasks are similar in that they both require controlling a prepotent response. The results indicated that those children who were able to direct their attention away from tempting aspects of the rewards (temptation focus) in the delay-of-gratification task were faster at performing the go/no-go task without making errors. Prior studies have indicated that poor performance on the go/no-go task is associated with immature development of frontal-striatal regions. The results of the current study indicate that the temptation focus measure in the delay-of gratification task may be a marker of the subsequent development of frontal-striatal circuitry. Eigsti, I.M., Zayas, V., Mischel, W., Shoda, Y., Ayduk, O., Dadlani, M., Davidson, M., Aber, J.L., and Casey, B.J. Predicting Cognitive Control from Preschool to Late Adolescence and Young Adulthood. Psychological Science, 17 (6), pp. 478-484, 2006.

Phonological Development and Frontal Cortex

The left inferior frontal gyrus has been previously identified as a key area in language production. Dr. Elizabeth Sowell and her colleagues examined whether changes in cortical gray matter thickness in this specific region of the brain are associated with developmental improvements in phonological processing (a linguistic skill) in normally developing children. Forty-five children (mean age of 6.7 years) were administered two measures of phonological processing (the Lindamood Auditory Conceptualization Test and the Elision subtest of the Comprehensive Test of Phonological Processing) and underwent magnetic resonance imaging (MRI). These same children were reassessed with these measures approximately 2 years later. Motor functioning tasks were also administered to establish specificity of the phonological processing tasks with the left inferior frontal gyrus. The results indicated a positive correlation between thickness increase in the left inferior frontal gyrus and improving phonological skills, but not with improving hand motor skills. Understanding brain-behavior relationships in children with normal language development may enhance our understanding of the reported language deficits and learning difficulties in children exposed in utero to drugs of abuse. Lu, L., Leonard, C., Thompson, P., Kan, E., Jolley, J., Welcome, S., Toga, A., and Sowell, E. Normal Developmental Changes in Inferior Frontal Gray Matter are Associated with Improvement in Phonological Processing: A Longitudinal MRI Analysis. Cerebral Cortex. pp. 1-8, June 16, 2006.

Neuroimaging and Prenatal Drug Exposure

This article is a summary report of a symposium that brought together researchers who are investigating effects of prenatal substance abuse in humans and primates, and who are utilizing neuroimaging techniques in their studies. The purpose of the symposium was to assess strengths and weaknesses of the neuroimaging and data processing techniques, and to discuss strategies that may facilitate collection of imaging data in exposed and comparison children. Various imaging techniques were discussed, i.e., magnetic resonance imaging (MRI), positron emission tomography (PET), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and molecular imaging. Papers were presented by five groups, and are provided in this article. While the findings in this report are very preliminary, they emphasize the potential that neuroimaging methodologies have for understanding how drug exposure may affect brain development. Dow-Edwards, D.L., Benveniste, H., Behnke, M., et al. Neuroimaging of Prenatal Drug Exposure. Neurotoxicology and Teratology, 28, pp. 386-402, 2006.

Depression, Sensation Seeking, and Maternal Smoking as Predictors of Adolescent Cigarette Smoking

This study examined maternal and adolescent depression, maternal and teen sensation seeking, and maternal smoking, and their associations with adolescent smoking. Data were collected from a sample of 47 male and 66 female adolescents (ages 11-18 years) and their mothers from three different health clinics. The findings indicate that maternal sensation seeking was linked indirectly with adolescent smoking through teen sensation seeking, both of which were significantly associated with teen smoking (beta = 0.29, $p < 0.001$ and beta = 0.32, $p < 0.001$, respectively). Teen depression was associated positively with teen smoking (beta = 0.24, $p < 0.01$) when controlling for sensation seeking behaviors. Maternal smoking was also directly linked to adolescent smoking (beta = 0.20, $p < 0.05$). These findings underscore a potentially important role of sensation seeking in the origins of adolescent smoking, and clarify pathways of influence with regard to maternal attitudes and behaviors in subsequent teenage nicotine use. van de Venne, J., Bradford, K., Martin, C., Cox, M., and Omar, H.A. Scientific World Jr., 6, pp. 643-652, 2006.

ADHD, Sensation Seeking, and Pubertal Changes

This pilot study was designed to examine the relationship of pubertal changes and sensation seeking (SS) in adolescents with Attention Deficit Hyperactivity Disorder (ADHD). Patients with current or past histories of uncomplicated stimulant medication use for ADHD between the ages of 11 and 15 were recruited from a Child Psychiatry and a General Pediatric Clinic. SS was measured using the SS Scale for Children. Pubertal development was measured using Tanner staging, free testosterone, and DHEAS. Subjects and their parent were interviewed with the Diagnostic Interview Schedule for Children (DISC). SS total score was correlated with Tanner stage, free testosterone, and DHEAS ($p < or = 0.01$). The combined parent and child reports of symptoms of Oppositional Defiant Disorder from the DISC were inversely related to age ($p < or = 0.05$). Understanding SS in ADHD adolescents as they move through puberty will aid clinicians in monitoring ADHD adolescents and their trajectory into substance abuse and other high-risk behaviors. Martin, C.A., Guenthner, G., Bingcang, C., Smith, W.J., Curry, T., Omar, H.A., Raynes, M.K., and Kelly, T.H. A Pilot Study: Attention Deficit Hyperactivity Disorder, Sensation Seeking, and Pubertal Changes. Scientific World Jr., 6, pp. 637-642, 2006.

Vitamin D Status in Adolescents and Young Adults with HIV Infection

Vitamin D status affects immune function and may affect the progress of HIV infection. In this study, Dr. Craig Wilson and his colleagues from the Adolescent Trials Network for HIV/AIDS Interventions, a co-operative agreement co-funded by NIDA , assessed vitamin D intake and status in subjects with HIV infection and in matched control subjects to determine whether HIV infection was associated with vitamin D insufficiency. Plasma 25-hydroxyvitamin D [25(OH)D] concentrations and vitamin D intake were measured in a cross-sectional study of members of the Reaching for Excellence in Adolescent Health (REACH) cohort. The subjects were aged 14-23 y; 74% were female, and 72% were black. Mean (+/-SE) vitamin D intake from food was 30% greater ($P = 0.023$) in HIV-positive subjects (295 +/- 18 IU/d; $n = 237$) than in HIV-negative subjects (227 +/- 26 IU/d; $n = 121$). The prevalence of vitamin D supplement use was 29% (104 of 358 subjects) and did not differ significantly by HIV status ($P = 0.87$). Mean plasma 25(OH)D did not differ significantly ($P = 0.62$) between the HIV-positive (20.3 +/- 1.1 nmol/L; $n = 238$) and HIV-negative (19.3 +/- 1.7 nmol/L; $n = 121$) subjects, nor was HIV status a significant predictor of plasma 25(OH)D when multiple regression analysis was used to adjust for other variables. The prevalence of vitamin D insufficiency [plasma 25(OH)D < or = 37.5 nmol/L] in the subjects was 87% (312 of 359 subjects). The results indicate that HIV infection did not

influence vitamin D status. The prevalence of vitamin D insufficiency was high in both HIV-positive and HIV-negative REACH subjects, perhaps because these disadvantaged, largely urban youth have limited sun exposure. Stephensen, C.B., Marquis, G.S., Kruzich, L.A., Douglas, S.D., Aldrovandi, G.M., and Wilson, C.M. Vitamin D Status in Adolescents and Young Adults with HIV Infection, American Journal of Clinical Nutrition, 83 (5), pp. 1135-1141, 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Clinical Neuroscience Research

Cocaine Cues and Dopamine In Dorsal Striatum: Mechanism of Craving In Cocaine Addiction

Nora Volkow and colleagues at Brookhaven National Laboratory and the University of Pennsylvania used Positron Emission Tomography ligand imaging to test whether dopamine increases occur to drug-related stimuli in cocaine addicts and whether the dopamine increases are associated with drug craving. The ability of drugs of abuse to increase dopamine in nucleus accumbens underlies their reinforcing effects. However, preclinical studies have shown that with repeated drug exposure neutral stimuli paired with the drug (conditioned stimuli) start to increase dopamine by themselves, which is an effect that could underlie drug-seeking behavior. Positron emission tomography studies using [C-11] raclopride, a dopamine D-2 receptor radioligand sensitive to competition with endogenous dopamine, were conducted in eighteen cocaine-addicted subjects. Changes in dopamine were measured by comparing the specific binding of [C-11] raclopride when subjects watched a neutral video (nature scenes) versus when they watched a cocaine-cue video (scenes of subjects smoking cocaine). The specific binding of [C-11] raclopride in dorsal (caudate and putamen) but not in ventral striatum (in which nucleus accumbens is located) was significantly reduced in the cocaine-cue condition. The magnitude of this reduction correlated with self-reports of craving. Moreover, subjects with the highest scores on measures of withdrawal symptoms and of addiction severity (shown to predict treatment outcomes), had the largest dopamine changes in dorsal striatum. This provides evidence that dopamine in the dorsal striatum (region implicated in habit learning and in action initiation) is involved with craving and is a fundamental component of addiction. Because craving is a key contributor to relapse, strategies aimed at inhibiting dopamine increases from conditioned responses are likely to be therapeutically beneficial in cocaine addiction. Volkow, N.D., Wang, G.J., Telang, F., Fowler, J.S., Logan, J., Childress, A.R., Jayne, M., Ma, Y.M., and Wong, C. Journal of Neuroscience, 26, pp. 6583-6588, 2006.

Very Little Cigarette Smoking Results in Substantial Levels of Nicotinic Acetylcholine Receptor Occupancy

Arthur Brody and colleagues at University of California, Los Angeles and the PET Center at the NIDA Intramural Research Program used PET ligand imaging to determine the effect of cigarette smoking on nicotinic acetylcholine receptor (nAChR) availability in tobacco dependent smokers during early abstinence. nAChR occupancy was measured with 2-[18F] fluoro-3-(2(S)azetidinylmethoxy) pyridine. The effective dose required to displace 50% of the radiotracer (ED50) in the nAChR-rich thalamus was 1-3 puffs (15%) of a cigarette, or a peak plasma nicotine concentration of 0.83 ng/ml. Thus, very

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little cigarette smoking results in substantial brain nAChR occupancy during smokers' high risk period for relapse. Findings from the present study have implications for the treatment of tobacco dependence. Attempts to block the addicting properties of tobacco, including the use of nAChR antagonists, and nicotine vaccines, are currently being used or evaluated for their potential to treat tobacco dependence. The present study points to nicotine replacement therapies (e.g., nicotine patch, gum, and lozenges, or vaccines) to produce high levels of nicotine in the in blood in order to produce substantial nAChR occupancy or blockade, to overcome the high levels of receptor occupancy produced by nicotine in tobacco. The methodology in this study also may prove useful for evaluating the pharmacological effects of such treatments and guiding efforts to enhance their efficacy. Brody, A.L., Mandelkern, M.A., London, E.D., Olmstead, R.E., Farahi, J., Scheibal, D., Jou, J., Allen, V., Tiongson, N., Chefer, S.I., Koren, A., and Mukhin, A.G. Archives General Psychiatry, 63, pp. 907-914, 2006.

Changes in Nicotine Receptor Levels During Smoking Cessation

Julie Staley and colleagues at Yale School of Medicine used SPECT ligang imaging to monitor changes in the number of nicotine receptors after individuals quite smoking. It was hypothesized that abnormal numbers of these receptors during early abstinence may contribute to a smoker's urge to smoke and impact their ability to remain abstinent. Using molecular imaging in nonhuman primates, the time interval necessary for smokers to abstain in order to be free of residual nicotine was established. Human smokers were then imaged after an average of 6.8 days of abstinence. Results indicated the nicotine receptor subtypes were higher throughout the cerebral cortex (26-36%) and in the striatum (27%) than in nonsmokers, suggesting higher levels of these receptors in recently abstinent smokers. Greater availability in recently abstinent smokers correlated with the days since last cigarette and the urge to smoke to relieve withdrawal symptoms but not the severity of nicotine dependence, severity of nicotine withdrawal, or the desire to smoke. These findings indicate that, when smokers quit smoking, they do so in the face of a significant increase in the receptors normally activated by nicotine and this increased availability impact the ability of smokers to maintain abstinence. Staley, J.K., Krishnan-Sarin, S., Cosgrove, K.P., Krantzler, E., Frohlich, E., Perry, E., Dubin, J.A., Estok, K., Brenner, E., Baldwin, R.M., Ttamagnan, E.G., Seibyl, J.P., Jatlow, P., Picciotto, M.R., London, E.D., O'Malley, S., van Dyke, C.H. Journal of Neuroscience, 26, pp. 8653-8657, 2006.

Neurobiological Substrates of Dread

Greg Berns and colleagues at Emory University used BOLD fMRI to examine the neuronal systems involved in dread, i.e. emotions associated with waiting for an adverse outcome. Given the choice of waiting for an adverse outcome or getting it over with quickly, many people choose the latter. Theoretical models of decision-making have assumed that this occurs because there is a cost to waiting - i.e., dread. Using functional magnetic resonance imaging, authors measured the neural responses to waiting for a cutaneous electric shock in healthy individuals. Some individuals dreaded the outcome so much that, when given a choice, they preferred to receive more voltage rather than wait. Even when no decision was required, these extreme dreaders were distinguishable from those who dreaded mildly by the rate of increase of neural activity in the posterior elements of the cortical regions associated with pain responsivity (e.g. posterior cingulate). This suggests that dread derives, in part, from the attention devoted to the expected physical response and not simply from fear or anxiety. Although these differences were observed during a passive waiting procedure, they correlated with individual behavior in a subsequent choice paradigm, providing evidence for a neurobiological link between the experienced disutility of dread and subsequent decisions about unpleasant

outcomes. Berns, G.S., Chappelow, J., Cekic, M., Zink, C.F., Pagnoni, G., Martin-Skurski, M.E. Science, 312, pp. 754-758, 2006.

Reduced Punishment Sensitivity in Neural Systems of Behavior Monitoring in Impulsive Individuals

Geoffery Potts and colleagues at Rice University used event-related potential recordings of the error-related negativity (ERN) to determine whether impulsive individuals show reduced brain responses during punishment. The ERN was recorded during a flanker task with performance-based monetarily rewarding and punishing trials in 37 undergraduate students separated into high- and low-impulsive groups based on a median split on self-reported Barrett Impulsiveness Scale. The high-impulsive group had a smaller medial frontal error-related negativity (ERN) on punishment trials than the low-impulsive group. The medial prefrontal neural system of behavior monitoring, indexed by the ERN, appears less sensitive to punishment signals in normal impulsivity. This reduced punishment sensitivity in impulsivity; a personality variation associated substance abuse may be related to the tendency to select short-term rewards despite potential long-term negative consequences in these individuals. Potts, G.F., George, M.R.M., Martin L.E., and Barratt, E.S. Neuroscience Letters, 397, pp. 130-134, 2006.

Controlling the Integration of Emotion and Cognition - The Role of Frontal Cortex in Distinguishing Helpful from Hurtful Emotional Information

Jennifer Beer and colleagues at the University of California, Berkeley examined the role of orbitofrontal cortex when it was appropriate to control (i.e., prevent) the influence of emotion in decision-making and to incorporate the influence of emotion in decision making. The orbitofrontal cortex has been identified as a neural area involved in incorporating emotion into decision-making. However, it is unclear whether this area's function specific to the integration of emotion and cognition, or does it more broadly govern whether emotional information should be integrated into cognition? The results suggest that activity in lateral orbitofrontal cortex is associated with evaluating the contextual relevance of emotional information for decision making. These findings provide a framework for interpreting the abnormalities in the orbitofrontal cortex that have been repeatedly observed in substance abusers, Beer, J.S., Knight, R.T., and D'Esposito, M. Psychological Science, 17, pp. 448-453, 2006.

Executive Dysfunction in Substance Dependent Individuals During Drug Use and Abstinence

Antoine Bechara and colleagues at the University of Southern California used neuropsychological testing to compare impairments in substance abusers on executive control tasks relying on different systems within the prefrontal cortex (PFC). Three different functional systems have been described: the dorsolateral prefrontal cortex (DLPC), orbitofrontal cortex (OFC), and anterior cingulate Cortex (ACC) circuits. Dysfunction within each PFC system is associated with different behavioral, cognitive, and emotional abnormalities. Substance abusers (including alcohol, cocaine, and methamphetamine polysubstance users, n=35) were compared with healthy controls (n = 36) on a series of behavioral (Frontal Systems Behavior Scale), cognitive (N-back. Go-No Go, and Wisconsin Card Sorting Tasks), and emotional (International Affective Picture System (IAPS)) tasks each of which was thought to tax a different component of these PFC functional systems. Substance Abusers exhibited greater behavioral problems in the apathy, disinhibition, and executive dysfunction subscales of the Frontal Systems Behavioral Scale. Behavioral deficits were significantly

associated with several real-life domains in which SDI typically have problems. SDI also showed poorer performance on cognitive tests of working memory, response inhibition and mental flexibility and abnormal processing of affective images from the IAPS. These cognitive, behavioral, and emotional measures were moderately correlated. Verdejo-Garcia, A., Bechara, A., Recknor, E.C., and Perez-Garcia, M. Journal of The International Neuropsychological Society, 12, pp. 405-415, 2006.

Neural Signatures of Economic Preferences for Risk and Ambiguity

Scott Huettel and colleagues at Duke University used functional magnetic resonance imaging (fMRI) to compare brain response associated with risk (uncertainty with known probabilities) versus ambiguity (uncertainty with unknown probabilities). People often prefer the known over the unknown, sometimes sacrificing potential rewards for the sake of surety. Overcoming impulsive preferences for certainty in order to exploit uncertain but potentially lucrative options may require specialized neural mechanisms. Individuals' preferences for risk (uncertainty with known probabilities) and ambiguity (uncertainty with unknown probabilities) were found to predict brain activation associated with decision making. Activation within the lateral prefrontal cortex was predicted by ambiguity preference and was also negatively correlated with an independent clinical measure of behavioral impulsiveness, suggesting that this region implements contextual analysis and inhibits impulsive responses. In contrast, activation of the posterior parietal cortex was predicted by risk preference. Together, this novel double dissociation indicates that decision making under ambiguity does not represent a special, more complex case of risky decision making, instead, these two forms of uncertainty are supported by distinct mechanisms. These findings may help clarify the mechanisms underlying increased impulsiveness in drug abusers. Huettel, S.A., Stowe, C.J., Gordon, E.M., Warner, B.T., and Platt, M.L., Neuron 49, pp. 765-775, 2006.

Anterior Cingulate Activity Modulates Nonlinear Decision Weight Function of Uncertain Prospects

Martin Paulus and colleagues at the University of Califonia, San Diego used fMRI to examine how healthy individuals used information about probabilities to guide decisions. The study was based on Prospect theory developed by Kahneman and Tversky, which has been among the most influential psychological models and explains many nonnormative decision-making phenomena, e.g. why people play the lottery or bet on long-shots. A Certainty Equivalent procedure was used during fMRI to identify the neural substrates that are important for nonlinear transformation of probabilities to decision weights. Differential activation in the anterior cingulate cortex during high versus low probability prospects correlated highly ($r = 0.84$) with the degree of the nonlinearity of the transformation of probabilities to decision weights, which indicates that risk-seeking behavior for low probability prospects and risk-averse decision-making for mid to high probability prospects may be due to a lack of controlled processing by the anterior cingulate cortex. Since dysfunctional activity in the anterior cingulate has been observed in substance abusers under a number of conditions, these results may provide a basis for understanding impaired decision-making in substance abusers. Paulus, M.P., Frank, L.R. Neuroimage, 30, pp. 668-677, 2006.

The Medial Frontal Cortex Processes Events That Are Both Better or Worse Than Expected

Geoffery Potts and colleagues at Rice University investigated whether two event-related potential (ERP) components, the anterior positivity (P2a) and the

medial frontal negativity (MFN) reflect neural activity from the same region of the medial frontal cortex. A prominent theoretical model proposes that the dopamine (DA) system, via its reward prediction properties, provides a "gate" through which information gains access to limited-capacity frontal attentional control systems. The medial frontal event-related potential (ERP) index of attention selection, the anterior positivity (P2a), is thought to be associated with DA reward system input to the MFC for the identification of task-relevant perceptual representations. However, the P2a has a similar spatio-temporal distribution as the medial frontal negativity (MFN), elicited to error responses or choices resulting in monetary loss. The MFN has also been linked to DA projections to the MFC but for action monitoring rather than attention selection. This study used a passive reward prediction design containing neither instructed attention nor response to demonstrate that the ERP over medial frontal leads at the P2a/MFN latency probably reflects the same neurophysiological responses but is positive to unpredicted rewards and negative when a predicted reward is withheld. This result suggests that MFC activity is regulated by DA reward system input and may function to identify items or actions that exceed or fail to meet motivational prediction. Potts, G.F, Martin, L., Burton, P., and Montague, P.R. Journal of Cognitive Neuroscience 18, pp. 1112-1119, 2006.

Chronic Cocaine Self-Administration Is Associated with Altered Functional Activity in the Temporal Lobes of Non Human Primates

Porrino and colleagues at Wake Forest University characterize the effects of reinforcing doses of cocaine on cerebral metabolism in a nonhuman primate model of cocaine self-administration, following an extended history of cocaine exposure, using the quantitative 2-[C-14]deoxyglucose (2-DG) method. Previous studies utilizing a nonhuman primate model have shown that cocaine self-administration in its initial stages is accompanied by alterations in functional activity largely within the prefrontal cortex and ventral striatum. However, continued cocaine exposure may considerably change this response. Rhesus monkeys were trained to self-administer 0.03 mg/kg/injection (n = 4) or 0.3 mg/kg/injection (n = 4) cocaine and compared to monkeys trained to respond under an identical schedule of food reinforcement (n =6). Monkeys received 30 reinforcers per session for a total of 100 sessions. Metabolic mapping was conducted at the end of the final session. After this extended history, cocaine self-administration dose-dependently reduced glucose utilization throughout the striatum and prefrontal cortex similarly to the initial stages of self-administration. However, glucose utilization was also decreased in a dose-independent manner in large portions of the temporal lobe including the amygdala, hippocampus and surrounding neocortex. The recruitment of temporal structures indicates that the pattern of changes in functional activity has undergone significant expansion beyond limbic regions into association areas that mediate higher order cognitive and emotional processing. These data strongly contribute to converging evidence from human studies demonstrating structural and functional abnormalities in temporal and prefrontal areas of cocaine abusers, and suggest that substance abusers may undergo progressive cognitive decline with continued exposure to cocaine. Beveridge, T.J.R., Smith, H.R., Daunais, J.B., Nader, M.A., and Porrino, L.J. European Journal of Neuroscience, 23, pp. 3109-3118, 2006.

Cognitive Function and Mood in MDMA/THC Users, THC Users and Non-Drug Using Controls

Antoine Bechara and colleagues at University of Southern California tested the hypothesis that reported feelings of depression and anxiety and cognitive impairment (memory, executive function and decision making) are more severe in MDMA/THC users than in THC users. Repeated ecstasy (MDMA) use is reported to impair cognition and cause increased feelings of depression and

anxiety. Yet, many relevant studies have failed to control for use of drugs other than MDMA, especially marijuana (THC). The behavioral performance of 11 MDMA/THC users was compared to 15 THC users and 15 non-drug users matched for age and intellect. MDMA/THC users reported more intense feelings of depression and anxiety than THC users and non-drug users. Memory function was impaired in both groups of drug users. MDMA/THC users showed slower psychomotor speed and less mental flexibility than non-drug users. THC users exhibited less mental flexibility and performed worse on the decision making task compared to non-drug user s but these functions were similar to those in MDMA/THC users. It was concluded that MDMA use is associated with increased feelings of depression and anxiety compared to THC users and non-drug users. THC users were impaired in some cognitive abilities to the same degree as MDMA/THC users, suggesting that some cognitive impairment attributed to MDMA is more likely due to concurrent THC use. Lamers, C.T.J., Bechara, A., Rizzo, M., and Ramaekers, J.G. Journal of Psychopharmacology, 20, pp. 302-311, 2006.

Cerebellar Vermis Involvement in Cocaine-Related Behaviors

Carl Anderson and colleagres at McLean Hospital used a combination of fMRI and PET ligand imaging to test the hypothesis that the vermis areas of the cerebellum would be activated in cocaine abusers by cocaine-related cues and, in healthy humans, would accumulate DAT-selective ligands. Although the cerebellum is increasingly being viewed as a brain area involved in cognition, it typically is excluded from circuitry considered to mediate stimulant-associated behaviors since it is low in dopamine. In the fMRI study, cocaine-related cues selectively induced neural activation in lobules II-III and VIII-IX in cocaine users. Studies in primates have shown that cerebellar vermis (lobules II-III and VIII-IX) contains dopamine transporter immunoreactivity (DAT-IR). A positron emission tomography imaging study of healthy humans using the DAT-selective ligand using [C-11] altropane found appreciable ligand accumulation in vermis regions (lobules VIII-IX), suggestive of DAT presence in this region. These data suggest that parts of cerebellar vermis could mediate some of cocaine's persisting and acute effects. In light of prior findings illustrating vermis connections to midbrain dopamine cell body regions, established roles for the vermis as a locus of sensorimotor integration and motor planning, and findings of increased vermis activation in substance abusers during reward-related and other cognitive tasks, the vermis could be considered one of the structures involved in cocaine- and other incentive-related behaviors. Anderson, C.M., Maas, L.C., Frederick, B.D., Bendor, J.T., Spencer, T.J., Livni, E., Lukas, S.E., Fischman, A.J., Madras, B.K., Renshaw, P.F., and Kaufman, M.J. Neuropsychopharmacology, 31, pp. 1318-1326, 2006.

Distribution of Norepinephrine Transporters in the Non-Human Primate Brain

Linda Porrino and colleagues at Wake Forest University used the selective ligand [H-3]nisoxetine to describe autoradiographically the normal regional distribution of the norepinephrine transporter (NET) in the non-human primate central nervous system. Noradrenergic terminals in the central nervous system are widespread, as such this system plays a role in varying functions such as stress responses, sympathetic regulation, attention, and memory processing, and its dysregulation has been linked to several pathologies. In particular, the NET transporter is a target in the brain of many therapeutic and abused drugs. The NET transporter in the monkey brain was distributed heterogeneously, with highest levels occurring in the locus coeruleus complex and raphe nuclei, and moderate binding density in the hypothalamus, midline thalamic nuclei, bed nucleus of the stria terminalis, central nucleus of the amygdala, and brainstem nuclei such as the dorsal motor nucleus of the vagus and nucleus of the solitary tract. Low levels of binding to the norepinephrine transporter were measured in

basolateral amygdala and cortical, hippocampal, and striatal regions. The distribution of the NET in the non-human primate brain was comparable overall to that described in other species, however disparities exist between the rodent and the monkey in brain regions that play a role in such critical processes as memory and learning. The differences in such areas point to the possibility of important functional differences in noradrenergic information processing across species, and suggest the use of caution in applying findings made in the rodent to the human condition. Smith, H.R., Beveridge, T.J.R., and Porrino, L.J. Neuroscience 138, pp. 703-714, 2006.

Methadone Maintenance Improves Cognitive Performance After Two Months Of Treatment

Stacy Gruber and colleagues at McLean Hospital examined neurocognitive effects associated with Methadone maintenance (MM). The present study examined cognitive function in 17 opiate-dependent subjects at baseline and after 2 months of MM treatment. Subjects demonstrated significant improvements from baseline on measures of verbal learning and memory, visuospatial memory, and psychomotor speed and reduced frequency of drug use (Addiction Severity Index) relative to baseline, although the total percentage of urine samples positive for additional illicit substances was slightly increased. No effect of illicit drug use was observed when the sample was stratified by urine toxicology results, suggesting that improvements in cognition were not associated with additional illicit drug use. Results suggest that opiate-dependent subjects exhibit significant improvement in cognitive function after MM treatment. Gruber, S.A., Silveri, M.M., Renshaw, P.F., Tzilos, G.K., Pollack, M., Kaufman, M.J., and Yurgelun-Todd, D.A. Experimental and Clinical Psychopharmacology 14, pp. 157-164, 2006.

Affect Modulates Appetite-Related Brain Activity To Images Of Food

Deborah Yugelun-Todd and colleagues used fMRI to determine whether affect ratings predicted regional brain responses to high and low-calorie foods in healthy individuals. Thirteen normal-weight adult women viewed photographs of high and low-calorie foods during BOLD functional magnetic resonance imaging (fMRI). Positive and negative affect had different effects on several important appetite-related regions depending on the calorie content of the food images. When viewing high-calorie foods, positive affect was associated with increased activity in satiety-related regions of the lateral orbitofrontal cortex, but when viewing low calorie foods, positive affect was associated with increased activity in hunger-related regions including the medial orbitofrontal and insular cortex. The opposite pattern of activity was observed for negative affect. These findings describe the neurobiologic substrates involved in the commonly reported increase in cravings for calorie-dense foods during heightened negative emotions. Killgore, W.D.S., and Yurgelun-Todd, D.A. International Journal Of Eating Disorders, 39, pp. 357-363, 2006.

Caudate Blood Flow and Volume Are Reduced in HIV+ Neurocognitively Impaired Patients

John Detre and colleagues at the University of Pennsylvania used continuous arterial spin labeled MRI (ASL) to evaluate the effects of HIV-associated neurocognitive impairment on caudate blood flow and volume. Caudate blood flow and volume of 42 HIV+ patients (23 subsyndromic and 19 HIV neurosymptomatic) on highly active antiretroviral therapy was compared to 17 seronegative controls. Decreased caudate blood flow and volume was associated with increased HIV-associated neurocognitive impairment. Compared with seronegative controls, baseline caudate blood flow was reduced

in HIV+ neurosymptomatic patients with a similar decreasing trend for subsyndromic HIV+ patients. Differences in caudate volume were observed only for neurosymptomatic HIV+ patients compared with controls. There was no significant correlation between caudate blood flow and volume for each group. These results demonstrate that decreasing levels in caudate blood flow and volume were associated with significantly increasing HIV-associated neurocognitive impairment, with the greatest decreases observed for more severely impaired patients. However, reductions in caudate blood flow and volume were poorly correlated. Changes in residual caudate blood flow may act as a surrogate biomarker for classifying the degree of HNCI HIV-associated neurocognitive impairment. Ances, B.M., Roc, A.C., Wang, J., Korczykowski, M., Okawa, J., Stern, J., Kim, J., Wolf, R., Lawler, K., Kolson, D.L., and Detre, J.A. Neurology, 66, pp. 862-866, 2006.

Prospective Memory in HIV-1 Infection

Dr. Igor Grant and colleagues at the University of California, San Diego investigated whether prospective memory (ProM) is one of the cognitive deficits associated with HIV-1 infection. ProM is a form of episodic memory that involves the complex processes of forming, monitoring, and executing future intentions vis-a-vis ongoing distractions. Although ProM is thought to be largely dependent on prefronto-striatal circuits, which is known to be altered with HIV infection, ProM has not previously been examined in an HIV-1 sample. In the current study ProM was compared in 42 participants with HIV-1 infection and 29 demographically similar seronegative healthy comparison (HC) subjects. The HIV-1 sample demonstrated deficits in time- and event-based ProM, as well as more frequent 24-hour delay ProM failures and task substitution errors relative to the HC group. In contrast, there were no significant differences in recognition memory performance, indicating that the HIV-1 group was able to accurately retain and recognize the ProM intention when retrieval demands were minimized. Secondary analyses revealed that ProM performance correlated with validated clinical measures of executive functions, episodic memory (free recall), and verbal working memory, but not with tests of semantic memory, retention, or recognition discrimination. Taken together, these findings indicate that HIV-1 infection is associated with ProM impairment that is primarily driven by a breakdown in the strategic (i.e., executive) aspects of retrieving future intentions, which is consistent with existing evidence of prefronto-striatal circuit neuropathogenesis associated with HIV infection. Carey, C.L., Woods, S.P., Rippeth, J.D., Heaton, R.K., Grant, I., and Neurobehavioral Research Center (HNRC) Group. J Clin Exp Neuropsychol, 28, pp. 536-548, 2006.

Additive Deleterious Effects of Methamphetamine Dependence and Immunosuppression on Neuropsychological Functioning in HIV Infection

Igor Grant and colleagues at the University of California, San Diego investigated the combined effects of MA dependence (MA) and immunosuppression (i.e., CD4 lymphocyte count <200) on neuropsychological (NP) functioning in 284 HIV+ individuals. Prevalence of NP impairment was examined in four demographically comparable groups: MA+/CD4 < 200; MA+/CD4 > or = 200; MA-/CD4 < 200; and MA-/CD4 > or = 200. Results revealed that both MA dependence and immunosuppression were significant predictors of NP impairment. More importantly, additive effects were evident whereby the MA+/CD4 < 200 group exhibited the highest rate of NP impairment. These findings demonstrate that MA dependence conveys an additive deleterious impact on NP status in immunosuppressed persons with HIV infection, which perhaps reflects the combined effects of neuropatho-physiological mechanisms in fronto-striatal circuits. Carey, C.L., Woods, S.P., Rippeth, J.D., Gonzalez, R., Heaton, R.K., and Grant. I. AIDS Behavior, 10, pp.

185-90, 2006.

Cortical and Subcortical Neurodegeneration is Associated with HIV Neurocognitive Impairment

Igor Grant and colleagues from University of California, San Diego, investigated the association between markers of regional neurodegeneration (ND) in post-mortem tissue and degree of neuro-cognitive impairment in persons with HIV. In a prospectively followed cohort of HIV+ individuals, they examined the relationship between antemortem neuropsychological (NP) abilities and postmortem neuropathological data. Twenty-seven HIV+ individuals with both NP and neuropathological data were identified. Laser confocal scanning microscopy was used to determine the degree of ND based on microtubule-associated protein (MAP2; reflecting neuronal cell bodies and dendrites) and synaptophysin (SYN; a measure of presynaptic terminals). A regional combined score, based on the distribution of percentage neuropil occupied by MAP2 and SYN and emphasizing severity of ND, was created for each brain ROI: MFC, hippocampus, and putamen. The regional combined scores from each brain region studied were better correlated with level of global NP impairment than measures of SYN and MAP2 individually. Hippocampal and putamen regional combined scores were independent predictors of degree of antemortem NP impairment The correlations among regional ND measures demonstrated that there is an uneven distribution across multiple brain regions. As the anatomic distribution and temporal progression of neuropathologic changes appears to differ across individuals, it is important to consider both cortical and subcortical brain regions in studies of neuropathogenesis and treatment of HIV-related brain disease. Furthermore, combining information from several markers of neural injury provided the strongest association with degree of neurocognitive impairment during life. Moore, D.J., Masliah, E., Rippeth, J.D., Gonzalez, R., Carey, C.L., Cherner, M., Ellis, R.J., Achim, C.L., Marcotte, T.D., Heaton, R.K., Grant, I., and HNRC Group. AIDS, pp. 879-887, April 4, 2006.

A Battery Approach for Measuring Neuropsychological Change

Igor Grant and colleagues from the University of California, San Diego, investigated the specificity of a modified Reliable Change Index (RCI) methodology applied across a focused battery of commonly used neuropsychological tests. Fifty-seven healthy controls underwent NP assessment at two time points separated by approximately 1 year. Test-retest reliability coefficients and standard RCI confidence intervals for the individual tests were broadly comparable with prior research in healthy populations. Battery change scores were generated by calculating z-scores of change for each individual test, which were summed across the entire test battery. The RCI methodology was applied to the summed z-score to provide a 90% confidence interval as an indicator of overall cognitive stability. These battery RCI normative standards demonstrated adequate specificity when applied to 29 persons with HIV-1 infection who were classified as medically and neurologically stable. Findings from this study represent the first steps towards establishing normative standards for determining reliable changes in performance across a commonly used battery of NP tests. Woods, S.P., Childers, M., Ellis, R.J., Guaman, S., Grant, I., Heaton, R.K., and The HIV Neuro-behavioral Research Center (HNRC) Group. Archives of Clinical Neuropsychology, 21, pp. 83-89, 2006.

Action (Verb) Fluency Predicts Dependence in Instrumental ADL's in Persons Infected with HIV-1

Igor Grant and colleagues from the University of California, San Diego, evaluated the ecological validity of Action Fluency as a predictor of

instrumental activities of daily living (IADL) among persons with HIV-1 infection. Based on hypothesized neural dissociation between the retrieval of nouns and verbs, several studies now support the construct validity of Action (verb) Fluency as a measure of frontostriatal systems function. Relative to traditional noun- and letter-cued verbal fluency tests, Action Fluency is more sensitive to HIV-1-associated neuropsychological impairment, which may reflect inefficiencies engaging motor representations during action retrieval in this population. Accordingly, impaired Action Fluency might adversely impact IADL by disrupting the production and organization of script-based action schemas upon which successful IADL performance depends. Action, Letter (FAS), and Noun (animal) fluency were compared in 21 HIV-1-infected participants with self-reported IADL decline relative to 76 demographically comparable HIV-1-infected participants who reported no IADL declines. Results revealed significant between-group differences in Action and Letter Fluency, but not Noun Fluency. Action Fluency achieved an overall hit rate of 76% and was more sensitive than Letter Fluency in classifying IADL dependent participants. Individuals with impaired Action Fluency performance had a fivefold risk of concurrent IADL decline as compared to those who performed within normal limits, suggesting that Action Fluency may possess incremental ecological validity. Woods, S.P., Morgan, E.E., Dawson, M., Scott, J.C., Grant, I., and The HNRC Group. Journal of Clinical and Experimental Neuropsychology, 28, pp. 1030-1042, 2006.

Brain Dopamine Gene Variants Influence Smoking-Induced Dopamine Release

Arthur Brody and colleagues at University California, Los Angeles used PET ligand imaging to investigate whether common gene variants of the brain DA pathway could account for the considerable inter-individual variability that has been observed in the extent of smoking-induced DA release in the ventral striatum in humans. Positron emission tomography (PET) scanning with the radiotracer 11C-raclopride was performed to measure dopamine release, and genotyping was perfomed using blood samples. Thirty five subjects smoked during the scanning and 10 did not. Those smokers who had a specific combination of Dopamine-relating gene polymorphines (at least one 9 allele of the DA transporter variable nucleotide tandem repeat, fewer than 7 repeats of the D4 variable nucleotide tandem repeat, and the val/val catechol-O-methyltrans-ferase genotype) had greater decreases in binding potential (an indirect measure of DA release) with smoking than those with the alternate genotypes. When compared to those who did not smoke during scanning, an overall decrease in the smokers' ventral striatal binding potential was noted; albeit, smaller in magnitude than previously reported. These results may have future implications for subtyping smokers based on clinical characteristics and possibly in identifying smokers who would be more likely to respond to DA pharmacotherapies or therapies that affect the brain DA system. Brody, A.L., Mandelkern, M.A., Olmstead, R.E., Scheibal, D., Hahn, E., Shiraga, S., Zamora-Paja, E., Farahi, J., Saxena, S., London, E.D., and McCracken, J.T. Archives General Psychiatry, 63, pp. 808-816, 2006.

Functional Imaging of Tobacco Use

Based on a review of the literature on functional brain imaging studies of tobacco use and dependence, Arthur Brody of the University California, Los Angeles proposed a model of brain function in smokers. Many research groups have examined the effects of acute and chronic nicotine/ cigarette exposure on brain activity using functional imaging. Responses to acute administration of nicotine/smoking include: a reduction in global brain activity; activation of the prefrontal cortex, thalamus, and visual system; activation of the thalamus and visual cortex during visual cognitive tasks; and increased dopamine (DA) concentration in the ventral striatum/nucleus accumbens. Responses to chronic

nicotine/cigarette exposure include decreased monoamine oxidase (MAO) A and B activity in the basal ganglia and a reduction in _4_2 nicotinic acetylcholine receptor (nAChR) availability in the thalamus and putamen. Taken together, these findings indicate that smoking enhances neurotransmission through cortico-basal ganglia-thalamic circuits either by direct stimulation of nAChRs, indirect stimulation via DA release or MAO inhibition, or a combination of these factors. Activation of this circuitry may be responsible for the effects of smoking seen in tobacco dependent subjects, such as improvements in attentional performance, mood, anxiety, and irritability. Brody, A.L. Journal of Psychiatric Research, 40, pp. 404-418, 2006.

Working Memory in Cigarette Smokers During Abstinence

Edythe London and colleagues at University California, Los Angeles examined the effect of cigarette smoking and withdrawal on working memory as measured by the N-Back task. Participants included 15 smokers and 22 matched non-smokers. The N-Back Task was administered in two test blocks on each of two days. Smokers were tested in separate sessions after 13 or more hours of abstinence or one hour after smoking. Smokers inhaled one cigarette between the blocks on each test day. Results indicated that performance of smokers after 13 hours but not 1 hour of abstinence was significantly less accurate than that of non-smokers. A within-subject comparison revealed that in the abstinence session, smokers had significantly longer response latencies (in the 2-back condition) and made more overall errors compared to the satiety session. Smoking between test blocks in the abstinence session did not significantly affect performance although it significantly reduced craving. These findings provide further evidence for a deficit in working memory associated with acute abstinence from smoking, which may contribute to the difficulty of smoking cessation. Mendrek, A., Monterosso, J., Simon, S.L., Jarvik, M., Brody, A., Olmstead, R., Domier, C.P., Cohen, M.S., Ernst. M., and London, E.D. Addictive Behaviors, 31, pp. 833-844, 2006.

Ethnic Differences in Enhanced Cue-Elicited Brain Activation

Okuyemi and colleagues used fMRI imaging to investigate differences in brain reactivity to smoking cues between ethnic groups. African-Americans exhibit a different pattern of reactivity to smoking related cues than Caucasians (CC). Although African Americans (AA) are more likely to attempt to quit smoking than Caucasians (CC) in any given year, recent evidence suggests success rates are lower for AA. However, factors contributing to these differences are not well known. Seventeen smokers (8 AA, 9 CC) were studied after 12-hour abstinence as were 17 non-smokers (8 AA, 9 CC) matched by age, gender, years of education, and handedness. The AA and CC smoking groups were also matched for number of cigarettes smoked per day. Participants underwent morning fMRI scanning while viewing images of AA models and CC models who were either smoking (smoking cues) or engaging in everyday activities (neutral cues), interspersed with a fixation baseline period. There was a strong ethnicity X condition interaction among smokers in several brain regions identified a priori on the basis of prior cue-reactivity brain imaging studies.. AA smokers showed a greater increase in response to smoking (versus neutral) cues than CC smokers in the medial pre-frontal cortex, right lateral orbitofrontal cortex, and bilateral ventrolateral pre-frontal cortex. In smoking versus baseline contrasts, additional areas of greater activation were found in AA, including the right amygdala and left caudate nucleus. No significant differences in cue-elicited brain activation were found between AA and CC non-smokers. Although preliminary, these findings suggest that variation in brain activation in response to smoking cues smokers in may reflect fundamental differences in attention to smoking cues between AA and CC, which may in turn contribute to differences in effectiveness of nicotine dependence treatments among ethnic

populations. Okuyemi, S.K., Powell, J.N., Savage, C.R., Hall, S.B., Nolan, N., Holsen, L.M., McClernon, F.J., and Ahluwalia, J.S. Addiction Biology, 11, pp. 97-106, 2006.

Gender Differences Among Recreational Gamblers: Association With the Frequency of Alcohol Use

Marc Potenza and colleagues at Yale School of Medicine investigated the interactive effects of alcohol use and gender on health and gambling attitudes and behaviors in recreational gamblers. The Gambling Impact and Behavior Study surveyed by telephone 2,417 adults targeted to be representative of the U.S. adult population. Male and female recreational gamblers (n = 1,471) were stratified by frequency of alcohol use on measures of health and gambling. Significant Gender x Alcohol Use group interactions were observed such that moderate-to-high frequency alcohol consumption correlated with heavier gambling in men than in women, whereas such an association did not exist among abstinent or low frequency drinkers. There were few gender differences in the correlations between alcohol consumption and health. Future research should consider gender-related influences when examining alcohol use and gambling behaviors. Desai, R.A., Maciejewski, P.K., Pantalon, M.V., and Potenza, M.N. Psychology of Addictive Behaviors, 20, pp. 145-153, 2006.

Cue-Induced Stress Reduced Time To Relapse In Cocaine Dependent Patients

Rajita Sinha and associates at Yale School of Medicine presented patient specific image-provoking scripts to patients seeking treatment for cocaine dependence. Stress-inducing imagery was associated with earlier relapse compared to neutral imagery. The amount of cocaine used prior to treatment was also associated with time to relapse. While corticotropin and cortisol responses were induced by the stress imagery, they were not associated with time to relapse, but were associated with the amount of cocaine used when relapse did occur. By contrast, drug-cue-inducing imagery was not associated with either the relapse rate or the amount of cocaine used even though the craving it induced was correlated with craving induced by stress. Furthermore, corticotropin increases induced by stress cues was correlated with increases induced by drug cues. The same was true of cortisol. These data indicate that stress acts in different ways—directly to hasten relapse or indirectly on the HVA axis to influence drug-taking amounts. To some extent these results suggest that some parameters in treatment may be predictable by an individual's responses to stressors. Sinha, R., Garcia, M., Palikwal, P., Kreek, M.J., and Rounsaville, B.J. Archives of General Psychiatry, 63, pp. 324-331, 2006.

Physiological Responses To Psychological Stress During Early Abstinence From Smoking Predicts Early Relapse

While it is known that stress is associated with relapse, al 'Absi and colleagues at the University of Minnesota tried to define the effect by challenging treatment-seeking smokers 24 hours after abstinence with a "standard" public speaking test and psychological tasks and then measuring ACTH, (plasma) cortisol, blood pressure, affect, and withdrawal symptoms. Those who relapsed within a 4-week follow-up showed attenuated hormonal and cardiovascular responses to these stressors and had exaggerated withdrawal symptoms. These factors remained significant in stepwise regression analyses as well as analyses that included baseline smoking and psychological measures as co-variates. By understanding the physiological and psychological factors underlying relapse, better treatment strategies can be developed. al 'Absi, M., Hatsukami, D., and Davis, G.L. Psychopharmacology, 181, pp. 107-117, 2006.

Cognitive Deficits Were Found In Non-Clinically-Referred College Women Who Were Sexually Abused Prior To Age 18

Clinically-reported sexual abuse is associated with several disorders appearing in adutlthood including drug abuse. Teicher and colleagues at Mclean Hospital assessed cognitive effects in community-based subjects recruited by advertisement and assessed college women who endorsed at least three episodes of "forced contact sexual abuse" and were physically healthy on a number of cognitive tests. Some of the subjects had either current or past diagnoses of Major Depressive Disorder, Post-Traumatic Stress Disorder, or General Anxiety Disorder. Results showed that there were a constellation of deficits in some but not all tests. In particular, the abused group had a diminished capacity on a test requiring response inhibition, performed less well on the Math SAT tests (in spite of normal level verbal scores), and demonstrated memory deficits as a function of abuse duration. Navalta, C.P., Polcari, A., Webster, D.M., Boghossian, A., and Teicher, M.H. Journal of Neuropsychiatry and Clinical Neuroscience, 18(1), pp. 45-53, 2006.

P300, An Endophenotype Related Externalizing As A Possible Factor Underlying Several Disorders Including Substance Abuse

Iacono, McGue, and associates at the University of Minnesota determined, by principal components analysis of symptom counts from several assessments of their subjects, that "externalizing" was a strong common factor. They then assessed the P300 evoked potential from an oddball visual task that has been shown to be attenuated in subjects of alcohol-risk studies. The results showed that higher scores on the externalizing factor, reflecting greater severity and breadth of externalizing symptoms, were associated with smaller P300 amplitude. There was no higher loading on variables defining individual diagnostic variables supporting that the P300 endophenotype was related to a common neurobiological of all the disorders. The current belief based on the broad literature is that the attenuated evoked potential is related to a diminished capacity for neuronal inhibition which is associated with these disorders. It is suggested in light of these findings that this endophenotype be the target of future research as, for example, the associated genotype. Patrick, C.J., Bernt, E.M., Malone, S.M., Iacono, W.G., Krueger, R.F., and McGue, M. Psychophysiology, 43, pp. 84-92, 2006.

Neuropsychology and Neuropharmacology Of P3a And P3b

John Polich and James Criado of Scripps Institute reviewed literature supporting a distinction between the P3a and P3b subcomponents of the P300 evoked response potential (ERP). Abnormalities in the P300 have been suggested as biomarkers of the risk for substance abuse, and the P3a component has been suggested as a biomarker for relapse. The critical factor for eliciting P3a is how target/standard discrimination difficulty rather than novelty modulates task processing. The neural loci of P3a and P3b generation were sketched and a theoretical model was developed. P3a originates from stimulus-driven disruption of frontal attention engagement during task processing. P3b originates when temporal-parietal mechanisms process the stimulus information for memory storage. The neuropharmacological implications of this view are then outlined by evaluating how acute and chronic use of ethanol, marijuana, and nicotine affect P3a and P3b. The findings suggest that the circuit underlying ERP generation is influenced in different ways for acute intake and varies between chronic use levels across drugs. Theoretical implications are assessed. Polich J., and Criado J.R. International Journal of Psychophysiology 60, pp. 172-185, 2006.

Genes Contributed To The Covariance Between Conduct Disorder

And Dependence Vulnerability

Stallings and Hewitt in Crowley's group at Boulder's Institute for Behavioral Genetics examined the genetic, shared and non-shared environmental factors contributing to both conduct disorders and dependence vulnerability or to dependence vulnerability alone. The subjects were nearly 900 twin pairs encompassing all five groups—monozygotic males and females, dizygotic males and female, and dizygotic male/female pairs. Symptoms of both disorders were significantly heritable and all three factors contributed to the co-variation: genes contributed 35% of the phenotypic covariance, shared environment contributed 46%, and non-shared environment contributed the remaining 19%. Finally, it was noted that the etiology of the comorbidity was similar in males and females. Button, T.M.M., Hewitt, J.K., Rhee, S.H., Young, S.E., Corley, R.P., Stallings, M.C. Twin Research and Human Genetics, 9(1), pp. 38-45, 2006.

Abstinence From Cocaine Affects Sleep Suggestive of Insomnia

R. Malison, P. Morgan, and colleagues at Yale in collaboration with R. Stickgold and colleagues at Harvard assessed sleep, vigilance, and procedural learning in a 23-day inpatient study of self-administered cocaine and abstinence. The protocol provided for a test day of cocaine use followed in 4 or 17 days with three days of cocaine bingeing (or placebo). Polysomnography, EEG spectral analysis, and subjective measures were obtained throughout. Simple and vigilant response times were measured daily; procedural learning of a motor sequence was assessed on study days preceding or following cocaine binges. Results demonstrated that with sustained abstinence, chronic cocaine users exhibited decreased sleep, impaired vigilance and sleep-dependent procedural learning, and abnormal spectral activity, all of which were suggestive of chronic insomnia. By contrast, these same subjects reported improving sleep efficiency, apparently unaware of their dysregulated sleep in what the authors are calling "occult" insomnia. Morgan, P.T., Pace-Schott, E.F., Sahul, Z.H., Coric, V., Stickgold, R., and Malison, R.T. Drug and Alcohol Dependence, 82, pp. 238-249, 2006.

Gene Variants of the Dopa Decarboxylase (DDC) Gene Are Associated With Smoking Behavior

J.Gelernter and collaborators genotyped 18 SNPs in a region that included the DDC and flanking genes from families of either European or African American heritage in search of variants associated with measures of smoking. Several SNPs were significantly related in both EA and AA samples suggesting a link to nicotine dependence. The SNP with the most significant association is in the same intron as the splice site for a neuronal isoform of DDC. Whether this means that an alternatively spliced form of the gene is the link between DDC and nicotine dependence requires additional studies. This study confirms an earlier study by others linking this gene to nicotine dependence. Yu, Y., Panhuysen, C., Kranzler, H.R., Hesselbrock, V., Rounsaville, B., Weiss, R., Brady, K., Farrer, L.A., and Gelernter, J. Human Molecular Genetics, 15, pp. 2192-2199, 2006.

Haplotypes of the Neurotrophic Tyrosine Kinase Receptor 2 Gene (NTRK2) Are Significantly Associated With Nicotine Dependence

Li and associates selected NTRK2 for further study in association with smoking because it lies in a suggestive linkage region on chromosome 9 that they and others had found. European and African American samples were analyzed separately. Three SNPs showed significant association with measures of nicotine dependence in the European American group; only one was suggestive

in the African American group. Haplotype analyses with combinations of these SNPs were also significant in the EA sample. This study is believed to be the first to demonstrate the association of NTRK2 on nicotine dependence and suggest it is a biological candidate in its determination. Beuten, J., Ma, J.Z., Payne, T.J., Dupont, R.T., Lou, X.-Y., Crews, K.M., Elston, R.C., and Li, M.D. Biological Psychiatry, Epub ahead of print, doi:10.1016, 2006.

A Cognitive Neuroscience Perspective on Psychopathy: Evidence For Paralimbic System Dysfunction

Kent Kiehl of the Institute of Living reviewed studies of behavioral and cognitive changes associated with focal brain lesions or insults and results from psychophysiology, cognitive psychology and cognitive and affective neuroscience in health and psychopathy to formulate hypotheses regarding the brain regions implicated in psychopathy. There is a high degree of co-occurrence between psychopathy and substance abuse. Psychopathy is a complex personality disorder that includes interpersonal and affective traits such as glibness, lack of empathy, guilt or remorse, shallow affect, and irresponsibility, and behavioral characteristics such as impulsivity, poor behavioral control, and promiscuity. Much is known about the assessment of psychopathy, however, relatively little is understood about the relevant brain disturbances. The review illustrates that the brain regions implicated in psychopathy include the orbital frontal cortex, insula, anterior and posterior cingulate, amygdala, parahippocampal gyrus, and anterior superior temporal gyrus. The relevant functional neuroanatomy of psychopathy thus includes limbic and paralimbic structures that may be collectively termed 'the paralimbic system'. The paralimbic system dysfunction model of psychopathy is discussed as it relates to the extant literature on psychopathy. Kiehl, K.A. Psychiatry Research 142, pp. 107-128, 2006.

Perfusion fMRI For Measurement of Continuous Changes In Neural Activity With Learning

John Detre and colleagues at the University of Pennsylvania examined whether arterial spin labeled (ASL) perfusion MRI can be used to detect continuous, gradual changes in neural activity. Unlike BOLD imaging, the perfusion signal is stable over long time-scales, allowing for accurate assessment of continuous performance. In addition, perfusion fMRI provides an absolute measure of blood flow so signal changes can be interpreted without reference to a baseline. The task we used was the serial response time task, a sequence-learning task. There were reliable correlations between performance improvements and decreases in blood flow in premotor cortex and the inferior parietal lobe, supporting the model that learning procedures that increase efficiency of processing will be reflected in lower metabolic needs in tissues that support such processes. More generally, the results show that perfusion fMRI may be applied to the study of mental operations that produce gradual changes in neural activity, such as cue-elicited craving. Olson, I.R., Rao, H.Y., Moore, K.S., Wang, J.J., Detre, J.A., and Aguirre, G.K. Brain and Cognition, 60, pp. 262-271, 2006.

Functional Reintegration of Prefrontal Neural Networks For Enhancing Recovery After Brain Injury

Mark D'Esposito and colleagues at the University of California, Berkeley describe approaches to cognitive training that are hypothesized to specifically enhance PFC function. The training was based on a theoretical framework regarding the effects of training on the functional integration of processes across distributed networks of brain regions. Functions of the prefrontal cortex (PFC) are fundamental to learning and rehabilitation after brain injuries, but

the PFC is particularly vulnerable to trauma and has been suggested to be dysfunctional in substance abusers. Specific outcome measurements that may be used to test these hypotheses in clinical trials are proposed. This neural network-level approach may guide cognitive rehabilitation and facilitate development of adjunctive biologic treatments to enhance the effects of training. Chen, A.J.W., Abrams, G.M., and D'Esposito, M. Journal of Head Trauma Rehabilitation, 21, pp. 107-118, 2006.

A Functional Magnetic Resonance Imaging Study of the Effects of Pergolide, A Dopamine Receptor Agonist, on Component Processes of Working Memory

Mark D'Esposito and colleagues at the University of California, Berkeley tested the effects of the mixed D1-D2 dopamine receptor agonist pergolide on component processes of human working memory using functional magnetic resonance imaging (fMRI). Working memory is dependent on a network of prefrontal and posterior cortical regions. An event-related trial design allowed separation of the effects on encoding, maintenance, and retrieval processes. Subjects were tested with spatial and object memoranda to investigate modality-specific effects of dopaminergic stimulation. Baseline working memory capacity was also measured as previous studies have shown that effects of dopamine agonists vary with working memory span. Pergolide improved reaction time for high-span subjects and impaired reaction time for low-span subjects. This span-dependent change in behavior was accompanied by span-dependent changes in delay-related activity in the premotor cortex. Modality-specific effects of pergolide were only found only during the response period. Pergolide increased activity for spatial memoranda and decreased activity for object memoranda in task-related regions including the prefrontal and parietal cortices. These findings may provide a framework to investigate dopamine related alternation in working memory function associated with use of illicit drugs that act through the dopaminergic system. Gibbs, S.E.B., D'Esposito, M. Neuroscience, 139, pp. 359-371, 2006.

Peripheral Blood Pressure Changes Induced By Dobutamine Do Not Alter BOLD

Si-Jiang Li and colleagues at the Medical College of Wisconsin investigated whether peripheral blood pressure changes induced by pharmacological agents could independently produce a change in the blood oxygenation level-dependent (BOLD) fMRI signal, resulting in difficulties distinguishing or interpreting drug-induced neural activations. Cocaine-dependent subjects were administered intravenous dobutamine, a beta-adrenergic receptor agonist that does not cross the blood-brain barrier, to increase the mean arterial blood pressure (MABP), while examining the effects of MABP changes on the BOLD fMRI signal. Dobutamine infusion significantly increased the MABP from 93.8 mm Hg to 106 +/- 12 mm Hg, but did not produce a significant change in the global BOLD signal. However, a few voxels in the anterior cingulate did exhibit BOLD signal changes that paralleled the changes in blood pressure (BP). Our observations support the conclusion that following the infusion of psychoactive agents, brain BOLD signals accurately reflect neuronal activity, even in the face of relatively large peripheral cardiovascular effects that transiently increase systemic BP. Liu, H., Rainey, C., Lauer, K.K., Piacentine, L., Bloom, A., Risinger, R., Ward, B.D., Stein, E., and Li, S.J. Neuroimage, 30, pp. 745-752, 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Epidemiology and Etiology Research

Individual Differences in Childhood Neurobehavior Disinhibition Predict Decision to Desist Substance Use during Adolescence and Substance Use Disorder in Young Adulthood

Genetic, physiological and psychological investigations have demonstrated that deficient inhibitory regulation amplifies the risk for substance use disorder (SUD). This study extends this line of research by determining the association between childhood neurobehavior disinhibition and decision to desist substance use following prevention intervention during adolescence. The sample consisted of 302 boys who were evaluated at ages 10-12, 12-14, 16, and 19. Results indicated that childhood neurobehavior disinhibition negatively co varied with decision to desist substance use during adolescence. These two variables predicted acceleration of drug consumption frequency during adolescence and DSM-IV diagnosis of SUD by age 19. Decision to desist drug use did not mediate the association between neurobehavior disinhibition and substance use/SUD. The findings indicate that substance abuse prevention would be potentiated by ameliorating childhood neurobehavior disinhibition. Kirisci, L., Tarter, R., Reynolds, M., and Vanyukov, M. Individual Differences in Childhood Neurobehavior Disinhibition Predict Decision to Desist Substance use during Adolescence and Substance use Disorder in Young Adulthood: a Prospective Study. Addict Behav, 31(4), pp. 686-696, 2006.

Misuse and Diversion of ADHD Medications

Little is known about the risks and characteristics of attention-deficit/hyperactivity disorder (ADHD) patients who misuse or divert their stimulant medications. As part of a 10-year longitudinal study of youths with ADHD, the authors evaluated medication diversion or misuse at the last follow-up period. Data for this study were drawn from 98 subjects receiving psychotropic medications, with a mean age of 20.8 years; of these, 55 (56%) had ADHD and the other 43 (44%) were treated as controls medicated for other conditions. Structured psychiatric interviews for diagnosis and a self-report questionnaire regarding medication use were employed. The authors found that 11% of the ADHD group reported selling their medications compared with no subjects in the control group. An additional 22% of the ADHD group reported misusing their medications compared with 5% of the control subjects and that those with conduct or substance use disorders accounted for the misuse and diversion. A minority of subjects reported escalating their doses and concomitant use with alcohol and drugs. Thus, the majority of ADHD individuals in this clinical sample, particularly those without conduct or substance use disorders, report using their medications appropriately. These findings suggest a need to monitor medication use in ADHD individuals with conduct and/or substance use disorders and to consider

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selecting agents with a low likelihood of diversion or misuse in this group. Wilens, T., Gignac, M., Swezey, A., Monuteaux, M., and Biederman, J. Characteristics of Adolescents and Young Adults with ADHD who Divert or Misuse Their Prescribed Medications. J Am Acad Child Adolesc Psychiatry, 45(4), pp. 408-414, 2006.

Application of Item Response Theory to Quantify Substance Use Disorder Severity

The present investigation had two main goals: (1) Determine whether binary substance use disorder (SUD) diagnoses are indicators of a unidimensional trait indexing severity of disorder; and, (2) demonstrate the predictive, concurrent and construct validity of the SUD severity scale. A sample of boys (n=288) and their biological parents (n=496) were administered structured diagnostic interviews to diagnose SUD. Item response theory (IRT) was applied to determine whether the diagnoses are indicators of a unidimensional trait. The score on this scale was correlated with substance use behavior, violence, treatment history, risky sex, and social adjustment. SUD diagnoses are indicators of a unidimensional latent trait. Maternal and paternal SUD severity predicted son's SUD severity at age 19. The score on the SUD severity scale correlated with drug use frequency, number of different drugs used in lifetime, treatment seeking, illegal behavior, social maladjustment, and risky sex. In conclusion, SUD can be quantified on an interval scale indexing severity of disorder. Kirisci, L., Tarter, R., Vanyukov, M., Martin, C., Mezzich, A., and Brown, S. Application of Item Response Theory to Quantify Substance Use Disorder Severity. Addict Behav, 31(6), pp. 1035-1049, 2006.

Is There Epidemiological Evidence to Support the Idea that a Cocaine Dependence Syndrome Emerges Soon after Onset of Cocaine Use?

The present study uses latent class methods and multiple regression to shed light on hypothesized cocaine dependence syndromes experienced by community residents who initiated cocaine use within 24 months of survey assessment and explores possible variation in risk. Identified within public use data files from the United States National Household Surveys on Drug Abuse (NHSDA), and with assessments completed between 1995 and 1998, the study sample consists of 927 recent-onset cocaine users, defined as having initiated cocaine use no more than 24 months prior to assessment (approximate median elapsed time since onset of use approximately 12-13 months). The NHSDA included items to assess seven clinical features often associated with cocaine dependence, which were used in latent class modeling. Empirically derived latent classes, in conjunction with prior theory, tend to support a three-class solution, according to which 4% of recent-onset users are members of a class that resembles the DSM-IV cocaine dependence syndrome (mean: 5.4 clinical features (CF)); 16% might be in a cocaine dependence prodrome (mean: 2.4 CF); 80% of recent-onset cocaine users had few or no clinical features (mean<1 CF). Results from latent class regressions indicate that susceptibility to rapid transition from first cocaine use to onset of the LCA-assigned cocaine dependence syndrome might depend upon whether the user starts smoking crack-cocaine and, independently, age at first cocaine use. Reboussin, B.A., and Anthony, J. Is there Epidemiological Evidence to Support the Idea that a Cocaine Dependence Syndrome Emerges Soon after Onset of Cocaine Use? Neuropsychopharmacology, 31, pp. 2055-2064, 2006.

Is Prenatal Smoking Associated with a Developmental Pattern of Conduct Problems in Young Boys

Prenatal smoking is robustly associated with increased risk of conduct problems

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in offspring. This study used a developmental framework to examine the association of exposure with (1) oppositional defiant disorder and attention-deficit/hyperactivity disorder in young boys and (2) the pattern of delinquent behavior at adolescence. Using diagnostic measures and repeated measures of delinquency, the researchers compare exposed and non-exposed boys from the youngest cohort of the Pittsburgh Youth Study (N = 448). Exposed boys were significantly more likely to (1) develop oppositional defiant disorder and comorbid oppositional defiant disorder-attention-deficit/hyperactivity disorder but not attention-deficit/hyperactivity disorder alone and (2) to have an earlier onset of significant delinquent behavior. The early emergence and developmental coherence of exposure-related conduct problems is striking and is consistent with a behavioral teratological model. Phenotypically, exposure-related conduct problems appear to be characterized by socially resistant and impulsively aggressive behavior. Whether prenatal smoking plays an etiological role in or is a risk marker for the development of conduct problems, exposed offspring are at increased risk of an early-starter pathway to conduct problems. Wakschlag, L., Pickett, K., Kasza, K., and Loeber, R. Is Prenatal Smoking Associated with a Developmental Pattern of Conduct Problems in Young Boys? J Am Acad Child Adolesc Psychiatry, 45(4), pp. 461-470, 2006. The Growth in Marijuana Use among American Youths During the 1990s and the Extent of Blunt Smoking Marijuana use among American youths and young adults increased substantially during the 1990s. This paper reviews that trend using data collected 1979-2003 by the National Survey on Drug Use and Health (NSDUH). The data suggest that the increase in marijuana use started first among persons age 12-20. Among 18-20 year-olds, the increase started earlier among whites and blacks than Hispanics, among males before females, and surprisingly in areas that are not part of an MSA as opposed to those with a population in excess of a million. Much of the increase in marijuana use could have been attributable to the growing popularity of blunts. Starting in 2000, the NSDUH explicitly asked youth's age 12-17 (but not older respondents) about smoking blunts. Of the 9% of youths who reported past-30-day use of marijuana 2000-03, more than half reported smoking blunts. On the other hand, the data also indicate that blunts have not fully supplanted other ways that youths consume marijuana. Blunts were more common among youths that were black, older, male, and from metropolitan areas. Many blunt smokers reported they had not used marijuana, which suggests that they did not define smoking blunts as marijuana use. Even fewer reported that they had used cigars, suggesting they did not define smoking blunts as cigar use. Golub, A., Johnson, B., and Dunlap, E. The Growth in Marijuana Use Among American Youths During the 1990s and the Extent of Blunt Smoking. J Ethn Subst Abuse, 4(3-4), pp. 1-21, 2005.

Childhood and Adolescent Antecedents of Drug and Alcohol Problems: A Longitudinal Study

Despite the serious health and economic consequences of drug and alcohol abuse and dependence, few studies have prospectively examined the etiology of this problem in non-clinical populations. This longitudinal study examines childhood and adolescent antecedents of drug and alcohol problems in adulthood among an African American cohort (n=1242; 51% female) from Woodlawn, a neighborhood in Chicago. The participants were followed from age 6 to 32 years, and data were collected in first grade, adolescence, and adulthood. Structural equation modeling showed that, for both males and females, educational attainment was directly associated with a reduced risk for substance use problems. For males, first grade shyness was directly associated with a reduced risk of substance use problems, and adolescent substance use was directly associated with an increased risk. First grade aggression, low family socioeconomic status (SES), and low school bonds were indirectly associated with substance use problems for both males and females. For males, first grade underachievement had an indirect effect, and, for females,

first grade shyness and strong parental supervision had indirect effects. This study is among the first to identify life course trajectories to substance use problems among an African American, community-based population. These results help to identify the targets and timing of interventions that may help to reduce the risk of drug and alcohol problems in adulthood. Fothergill, K., and Ensminger, M. Childhood and Adolescent Antecedents of Drug and Alcohol Problems: A Longitudinal Study. Drug Alcohol Depend, 82(1), pp. 61-76, 2006.

Eligibility for Treatment of Hepatitis C Virus Infection among Young IDUs in three US Cities

Researchers assessed the eligibility for HCV treatment of 404 injection drug users aged 18-35 who tested positive for hepatitis C virus (HCV) RNA. They found that 96% had conditions that represent potentially unwarranted contraindications for HCV treatment, including recent use of injecting drugs (89%), moderate-to-severe depression (69%), and heavy use of alcohol (65%). These findings suggest that restrictive eligibility criteria for HCV treatment would deny it to a large proportion of individuals who would potentially have high benefit from it. A high prevalence of conditions that represent potentially unwarranted contraindications for anti-HCV treatment. In particular, most subjects (89%) had injected drugs recently, and 63% had symptoms of either depression or problem drinking. Thus, the application of multiple exclusion criteria to this population may deny treatment to the vast majority—perhaps 96%—of IDUs with HCV infection. Hagan, H., Latka, M., Campbell, J., Golub, E., Garfein, R., Thomas, D., Kapadia, F., Strathdee, S., and Strathdee, S. Eligibility for Treatment of Hepatitis C Virus Infection Among Young Injection Drug Users in 3 US cities. Clin Infect Dis, 42(5), pp. 669-772, 2006.

Environmental Disorder Explains Association between Income Inequality and Risk of Fatal Overdose

Accidental drug overdose is a substantial cause of mortality for drug users. The investigators hypothesize that the level of environmental disorder, the level of police activity, and the quality of the built environment in a neighborhood mediate this association. Data from the New York City (NYC) Mayor's Management Report, the NYC Police Department, and the NYC Housing and Vacancy Survey were used to define constructs for the level of environmental disorder, the level of police activity and the quality of the built environment, respectively. In multivariable models the odds of death due to drug overdose in neighborhoods in the top decile of income inequality compared to the most equitable neighborhoods decreased from 1.63 to 1.12 when adjusting for the three potential mediators. Path analyses show that the association between income inequality and the rate of drug overdose mortality was primarily explained by an indirect effect through the level of environmental disorder and the quality of the built environment in a neighborhood. Implications of these findings for the reduction of drug overdose mortality associated with the distribution of income are discussed. Nandi, A., Galea, S., Ahern, J., Bucciarelli, A., Vlahov, D., and Tardiff, K. What Explains the Association between Neighborhood-level Income Inequality and the Risk of Fatal Overdose in New York City? Soc Sci Med, 63(3), pp. 662-674, 2006.

Risk Factors for HIV Infection among Men who have Sex with Men

Risk factors for HIV acquisition were examined in a recent cohort of men who have sex with men (MSM). A longitudinal analysis was conducted of 4295 HIV-negative MSM enrolled in a randomized behavioral intervention trial conducted in six US cities. MSM were enrolled and assessed for HIV infection and risk behaviors semi-annually, up to 48 months. In multivariate analysis, men

reporting four or more male sex partners, unprotected receptive anal intercourse with any HIV serostatus partners and unprotected insertive anal intercourse with HIV-positive partners were found to be at increased risk of HIV infection, as were those reporting amphetamine or heavy alcohol use and alcohol or drug use before sex. Some depression symptoms and occurrence of gonorrhea also were independently associated with HIV infection. The attributable fractions of high number of male partners, use of alcohol or drugs before sex, and unprotected receptive anal intercourse with unknown status partners and the same with presumed negative partners accounted for 32.3, 29.0, 28.4 and 21.6% of infections, respectively. These findings indicate the importance of strategies to identify men in need. Interventions are needed to help men reduce their number of sexual partners, occurrences of unprotected anal intercourse, alcohol or drug use before sex, and address other mental health issues. Koblin, Husnik, Colfax, Huang, Madison, Mayer, Barresi, Coates, Chesney, and Buchbinder. Risk Factors for HIV Infection among Men who have Sex with Men. AIDS, 20(5), pp. 731-739, 2006.

Estimates of IDU at the National and Local Level in Developing and Transitional Countries, and Gender and Age Distribution

This study sought to update available national and sub national estimates of IDUs in developing/transitional countries, and provide indicative estimates of gender and age distribution. Literature reviews were conducted of both "grey" and published literature, including updates from previously reported estimates, on estimates of IDU population and data sources giving age and gender breakdowns. The scope area was developing/transitional countries and the reference period was 1998-2005. Estimates of IDU numbers were available in 105 countries and 243 sub national areas. The largest IDU populations were reported from Brazil, China, India, and Russia. Sub national areas with the largest IDU populations (35,000-79,000) were: Warsaw (Poland); Barnadul, Irtkustk, Nizhny-Novgorod, Penza, Voronez, St. Petersburg, and Volgograd (Russia); New Delhi and Mumbai (India); Jakarta (Indonesia), and Bangkok (Thailand). By region, Eastern Europe and Central Asia have the largest IDU prevalence, followed by Asia and Pacific. In the Middle East and Africa the median value equals 0.2% and in Latin America and the Caribbean, 0.12%. Greater dispersion of national IDU prevalence's was observed in Eastern Europe and Central Asia, and Asia and Pacific. Sub national areas with the highest IDU prevalence among adults (8-14.9%) were Shymkent (Kazakhstan), Balti (Moldova), Astrakhan, Barnadul, Irtkustk, Khabarovsk, Kaliningrad, Naberezhnyje Chelny, Penza, Togliatti, Volgograd, Voronez, and Yaroslavl (Russia), Dushanbe (Tajikistan), Ashgabad (Turkmenistan), Ivano-Frankivsk and Pavlograd (Ukraine) and Imphal, Manipur (India). Data on the IDU age/gender distributions are scarce or unavailable for many countries. The proportion of IDU men was 70%-90% in Eastern Europe and Central Asia, and there was a marked absence of data on women outside this region. In conclusion, data on IDU prevalence available to national and international policymakers are of an unknown and probably yet to be tested quality. This study provides baseline figures, but steps need to be taken to improve the reporting and assessment of these critical data. Aceijas, C., Friedman, S., Cooper, H., Wiessing, L., Stimson, G., and Hickman, M. Estimates of Injecting Drug Users at the National and Local Level in Developing and Transitional Countries, and Gender and Age Distribution. Sex Transm Infect, 82(3), pp. 10-17, 2006.

Non-fatal Overdose and Subsequent Drug Treatment among Injection Drug Users

Researchers interviewed 924 injection drug users (IDUs) in Baltimore, Maryland to characterize overdose events and determine the circumstances under which they lead to drug treatment. Overall, 366 (39.7%) reported at

least one non-fatal drug overdose. Most (96.2%) used heroin on the day of their last overdose and almost half (42.6%) used heroin and alcohol but few (4.1%) used tranquilizers or benzodiazepines. Five percent were in drug treatment when the overdose occurred and 7.1% had been incarcerated 2 weeks prior. One in four IDUs (26.2%) sought drug treatment within 30 days after their last overdose of whom 75% enrolled. Speaking with someone about drug treatment after the overdose was associated with treatment seeking (AOR 5.22; 95% CI: 3.12, 8.71). Family members were the most commonly cited source of treatment information (53.7%) but only those who spoke with spouses, crisis counselors and hospital staff were more likely to seek treatment. Not being ready for treatment (69.6%) and not viewing drug use as a problem (30.7%) were the most common reasons for not seeking treatment and being placed on a waiting list was the most common reason for not subsequently enrolling in treatment (66.7%). Of the IDUs treated by emergency medical technicians, ER staff or hospital staff, only 17.3%, 26.2% and 43.2% reported getting drug treatment information from those sources, respectively. Interventions that provide drug treatment information and enhance motivation for treatment in the medical setting and policies that reduce barriers to treatment entry among motivated drug users are recommended. Pollini, R., McCall, L., Mehta, S., Vlahov, D., and Strathdee, S. Non-fatal Overdose and Subsequent Drug Treatment Among Injection Drug Users. Drug Alcohol Depend, 83(2), pp. 104-110, 2006.

Mediators of the Stress-substance-use Relationship in Urban Male Adolescents

Exposure to chronic or severe acute stressors throughout the lifespan has been linked with numerous negative behavioral, emotional, cognitive, and physical consequences. Adolescence is considered to be a particularly vulnerable period given that the brain is experiencing dramatic developmental change during this time. The present study examined a sample of adolescents (N=125) considered to be at high risk for stress exposures and drug use by virtue of their environment and low income levels to identify possible neurocognitive (i.e., impulsivity, delay of gratification, emotional perception, and risky decision-making) and social competency mechanisms that may mediate this relationship. Using Mplus, a mediational model was tested using full information maximum likelihood estimates. Risky decision-making and poor social competency skills were related to previous stressful experiences; however, only social competencies mediated the effect of stressors on reports of past year marijuana, alcohol, and poly-drug use. As such, stress appears to exert its negative impact through alterations in abilities to generate and execute pro-social decisions and behaviors. Interventions that directly address the effects of stress on social competencies may be especially important for children who have experienced adversity including those exposed to parental divorce, parental psychopathology, neglect or abuse, parental death, and poverty. Fishbein, D., Herman-Stahl, M., Eldreth, D., Paschall, M., Hyde, C., Hubal, R., Hubbard, S., Williams, J., and Ialongo, N. Mediators of the Stress-Substance-Use Relationship in Urban Male Adolescents. Prev Sci, 7(2), pp. 113-126, 2006.

Predictors of Contact Difficulty and Refusal in a Longitudinal Study

Attrition presents a serious problem to researchers collecting longitudinal data. Participant loss threatens both the internal and external validity of research findings. This study sought to examine predictors related to contact difficulty and refusals in a longitudinal study. Data for this paper came from the Developmental Trends Study, a longitudinal study investigating the development of disruptive behaviour disorders in a sample of 177 clinic-referred boys. Annual follow-up assessments were conducted, ages for the

periods examined ranged from 11 to 19 years. The predictor domains during project years 1-4 included demographics, child functioning, parental functioning, parenting skills and participant dispersion. The results indicated that participant's older age, low socioeconomic status, the presence of callous and un-emotional behaviours, and having a father with antisocial personality disorder predicted contact difficulty, while participant's older age, living in a rural environment and attention deficit hyperactivity disorder were predictive of refusals. Participant dispersion was not significantly related to either contact difficulty or refusal status. Investigating a broader range of variables may better allow researchers to identify participants who may be at risk of attrition. Early identification of 'difficult' participants enables development of retention strategies to minimize attrition. Cotter, R., Burke, J., Loeber, R., and Mutchka, J. Predictors of Contact Difficulty and Refusal in a Longitudinal Study. Crim Behav Ment Health, 15(2), pp. 126-137, 2005.

Use of Structural Equation Modeling in Analysis of MRI Data

Peter Bentler's group at UCLA reported a new application of structural equation modeling (SEM to analysis of data from brain imaging studies. The ultimate goal of brain connectivity studies is to propose, test, modify, and compare certain directional brain pathways. Path analysis or SEM is an ideal statistical method for such studies. In this work, the authors propose a two-stage unified SEM plus GLM (General Linear Model) approach for the analysis of multi-subject, multivariate functional magnetic resonance imaging (fMRI) time series data with subject-level covariates. In Stage 1, the fMRI multivariate time series are analyzed for each subject individually via a unified SEM model by combining longitudinal pathways represented by a multivariate autoregressive (MAR) model, and contemporaneous pathways represented by a conventional SEM. In Stage 2, the resulting subject-level path coefficients are merged with subject-level covariates such as gender, age, IQ, etc., to examine the impact of these covariates on effective connectivity via a GLM. This approach is exemplified via the analysis of an fMRI visual attention experiment. Furthermore, the significant path network from the unified SEM analysis is compared to that from a conventional SEM analysis without incorporating the longitudinal information as well as that from a Dynamic Causal Modeling (DCM) approach. Hum Brain Mapping 2006 (prepublication article online). (c) 2006 Wiley-Liss, Inc. Kim, Zhu, Chang, Bentler, and Ernst. Unified Structural Equation Modeling Approach for the Analysis of Multi-subject, Multivariate Functional MRI Data. Hum Brain Mapp, published online May 22, 2006.

Impact of Marriage on HIV Risk Behaviors

Studies among normative samples generally demonstrate a positive impact of marriage on health behaviors and other related attitudes. This study used a multilevel latent variable approach to examine the impact of marriage on HIV/AIDS risk behaviors and attitudes among impoverished, highly stressed, homeless couples, many with severe substance abuse problems. A multilevel analysis of 368 high-risk sexually intimate married and unmarried heterosexual couples assessed individual and couple-level effects on social support, substance use problems, HIV/AIDS knowledge, perceived HIV/AIDS risk, needle sharing, condom use, multiple sex partners, and HIV/AIDS testing. More variance was explained in the protective and risk variables by couple-level latent variable predictors than by individual latent variable predictors, although some gender effects were found (e.g., more alcohol problems among men). The couple-level variable of marriage predicted lower perceived risk, less deviant social support, and fewer sex partners but predicted more needle sharing. Stein, Nyamathi, Ullman, and Bentler. Impact of Marriage on HIV/AIDS Risk Behaviors Among Impoverished, At-Risk Couples: A Multilevel Latent Variable Approach. AIDS Behav, published online February 3, 2006.

Probable Cigarette Dependence, PTSD, and Depression after an Urban Disaster

Disaster exposure may exacerbate psychopathology and substance-related disorders. Four months after September 11, 2001, using random-digit dialing to contact a representative sample of adults (N = 2001) living in New York City, the researchers assessed cigarette smoking and symptoms of probable cigarette dependence using measures from the National Survey on Drug Use and Health. A total of 36.8% of smokers reported increased cigarette use; 10.4% of respondents reported three or more symptoms of cigarette dependence and were considered cases of probable cigarette dependence based on DSM-IV criteria. Cases were more likely to report an increase in cigarette use since September 11 than non-cases (69.4% among cases vs. 2.2% among non-cases, $p < 0.001$). Cases were more likely to have probable posttraumatic stress disorder (PTSD) and depression than non-cases (18.1% vs. 5.7% for PTSD, $p < 0.001$; 23.6% vs. 6.0% for depression, $p < 0.001$). Increased cigarette use since September 11 was associated with probable PTSD among cases (23.4% vs. 6.4%, $p = 0.011$) and non-cases (15.1% vs. 5.5%, $p = 0.034$) but was associated with probable depression only among cases of probable cigarette dependence (28.3% vs. 13.3%, $p = 0.027$). This study showed the co-occurrence of probable cigarette dependence with increased cigarette use and the co-occurrence of probable cigarette dependence with probable PTSD and depression after September 11. Nandi, A., Galea, S., Ahern, J., and Vlahov, D. Probable Cigarette Dependence, PTSD, and Depression after an Urban Disaster: Results from a Population Survey of New York City Residents 4 Months after September 11, 2001. Psychiatry, 68(4), pp. 299-310, 2005.

Perspectives on Health among Adult Users of Illicit Stimulant Drugs in Rural

Although the non-medical use of stimulant drugs such as cocaine and methamphetamine is increasingly common in many rural areas of the United States, little is known about the health beliefs of people who use these drugs. This research describes illicit stimulant drug users' views on health and health-related concepts that may affect their utilization of health care services. A respondent-driven sampling plan was used to recruit 249 not-in-treatment, non-medical stimulant drug users who were residing in 3 rural counties in west central Ohio. A structured questionnaire administered by trained interviewers was used to collect information on a range of topics, including current drug use, self-reported health status, perceived need for substance abuse treatment, and beliefs about health and health services. Participants reported using a wide variety of drugs non-medically, some by injection. Alcohol and marijuana were the most commonly used drugs in the 30 days prior to the interview. Powder cocaine was used by 72.3% of the sample, crack by 68.3%, and methamphetamine by 29.7%. Fair or poor health status was reported by 41.3% of the participants. Only 20.9% of the sample felt they needed drug abuse treatment. Less than one third of the sample reported that they would feel comfortable talking to a physician about their drug use, and 65.1% said they preferred taking care of their problems without getting professional help. These findings show that stimulant drug users in rural Ohio are involved with a range of substances and hold health beliefs that may impede health services utilization. Siegal, H., Draus, P., Carlson, R., Falck, R., and Wang, J. Perspectives on Health Among Adult Users of Illicit Stimulant Drugs in Rural Ohio. J Rural Health, 22(2), pp. 169-173, 2006.

Estimated Numbers of Men and Women Infected with HIV/AIDS in Tijuana, Mexico

Tijuana, Mexico, just south of San Diego, California, is located by the busiest land border crossing in the world. Although UNAIDS considers Mexico to be a country of "low prevalence, high risk," recent surveillance data among sentinel populations in Tijuana suggests HIV prevalence is increasing. The aim of this study was to estimate the number of men and women aged 15 to 49 years infected with HIV in Tijuana. Gender and age-specific estimates of the Tijuana population were obtained from the 2000 Mexican census. Population and HIV prevalence estimates for at-risk groups were obtained from published reports, community based studies, and data from the Centro Nacional para la Prevención y Control del VIH/SIDA (CENSIDA). Age-specific fertility rates for Mexico were used to derive the number of low and high-risk pregnant women. Numbers of HIV-positive men and women were estimated for each at-risk group and then aggregated. A high growth scenario based on current HIV prevalence and a conservative, low growth estimate were determined. A total of 686,600 men and women in Tijuana were aged 15 to 49 years at the time of the 2000 census. Considering both scenarios, the number of infected persons ranged from 1,803 to 5,472 (HIV prevalence: 0.26 to 0.80%). The majority of these persons were men (>70%). The largest number of infected persons were MSM (N = 1,146 to 3,300) and IDUs (N = 147 to 650). Data from this study suggest that up to one in every 125 persons aged 15-49 years in Tijuana is HIV-infected. Interventions to reduce ongoing spread of HIV are urgently needed. Brouwer, K., Strathdee, S., Magis-Rodr'guez, C., Bravo-Garc'a, E., Gayet, C., Patterson, T., Bertozzi, S., and Hogg, R. Estimated Numbers of Men and Women Infected with HIV/AIDS in Tijuana, Mexico. J Urban Health, 83(2), pp. 299-307, 2006.

Why Some Generations are More Violent than Others

Empirical longitudinal studies assessing why community-level violence rates change over time are lacking. Despite a wide-ranging literature, questions remain as to whether changes over time are due to factors occurring in specific periods (period effects) or individuals in successive cohorts (cohort effect). The objective was to assess the relative contribution of age, period, and cohort effects on violence trends. The authors assessed differences in self-reported violence between two cohorts of males (n = 1,009) from the Pittsburgh Youth Study, which tracked delinquency and risk factors from 1987 to 2000. The youngest cohort were aged 7-19 years, and the oldest cohort were aged 13-25 years. Yearly measures of violence were examined through generalized estimating equations. The oldest cohort reported higher levels of violence even after adjustment for age and major individual-level risk factors (odds ratio (OR) = 1.45, 95% confidence interval (CI): 1.17, 1.81) such as gang participation and drug dealing, as well as community-level factors (OR = 2.16, 95% CI: 1.65, 2.82). However, when period effects were included, cohort differences were rendered insignificant (OR = 1.23, 95% CI: 0.78, 1.94). The authors conclude that differences in the rates of violence over time may be attributed to changing social factors (period effects) and not to differences between the individuals (cohort effect) of cohorts. Fabio, A., Loeber, R., Balasubramani, G., Roth, J., Fu, W., and Farrington, D. Why Some Generations Are More Violent than Others: Assessment of Age, Period, and Cohort Effects. Am J Epidemiol, 164(2), pp. 151-160, 2006.

Psychiatric Disorders and Their Correlates among Young Adult MDMA Users in Ohio

This study describes the lifetime prevalence, correlates, and age of onset of selected psychiatric disorders among a community sample of MDMA users (n = 402), aged 18 to 30, in Ohio. Participants responded to interviewer-administered questionnaires, including sections of the computerized Diagnostic Interview Schedule for DSM-IV. Fifty-five percent of the sample had at least one lifetime disorder, with major depression (35.3%) and antisocial personality

disorder (ASPD) (25.4%) the most common. Proportionately more women were diagnosed with depression, generalized anxiety disorder, and posttraumatic stress disorder (PTSD), while proportionately more men were diagnosed with ASPD. Proportionately more non-White participants had attention deficit/hyperactivity disorder (AD/HD). Higher levels of education were associated with proportionately less PTSD, ASPD, and AD/HD. Higher frequencies of MDMA use were associated with proportionately more ASPD and AD/HD. Comparing the age of first MDMA use with the age of onset for selected psychiatric disorders revealed that for most participants disorders preceded use. Multivariate analysis revealed participants with more than a high school education were less likely to have experienced a lifetime disorder, while those who had used MDMA more than 50 times were more likely. Variations in the prevalence of psychiatric disorders have practical implications for drug abuse prevention and treatment programs. Falck, R., Carlson, R., Wang, J., and Siegal, H. Psychiatric Disorders and Their Correlates Among Young Adult MDMA Users in Ohio. J Psychoactive Drugs, 38(1), pp. 19-29, 2006.

HIV/AIDS and Injection Drug Use in the Neighborhoods of Dar es Salaam, Tanzania

This study examines the intersection between needle-sharing practices and HIV recovered from used syringes collected from 73 heroin injection drug users (IDUs) in Dar es Salaam, Tanzania, between October 2003 and January 2004. To extract blood residue, syringes were flushed and 10 micro-liters of solution mixed with 120 microliters of a latex solution was placed on a Capillus HIV-1/2 slide. Thirty-five (57%) of the useable syringes tested positive for HIV antibodies. Results varied significantly: 90% of syringes tested HIV positive in a mixed-income neighborhood 2 kilometers from the city center: 0% of syringes tested HIV positive in the outlying areas. In addition, semi structured interviews were conducted with 51 IDUs. The interviews were content coded, and codes were collapsed into emergent themes regarding syringe-use practices. Injecting is a recent practice, particularly among heroin users in neighborhoods far from the city center. Sharing syringes has resulted in a high proportion of used syringes containing HIV-positive blood residue. Geographic distance is an indicator of recent adoption of IDU in neighborhoods and correlates strongly with the distribution of syringes containing HIV-positive blood residue. McCurdy, S., Ross, M., Kilonzo, G., Leshabari, M., and Williams, M. HIV/AIDS and Injection Drug Use in the Neighborhoods of Dar es Salaam, Tanzania. Drug Alcohol Depend, 82(1), pp. S23-S27, 2006.

Correlates of Rural Methamphetamine and Cocaine Users: Results from a Multi-state Community Study

Use and production of methamphetamine (MA) has dramatically increased in the United States, especially in rural areas, with concomitant burdens on the treatment and criminal justice systems. However, cocaine is also widely used in many rural areas. The purpose of this article is to contrast MA and cocaine users in three geographically distinct rural areas of the US. Participants were recent not-in-treatment adult cocaine and MA users living in rural Ohio, Arkansas, and Kentucky, who were recruited by a referral recruitment method for sampling hidden community populations. Participants were interviewed for demographics, drug and alcohol use, criminal justice involvement, and psychological distress (Brief Symptom Inventory). The sample of 706 comprised 29% nonwhite and 38% female participants; the average age was 32.6 years; 58% had a high school education or higher, and 32% were employed. In the past 6 months, they had used either MA only (13%), cocaine only (52%), or both (35%). MA users were seldom (8.2%) nonwhite, but type of stimulant use did not vary by gender. Combined MA/cocaine users reported significantly greater use of alcohol and other drugs, including marijuana and non-prescribed opiates and tranquilizers, and reported significantly higher

psychological distress. MA users (with or without cocaine use) had greater odds of recent criminal justice involvement compared with cocaine-only users. There is a clear need for accessible substance-use treatment and prevention services in rural areas of the United States, including services that can address MA, cocaine, poly-drug use, and mental health needs. There is a particular need of these services for poly-drug users. Booth, B., Leukefeld, C., Falck, R., Wang, J., and Carlson, R. Correlates of Rural Methamphetamine and Cocaine users: Results from a Multi-state Community Study. J Stud Alcohol, 67(4), pp. 493-501, 2006.

Can Home-made Injectable Opiates Contribute to the HIV Epidemic among IDUs in the Countries of the Former Soviet Union?

Home-made preparation of heroin ("chornaya") is common in countries of the former Soviet Union (FSU), and the addition of blood during its preparation and the use of contaminated syringes to distribute it may play a role in the rapid spread of HIV-1 among IDUs. This study was designed to determine the viability of HIV-1 during these procedures. Field observations of home-made opiate manufacture in four FSU countries were used to develop a consensus protocol to replicate manufacture in the laboratory that included the addition of human blood contaminated with HIV-1. Following the addition of HIV-1-contaminated blood during manufacture or storage, attempts were made to recover viable HIV-1. The recovery was measured by propagation of the virus in stimulated white blood cells from uninfected donors. In experiments in which HIV-1 contaminated blood was added during manufacture, no viable HIV-1 was recovered. In experiments in which chornaya was introduced into HIV-contaminated syringes, the percentage of syringes containing viable HIV-1 was reduced. The reduction appeared to be related to the interaction of HIV-1 contaminated blood with a component of the poppies. While HIV-contaminated syringes used to dispense or inject home-made opiates might transmit HIV, the ability of chornaya to reduce HIV viability seems to make this route of transmission less efficient. The epidemic of HIV-1 among IDUs in the FSU appears to have resulted from well-recognized injection risk behaviors-including sharing syringes and drug solutions--rather than from opiate solutions harboring viable HIV-1. Abdala, N., Grund, J., Tolstov, Y., Kozlov, A., and Heimer, R. Can Home-made Injectable Opiates Contribute to the HIV Epidemic Among Injection Drug Users in the Countries of the Former Soviet Union? Addiction, 101(5), pp. 731-737, 2006.

HIV Prevalence, Sociodemographic, and Behavioral Correlates and Recruitment Methods among Injection Drug Users in St. Petersburg, Russia

In St. Petersburg, Russia, researchers sought to describe the characteristics of active high-risk IDU to evaluate the associations between behavioral and demographic characteristics and HIV-1 infection and to describe 3 discrete recruitment methods. Active high-risk IDUs were recruited in 3 ways: through street outreach, at facilities serving IDUs, and by network-based chain referral. Recruits were screened, counseled, and tested for HIV-1. Sociodemographic and behavioral data were collected. HIV-1 prevalence was analyzed as a function of sociodemographic and behavioral variables. During the 10-month recruitment period, data from 900 participants were collected: median age was 24 years, and in the previous month, 96% used heroin and 75% shared needles with others. The baseline HIV prevalence was 30% (95% confidence interval [CI]: 27 to 33). Recruitment through social networks was the most productive strategy. HIV-positive individuals were younger, but none of the other sociodemographic or behavioral characteristics differed significantly by HIV status. The estimated HIV prevalence of 30% places St. Petersburg among the worst IDU-concentrated epidemics in Europe. Recruitment through

network-based chain referral is a useful method for recruiting active IDUs. Sociodemographic and behavioral links to prevalent HIV infection remain to be elucidated. Shaboltas, A., Toussova, O., Hoffman, I., Heimer, R., Verevochkin, S., Ryder, R., Khoshnood, K., Perdue, T., Masse, B., and Kozlov, A. HIV Prevalence, Sociodemographic, and Behavioral Correlates and Recruitment Methods Among Injection Drug Users in St. Petersburg, Russia. J Acquir Immune Defic Syndr, 41(5), pp. 657-663, 2006.

Proximal and Distal Predictors of Drug Use among South African Adolescents

The purpose of this study was to determine the association of frequency of illegal drug use with five groups of factors: environmental stressors, parental drug use, parental child rearing, peer drug use, and adolescent personal attributes. The sample, 1468 male (45%) and female (55%) adolescents, aged 12 to 17 years (mean 14.76, SD 1.51), were interviewed at home in Durban and Capetown, South Africa. Regression analyses showed that personal attributes and peer substance use explained the largest percentage of the variance in the adolescents' frequency of illegal drug use. In addition, both of the parental factors and the environmental stressors contributed to the explained variance in adolescent drug use above and beyond the two more proximal domains at a statistically significant level. Knowing the contribution of more proximal vs. more distal risk factors for illegal drug use is useful for prioritizing targets for interventions. Targeting changes in the more proximal predictors (e.g., adolescent personal attributes) may be more effective as well as more feasible than trying to produce changes in the more distal factors, such as environmental stressors. Brook, J., Morojele, N., Pahl, K., and Brook, D. Predictors of Drug Use Among South African Adolescents. J Adolesc Health, 38(1), pp. 26-34, 2006.

Cigarette Smoking among South African Adolescents: Individual, Family, Peer and Cultural Predictors

This study assessed the interrelation among domains of ethnic factors; the individual's sense of well-being; personality, attitudes, and behaviors; sibling and peer smoking; and adolescent smoking behavior. The sample consisted of 1,468 South African adolescents selected from 4 ethnic groups self-identified as defined by current South African usage: Black (mainly Zulu and Xhosa), Indian, White, and Colored (mixed ancestry). In accordance with family interactional theory, there was a sequence of patterning from ethnic factors and the individual's sense of well-being to adolescent personality, attitudes, and behaviors and models of smoking. All of the 4 domains in the model also had a direct effect on adolescent smoking behavior. The findings suggest possible targets of therapeutic or preventive intervention with regard to adolescent smoking: ethnic factors; the individual's sense of well-being; personality, attitudes, and behaviors; and smoking within the peer group. Brook, J., Morojele, N., Brook, D., and Rosen, Z. Predictors of Cigarette use Among South African Adolescents. Int J Behav Med, 12(4), pp. 207-217, 2005.

Substance Abuse Amplifies the Risk for Violence in Schizophrenia Spectrum Disorder

This research seeks to elucidate the factors responsible for the association between schizophrenia and violence with or without co-occurring substance abuse. The present study had two aims: (1) ascertain whether substance abuse augments the risk for violence in patients with schizophrenia; and, (2) determine whether violence is differentially related to positive and negative symptoms of schizophrenia. A sample of 133 adults between 18 and 59 years of age who were admitted for treatment between November 2001 and January

2002 at the General Psychiatry Clinics of Bakirkšy Mental Health and Psychiatry Training and Research Hospital in Istanbul participated in this study. Patients with bizarre behavior and avolition-apathy symptoms were more likely to manifest violent behavior. In addition, patients with a history of criminal offenses and substance use disorder were more likely to exhibit violent behavior. Based on the results of this study, it is feasible to identify individuals with schizophrenic spectrum disorder who are at high risk for violence. Erkiran, OzŸnalan, Evren, Ayta lar, Kirisci, and Tarter. Substance Abuse Amplifies the Risk for Violence in Schizophrenia Spectrum Disorder. Addict Behav, epub, pp. 1-9, 2006.

Determinants of Suicide

Across the US, firearms are used in approximately 60% of all suicide deaths. Little research has assessed the role and determinants of firearms in suicide in major urban areas. The authors collected data on all suicide deaths between 1990 and 2000 from the Office of the Chief Medical Examiner of New York City (NYC) and assessed trends and correlates of firearm related suicide deaths. During the period studied, there were a total of 6008 suicides in NYC; 1200 (20.0%) were firearm related suicides There was a decrease in total suicides, total firearm suicides, and the proportion of firearm related suicides. In multivariable modeling, characteristics of suicide decedents associated with a greater likelihood of firearm suicide were: male, black race, residing in the outer boroughs, and use of cannabis. The proportion of suicides caused by firearms in NYC is low compared to other parts of the US; differential access to means of committing suicide and the differential importance of firearms in different racial and ethnic groups may contribute to this observation. Innovative, local population based interventions that target non-firearm related suicide may contribute to lower suicide mortality overall in urban areas. Piper, T., Tracy, M., Bucciarelli, A., Tardiff, K., and Galea, S. Firearm Suicide in New York City in the 1990s. Inj Prev, 12(1), pp. 41-45, 2006.

Sexual Risk Behaviors among Adolescent Mothers in an HIV Prevention Program

The purpose of this study was to determine the following: (1) whether adolescent mothers in a human immunodeficiency virus (HIV) prevention program had significantly greater perceived self-efficacy and perceived behavioral control to use condoms, and more favorable outcome expectancies and subjective norms regarding condom use than those in a health education control group, 3 months after intervention; and (2) the impact of the 3-month post-intervention theoretical variables on intentions to use condoms at 3 months and sexual risk behaviors at 6 months. Structural equation modeling with latent variables was used to assess the influence of theoretical variables and treatment condition using data from 496 participants (78% Latinas, 18% African-Americans) who completed questionnaires at baseline and at 3- and 6-month follow-up evaluations. Substantial improvements were shown by both groups, with a slight advantage for the HIV prevention group, on all theoretical variables between pretest and the follow-up evaluations. In the predictive model, the intervention group reported significantly fewer sex partners. By using intentions to use condoms as a mediator, greater self-efficacy, hedonistic beliefs, positive subjective norms, and less unprotected sex predicted intentions to use condoms, which, in turn, predicted less unprotected sex. Lower subjective norms modestly predicted multiple partners. Significant indirect paths mediated through intentions to use condoms were observed. These data support a relationship among several constructs from social cognitive theory and the theory of reasoned action, and subsequent sexual risk behaviors. HIV-prevention programs for adolescent mothers should be designed to include these theoretical constructs and to address contextual factors influencing their lives. Koniak-Griffin, D., and Stein, J. Predictors of

Sexual Risk Behaviors Among Adolescent Mothers in a Human Immunodeficiency Virus Prevention Program. J Adolesc Health, 38(3), pp. 297-311, 2006.

Choice of Tobacco Products by Blunt Smokers

An important part of blunt (marijuana in a cigar shell) smoking is the ritual of the preparation process and the selection of tobacco product for the blunt. This article explores reasons for selection from the different tobacco products available in the legal commercial market. Based upon three years of ethnographic research with 92 focal subjects, the analysis focuses upon the practical, sub cultural, and symbolic reasons that blunt smokers give for choosing tobacco products (cigars for blunts-CFBs) employed in the blunt preparation process. The blunt ritual also functions within the marijuana subculture to differentiate blunt smokers from joints/pipes smokers. This analysis explores the reasons users give for selecting among the most popular inexpensive cigar brands (Dutch Masters, Phillies Blunts, and Backwoods) all owned and marketed by a single cigar conglomerate. Blunt chasing--the smoking of a cigarillo or cigar following a blunt--is an emergent phenomenon that further expands the market for tobacco products among blunt smokers. Recently, many different flavors have been added to these tobacco products in order to attract young and minority blunt consumers. Sifaneck, S., Johnson, B., and Dunlap, E. Cigars-for-blunts: Choice of Tobacco Products by Blunt Smokers. J Ethn Subst Abuse, 4(3-4), pp. 23-42, 2005.

Settings for Informal Social Controls of Blunt Smoking

The importance of settings for marijuana use has been widely noted, but the way that informal social controls are organized to moderate the amounts consumed have not been well documented. An ethnographic study of blunts/marijuana use in New York City observed several hundred marijuana users in group locations and conducted intensive interviews with 92 focal subjects. The vast majority of blunt smokers preferred to consume in a group setting. Participants identified three group settings in which blunt smoking often occurred-sessions, cyphers, and parties. The analysis identifies various conduct norms, rituals, and behavior patterns associated with each of these settings. Regardless of the setting, group processes encouraged equal sharing of blunts, moderation in consumption, intermission and breaks between smoking episodes, and involvement in non-smoking activities. Blunt smoking groups rarely encouraged high consumption and intoxication from marijuana. Dunlap, E., Johnson, B., Benoit, E., and Sifaneck, S. Sessions, Cyphers, and Parties: Settings for Informal Social Controls of Blunt Smoking. J Ethn Subst Abuse, 4(3-4), pp. 43-79, 2005.

The Role of Coping and Problem Drinking in Men's Abuse of Female Partners

This article examines the relationship of coping and problem drinking to men's abusive behavior towards female partners. While previous research has demonstrated a consistent association between problem drinking and male abuse of intimate partners, virtually no studies have assessed the role of coping in relation to men 's violence. An ethnically diverse sample of 147 men in a court-mandated program for domestic violence offenders completed questionnaires at the first session. Path modeling was conducted to test the extent to which coping and problem drinking predicted both physical and psychological abuse. In addition, the relationships of problem drinking and physical abuse to injury of the men 's female partners were examined. Results indicated that both the use of avoidance and problem-solving coping to deal with relationship problems were related indirectly to abusive behavior through

problem drinking. Greater use of avoidance coping strategies was more likely among problem drinkers. By contrast, men who used higher levels of problem-solving coping were less likely to be problem drinkers. Avoidance, but not problem-solving coping also was directly and positively related to physical and psychological abuse. Men identified as problem drinkers were more likely to use both physical and psychological abuse. Finally, greater use of physical violence was strongly related to higher levels of injury among female partners, and served to mediate the relationship between problem drinking and injury. Snow, D., Sullivan, T., Swan, S., Tate, D., and Klein, I. The Role of Coping and Problem Drinking in Men's Abuse of Female Partners: Test of a Path Model. Violence Vict, 21(3), pp. 267-285, 2006.

Access to Highly Active Antiretroviral Therapy for Injection Drug Users: Adherence, Resistance, and Death

Injection drug users (IDUs) are a major risk group for HIV infection throughout the world and represent the focal population for HIV epidemics in Asia and Eastern Europe/Russia. HIV prevention programs have ranged from HIV testing and counseling, education, behavioral and network interventions, drug abuse treatment, bleach disinfection of needles, needle exchange and expanded syringe access, as well as reducing transition to injection and primary substance abuse prevention. With the advent of highly active antiretroviral therapy (HAART) in 1996, dramatic clinical improvements have been seen. In addition, the treatment's impact on reducing HIV viral load (and therefore transmission by all routes) provides a stronger rationale for an expansion of the focus on prevention to emphasize early identification and treatment of HIV infected individuals. However, treatment of IDUs has many challenges including adherence, resistance and relapse to high-risk behaviors, all of which impact issues of access and ultimately effectiveness of potent antiretroviral treatment. A major current challenge in addressing the HIV epidemic revolves around an appropriate approach to HIV treatment for IDUs. Vlahov, D., and Celentano, D. Access to Highly Active Antiretroviral Therapy for Injection Drug Users: Adherence, Resistance, and Death. Cad Saude Publica, 22(4), pp. 705-718, 2006.

Partner Concurrency among Drug Users with Large Numbers of Partners

The objective of this study was to measure the nature of concurrent sex partnering in two samples of drug users having large numbers of sex partners, and in which some or all participants were trading sex-for-money. The two samples included drug-using male sex workers (MSW) and male and female crack cocaine smokers (CS) having vaginal sex. Three measures were used to reflect the quality of concurrent partnering: the proportion of the samples having concurrent partners; the proportions of the samples having intimate, casual, and sex-for-money of partners; and overlap in concurrent partners. Proportions of each sample having concurrent partners were essentially the same. However, the kinds of concurrent partners and overlap in concurrent partners were significantly different. Concurrent partners in the MSW sample were mostly sex-for-money or sex-for-drugs partners. Most concurrent partners in the CS sample were initimate or casual sex partners. Overlap in concurrent partners was also significantly different. The measure of overlap for the CS sample was three times higher than that of the MSW sample. These data suggest that concurrent sex partnering in the two samples, beyond the proportion having concurrent partners, was different. The patterns of concurrent sex partners in each sample may reflect different reasons for engaging in concurrent partnering, and may be reflected in different overlap scores between the two samples. Efforts should be made in future studies to better capture the complexities of concurrent partnering and to examine the implications of these for disease spread and control. Williams, M., Ross, M.,

Atkinson, J., Bowen, A., Klovdahl, A., and Timpson, S. An Investigation of Concurrent Sex Partnering in Two Samples of Drug Users Having Large Numbers of Sex Partners. Int J STD AIDS, 17(5), pp. 309-314, 2006.

Support for Buprenorphine and Methadone Prescription to Heroin-Dependent Patients among New York City Physicians

Methadone and buprenorphine are treatments for heroin-dependent patients. Methadone is available through highly-regulated treatment centers while buprenorphine was approved in 2002 for prescription by certified physicians. Just prior to the approval of buprenorphine, the investigators conducted a random postal survey of 770 physicians in New York City to determine willingness to prescribe methadone or buprenorphine for heroin-dependent patients to be picked up at a pharmacy. Among 247 respondents, 36.3% would consider prescribing methadone and 17.9% were unsure, while 25.8% would consider prescribing buprenorphine and 31.8% were unsure. Willingness to prescribe methadone or buprenorphine was associated with more recent year of licensure ($p = 0.044$; $p = 0.033$), working in a hospital or clinic as opposed to an office setting ($p = 0.009$; $p = 0.024$), and being the director of a clinic or program ($p = 0.031$; $p = 0.008$). This preliminary study suggests that a substantial proportion of New York City physicians would prescribe methadone or buprenorphine to heroin-dependent patients. Coffin, P., Blaney, S., Fuller, C., Vadnai, L., Miller, S., and Vlahov, D. Support for Buprenorphine and Methadone Prescription to Heroin-Dependent Patients Among New York City Physicians. Am J Drug Alcohol Abuse, 32(1), pp. 1-6, 2006.

Drug Use, Drug Severity, and Help-seeking Behaviors of Lesbian and Bisexual Women

Illicit substance use and abuse may be an important contributor to behavioral health problems of lesbian and bisexual women. This paper describes the nature and extent of self-reported illicit and licit drug use, associated severity, and substance use-related help-seeking behaviors in an urban/metropolitan community sample of sexual minority women in California. Self-administered questionnaire data from 2011 lesbian and bisexual women recruited through multiple strategies were used. Multiple logistic regression was employed to describe patterns of reported drug use and to compare lifetime severity of drug use with demographic characteristics, recent drug use, indicators of current social and emotional problems, and help-seeking behaviors. Drug use, especially marijuana (33% used in the past year), was fairly common. Overall, 16.2% of the women in the study reported lifetime drug use that was associated with self-reported severity of substance use, and another 10.8% indicated moderate-risk use. Extent of lifetime drug use was positively correlated with self-reported recent drug use as well as current life problems. Of the respondents who evidenced more problematic drug use, 41.5% indicated that they had received professional help for a substance use problem, and 16.3% wanted but had not received such help. The women in this study reported elevated rates of illicit drug use that were frequently associated with impairment and specific life problems. A significant proportion wanted and had not received professional treatment for their drug use problems, suggesting an important need to examine pathways by which lesbians and bisexual women can obtain referrals and treatment for substance use problems. Corliss, H., Grella, C., Mays, V., and Cochran, S. Drug Use, Drug Severity, and Help-Seeking Behaviors of Lesbian and Bisexual Women. J Womens Health (Larchmt), 15(5), pp. 556-568, 2006.

Evaluation of Therapeutic Strategies: A New Method for Balancing Risk and Benefit

A patient-specific drug safety-efficacy index was developed that combined objective clinical trial information about dose-related efficacy and toxicity with subjective perspectives on efficacy-toxicity trades. Patient preferences were systematically assessed using the probability tradeoff technique (PTT). Toxicity ranges over which a drug's efficacy exceeded the patient 's minimally acceptable efficacy represented ranges of "surplus efficacy." These can be related to the dose interval in which a drug delivers this surplus efficacy. Seventy surplus efficacy functions (for 7 hypothetical drugs and 10 hypothetical preference curves) were simulated. The analysis showed that index values change markedly by dose and patient preference, suggesting that different patients will benefit from different drugs depending on the dose prescribed and each patient's subjective assessment of the efficacy/toxicity tradeoff. In most situations, drugs achieve positive surplus efficacy only over limited dose ranges. The model was sensitive to different preference curves and discriminated well among drugs with different efficacy or safety profiles. This index provides a new, systematic approach to choosing a specific therapeutic intervention and dosage, when known risks and benefits are reconciled against patient-specific preferences among an array of therapeutic alternatives. Troche, C., Paltiel, A., and Makuch, R. Evaluation of Therapeutic Strategies: A New Method for Balancing Risk and Benefit. Value Health, 3(1), pp. 12-22, 2006.

Emergency Department Utilization by Crack-Cocaine Smokers in Dayton, Ohio

The objective of this study was to determine the frequency, principal diagnoses, and correlates of emergency department (ED) visits made by persons with a history of crack-cocaine use (n = 333) over a 3-year period. Data were collected from participant self-reports and hospital records. During the study a total of 643 ED visits were made by 211 people, ranging from 53.5 to 76.7/100 persons/year. Injury and poisoning accounted for the largest single category of ED visits (29.5%). Men had lower odds of visiting the ED (OR=0.79, 95%CI=0.62-0.99), as did participants with higher levels of education (OR=0.83, 95%CI=0.73-0.94). Number of times in drug abuse treatment (OR=1.04, 95%CI=1.01-1.09), having a chronic disease (OR=1.46, 95%CI=1.06-1.99), and higher Addiction Severity Index composite medical scores (OR=1.62, 95%CI=1.15-2.29) increased the odds of an ED visit. Factors in addition to drug use are likely to affect ED utilization rates among crack-cocaine smokers. Siegal, H., Falck, R., Wang, J., Carlson, R., and Massimino, K. Emergency Department Utilization by Crack-Cocaine Smokers in Dayton, Ohio. Am J Drug Alcohol Abuse, 32(1), pp. 55-68, 2006.

From "Candy Kids" to "Chemi-Kids": A Typology of Young Adults who Attend Raves in the Midwestern United States

Although young people attending raves have been most visibly associated with the use of ecstasy and other "club drugs" in the United States, there is reason to believe that they are not a homogenous group in terms of their drug use practices. The purpose of this article is to begin developing a typology of young adult ecstasy users involved in the rave subculture--known as Ravers or Party Kids. The study is based on focus groups and qualitative interviews conducted between November 2001 and September 2003 with 36 current and former ecstasy users, aged 19-31, in central Ohio, as well as participant observation conducted in raves, clubs, and bars where "club drugs" are often used. Findings suggest the existence of five main subgroups in attendance at raves--Chemi-Kids, Candy Kids, non-affiliated Party Kids, Junglists, and Old School Ravers. These groups differ in regard to musical taste, philosophy, style of clothing worn, amount of time in the rave subculture, and most importantly, patterns of drug use. For example, while the use of ecstasy appears most common among Candy Kids, Junglists tend to be more involved with the use of ketamine and

Methamphetamine. The use of alcohol, cocaine, marijuana, and hallucinogens is also widespread in the rave subculture. The typology can aid in the development of communication strategies necessary for successful prevention activities among some categories of ecstasy users. McCaughan, J., Carlson, R., Falck, R., and Siegal, H. From "Candy Kids" to "Chemi-Kids": A Typology of Young Adults who Attend Raves in the Midwestern United States. Subst Use Misuse, 40(9-10), pp. 1503-1523, 2005.

Drug Use Practices among MDMA/Ecstasy Users in Ohio: A Latent Class Analysis

This study describes the drug use practices among 402 recent MDMA (3,4-methelyenedioxy- methamphetamine) users recruited in Ohio using respondent-driven sampling. About 64% of the participants were men, 81.6% were white, and the mean age was 20.9 years. Latent class analysis was used to identify subgroups of MDMA users. Use of cocaine, opioids, amphetamines, tranquilizers, inhalants, marijuana, and hallucinogens during the previous 6 months, and days of "drunkenness" in the past 30, were used for classification. A three-class model was preferable and reflected "Limited range," "Moderate range," and "Wide range" drug use patterns. For example, the conditional probability of using opioids during the previous 6 months was .07 in Class 1, .59 in Class 2, and .88 in Class 3. Other substances followed similar patterns. Predictors of class membership were examined in a multinomial logit model in which the "Limited range" Class was treated as the reference group. Participants who were white, younger, and who reported more than 10 occasions of MDMA use were more likely to be in the "Wide range" drug use Class. Latent class analysis is a useful method to help describe and understand variability in poly-drug use patterns. Carlson, R., Wang, J., Falck, R., and Siegal, H. Drug Use Practices among MDMA/Ecstasy Users in Ohio: A Latent Class Analysis. Drug Alcohol Depend, 79(2), pp. 167-179, 2005.

Non-medical Drug Use among Stimulant-Using Adults in Small Towns in Rural Ohio

This study describes the drug-use practices and treatment histories of 249 not-in-treatment, drug-using individuals living in small towns in rural Ohio. Respondent-driven sampling was used to recruit participants who answered questionnaires administered by interviewers. Descriptive statistics and latent class analysis (LCA) were used to examine the data. The illicit drugs most commonly used in the 6 months before entering the study were marijuana (89.6%), cocaine hydrochloride (80.3%), and crack cocaine (76.3%). Injection drug use was not uncommon. About a third of the sample experienced drunkenness frequently. Less than 14% had been in substance abuse treatment recently. LCA revealed two groups: (1) heavy users of virtually all drug classes and (2) moderate-to-light users of fewer drug classes. White and younger people were more likely to be classified in the heavy user group. The results suggest that comprehensive substance abuse prevention and treatment programs are needed in rural communities. Falck, R., Siegal, H., Wang, J., Carlson, R., and Draus, P. Non-medical Drug Use among Stimulant-Using Adults in Small Towns in Rural Ohio. J Subst Abuse Treat, 28(4), pp. 341-349, 2005.

Prevalence and Correlates of Current Depressive Symptomatology among a Community Sample of MDMA Users in Ohio

Research suggests that MDMA can cause serotonin depletion as well as serotonergic neurodegradation that may result in depression among users of the drug. Several small-scale studies have used various editions of the Beck Depression Inventory (BDI) to quantify depressive symptomatology among

MDMA users. This study represents the largest application of the BDI to date to explore symptoms of current depression among a community sample of young adult MDMA users (n = 402). Internal consistency testing of the BDI-II with this sample revealed Cronbach's alpha = .92. Results show a mean BDI-II score of 9.8, suggesting low levels of depressive symptomatology among study participants. Two-thirds of the sample had scores that placed them in the non-depressed/minimal depression category, while 4.7% had scores indicative of severe depression. Logistic regression analysis revealed that men were significantly less likely than women and people who used opioids were significantly more likely than non-users to have higher levels of depressive symptomatology. Higher lifetime occasions of MDMA use were marginally related to symptoms of serious depression. Falck, R., Wang, J., Carlson, R., and Siegal, H. Prevalence and Correlates of Current Depressive Symptomatology among a Community Sample of MDMA Users in Ohio. Addict Behav, 31(1), pp. 90-101, 2006.

Precursors to Borderline Personality Disorder among Maltreated Children

Potential precursors to borderline personality disorder (BPD) were investigated in a sample of 185 maltreated and 175 non-maltreated school-aged children attending a summer camp research program. Self-report, peer-report, and counselor-report measures were utilized to assess developmental constructs conceptualized to constitute vulnerability for later emerging BPD. These areas, including personality features, representational models of self, parent, and peers, interpersonal relationship difficulties with peers and adults, and suicidal/self-harm behavior, were used to develop a BPD precursors composite. Additionally, the efficiency of three attention networks was assessed with a computerized task. Maltreated children had higher mean scores on the BPD precursors composite, and children classified as having high levels of these precursors were more prevalent in the maltreatment group. No maltreatment group differences were found for the efficiency of the three attention networks; however, children with high levels of BPD precursors evinced less efficient processing of the conflict attention network, comparable to findings observed among adult patients with BPD. Child maltreatment and efficiency of the conflict attention network independently predicted scores on the BPD precursors composite. Experiential and biological contributions to risk for BPD and recommendations for prevention and intervention are discussed. Rogosch, F., and Cicchetti, D. Child Maltreatment, Attention Networks, and Potential Precursors to Borderline Personality Disorder. Dev Psychopathol, 17(4), pp. 1071-1089, 2005.

Behavioral Interventions for HIV-Positive and HCV-Positive Drug Users

The nature, context and frequency of use of various licit and illicit non-injection drugs associated with an elevated risk of HIV infection. Beyond HIV, a high proportion of HIV-infected IDUs are co-infected with HCV (hepatitis C virus). In this review, the researchers provide a brief review of the epidemiology of these problems, discuss behavioral interventions that can reduce ongoing high-risk behaviors among HIV-seropositive IDUs and MSM-DUs, and review the literature, which has evaluated their effectiveness. The majority of these interventions have focused on HIV-seronegative heterosexuals and therefore need to be considered in this larger context; however, where possible the researchers discuss the potential impact of these interventions among HIV-seropositive persons. In addition, the researchers briefly discuss interventions, which have the potential to simultaneously reduce ongoing transmission of both HIV and HCV. Finally, given the dearth of information on the effectiveness of behavioral interventions in reducing the burden of the HIV and HCV epidemics among persons already infected with either or both viruses, the

researchers describe some newer, promising interventions and offer suggestions for future studies. Strathdee, and Patterson. Behavioral Interventions for HIV-Positive and HCV-Positive Drug Users. AIDS Behav, 10(2), pp. 115-130, March 2006.

Impaired Oculomotor Response Inhibition in Children of Alcoholics: The Role of Attention Deficit Hyperactivity Disorder

Researchers administered 3 anti-saccade tasks to 67 10-12-year-old children having fathers with AUD and 12 children whose fathers had no psychiatric disorder in order to determine whether children at high risk for alcohol use disorder (AUD) are impaired at performing oculomotor response inhibition tasks sensitive to detecting prefrontal cortex dysfunction. Children of AUD+ fathers performed similar to children of AUD- fathers on measures of response latency and gain to target. Peak velocity discriminated the two groups on only one task. Children of AUD+ fathers exhibited a higher rate of prosaccade errors on the most difficult anti-saccade task. Within the AUD+ group of men, offspring who qualified for attention deficit hyperactivity disorder (ADHD; N = 13) exhibited more response suppression errors than children without ADHD on two of three tasks. No differences were observed between children without ADHD whose fathers either qualified for AUD+ or had no psychiatric disorder. Authors concluded inhibiting a response to a prepotent stimulus in children of AUD+ fathers is circumscribed to ADHD youths. These findings suggest that frontal-striatal mechanisms may underlie the risk for AUD among ADHD children. Habeych, M., Folan, M., Luna, B., and Tarter, R. Impaired Oculomotor Response Inhibition in Children of Alcoholics: The Role of Attention Deficit Hyperactivity Disorder. Drug Alcohol Depend, 82(1), pp. 11-17, 2006.

HIV Prevention and Street-based Male Sex Workers: An Evaluation of Brief Interventions

This study sought to evaluate the acceptability and the comparative efficacy of brief HIV risk reduction interventions to increase condom use among drug-using, street-based male sex workers (MSWs). Of the 399 street-based MSWs who participated in the evaluation of acceptability, 112 participated in the evaluation of efficacy. The primary outcome of concern was condom use during paid sexual encounters. In addition, changes in drug use, needle use, condom use beliefs, and condom use intention were also assessed. Results showed that almost two thirds of MSWs enrolled in a brief intervention completed it. Completion rates varied by age, race/ethnicity, sexual orientation, and HIV status. Condom use during paid sex increased post-intervention. In addition, intentions, outcome expectations, and normative expectations toward use of condoms increased pre-intervention to post-intervention. However, there were no significant differences between the standard and the standard-plus brief interventions in any of the outcomes measured. Brief interventions to reduce HIV risks are acceptable to MSWs and are efficacious for reducing unprotected anal sex during paid sexual encounters. Williams, M., Bowen, A., Timpson, S., Ross, M., and Atkinson, J. HIV Prevention and Street-based Male Sex Workers: An Evaluation of Brief Interventions. AIDS Educ Prev, 18(3), pp. 204-215, 2006.

Associations between Parenting Behaviors and Offspring Personality Disorder

Research has suggested that some types of parental child-rearing behavior may be associated with risk for offspring personality disorder (PD), but the association of parenting with offspring PD has not been investigated comprehensively with prospective longitudinal data. This study was designed to investigate the association of parental child-rearing behavior with risk for

offspring PD during adulthood. A community-based sample of 593 families were interviewed during childhood (mean age, 6 years), adolescence (mean ages, 14 and 16 years), emerging adulthood (mean age, 22 years), and adulthood (mean age, 33 years) of the offspring. The main outcome measure was the Structured Clinical Interview for DSM-IV Personality Disorders. Ten types of parenting behavior that were evident during the child-rearing years were associated with elevated offspring risk for PD during adulthood when childhood behavioral or emotional problems and parental psychiatric disorders were controlled statistically. Parental behavior in the home during the child-rearing years was associated with elevated risk for offspring PD at mean ages of 22 and 33 years. Risk for offspring PD at both assessments increased steadily as a function of the number of problematic parenting behaviors that were evident. Low parental affection or nurturing was associated with elevated risk for offspring antisocial (P = .003), avoidant (P = .01), borderline (P = .002), depressive (P = .02), paranoid (P = .002), schizoid (P = .046), and schizotypal (P<.001) PDs. Aversive parental behavior (eg, harsh punishment) was associated with elevated risk for offspring borderline (P = .001), paranoid (P = .004), passive-aggressive (P = .046), and schizotypal (P = .02) PDs. Parental behavior during the child-rearing years may be associated with risk for offspring PD that endures into adulthood. This risk may not be attributable to offspring behavioral and emotional problems or parental psychiatric disorder, and it may not diminish over time. Low parental nurturing and aversive parental behavior during child rearing may both be associated with elevated risk for offspring PDs. Johnson, J., Cohen, P., Chen, H., Kasen, S., and Brook, J. Parenting Behaviors Associated with Risk for Offspring Personality Disorder during Adulthood. Arch Gen Psychiatry, 63(5), pp. 579-587, 2006.

New York City IDUs' Memories of Syringe-Sharing Patterns and Changes During the Peak of the HIV/AIDS Epidemic

This paper provides an oral history from interviews with 23 injection drug users (IDUs) to learn what they recall about the mid-1970s to mid-1980s when they could not legally purchase or possess syringes, and when the threat of AIDS began to loom large. Several themes emerged, including: abrupt changes in syringe-sharing patterns; the effects of illnesses or deaths of others on their understanding of AIDS; and, racial/ethnic differences in responses to the threat of AIDS. Settings, such as "shooting galleries," helped HIV spread rapidly in the earliest stages of the city's AIDS epidemic. HIV entered the drug scene in the mid-1970s, just when IDUs were shifting from sharing homemade "works" (consisting of steel needles and syringes devised from rubber baby pacifiers and similar sources) among many IDUs to mass produced and distributed plastic, disposable needle and syringe sets. The IDUs in this study remember when they first became aware of AIDS and began to adjust their behaviors and social assumptions. Rockwell, Joseph, and Friedman. New York City Injection Drug Users' Memories of Syringe-Sharing Patterns and Changes During the Peak of the HIV/AIDS Epidemic. AIDS Behav, published online May 18, 2006.

The Methamphetamine Epidemic: Implications for HIV Prevention and Treatment

Methamphetamine and related amphetamine compounds are among the most commonly used illicit drugs, with over 35 million users worldwide. In the United States, admissions for methamphetamine treatment have increased dramatically over the past 10 years. Methamphetamine use is prevalent among persons with HIV infection and persons at risk for HIV, particularly among men who have sex with men. In addition to being associated with increased sexual risk behavior, methamphetamine causes significant medical morbidity, including neurologic deficits, cardiovascular compromise, dental decay, and skin infections, all of which may be worsened in the presence of HIV/AIDS. Methamphetamine use may also result in decreased medication adherence,

particularly during "binging" episodes. Behavioral counseling remains the standard of treatment for methamphetamine dependence, although the effectiveness of most counseling interventions has not been rigorously tested. Pharmacologic and structural interventions may prove valuable additional interventions to reduce methamphetamine use. Colfax, G., and Shoptaw, S. The Methamphetamine Epidemic: Implications for HIV Prevention and Treatment. Curr HIV/AIDS Rep, 2(4), pp. 194-199, 2005.

Impact of a Medically Supervised Safer Injecting Facility on Drug Dealing and Other Drug-related Crime

North America's first medically supervised safer injecting facility (SIF) recently opened in Vancouver, Canada. One of the concerns prior to the SIF's opening was that the facility might lead to a migration of drug activity and an increase in drug-related crime. This study examined crime rates in the neighborhood where the SIF is located in the year before versus the year after the SIF opened. No increases were seen with respect to drug trafficking (124 vs. 116) or assaults/robbery (174 vs. 180), although a decline in vehicle break-ins/vehicle theft was observed (302 vs. 227). The findings show that SIF was not associated with increased drug trafficking or crimes commonly linked to drug use. Wood, E., Tyndall, M., Lai, C., Montaner, J., and Kerr, T. Impact of a Medically Supervised Safer Injecting Facility on Drug Dealing and other Drug-related Crime. Subst Abuse Treat Prev Policy, 1, pp. 13-16, 2006.

Club Drugs and HIV Infection: A Review

Club drug use is common among populations with HIV and at high risk for HIV infection. Club drugs have a myriad of acute and chronic medical consequences. Club drug-related visits to the emergency department and admissions for treatment of substance use have increased dramatically over the past 15 years. Most epidemiological data support the role of club drugs in increasing sexual risk behavior, with some studies demonstrating an independent association between use of certain club drugs and HIV infection. The direct influence of club drugs on progression of HIV disease remains to be determined; however, club drugs may interact with certain retroviral medications and have been associated with decreased adherence to medication. Clinicians should ask all patients about patterns of club drug use, counsel patients about the risks associated with club drug use, and refer patients to appropriate behavioral treatment programs for substance use when clinically indicated. Colfax, G., and Guzman, R. Club Drugs and HIV Infection: A Review. Clin Infect Dis, 42(10), pp. 1463-1469, 2006.

Syringe Disposal Among Injection Drug Users in Harlem and the Bronx During the New York State Expanded Syringe Access Demonstration Program

Effective January 1, 2001, New York State enacted the Expanded Syringe Access Demonstration Program (ESAP), allowing syringes to be sold in pharmacies without a prescription or dispensed through doctors, hospitals, and clinics to adults. A concern in the assessment of ESAP is its effects on syringe disposal practices. Syringe use data regarding the last injection episode were combined from three projects (N = 1,030) recruiting injection drug users. Disposal of syringes by methods known to be safe decreased significantly over time after the implementation of ESAP. Syringes obtained either from syringe exchange programs or ESAP sources were more likely to be disposed of safely than syringes obtained from other sources. Efforts to enlist pharmacists and others involved in ESAP implementation to encourage safe disposal are needed. More detailed information on disposal practices is needed to capture the continuum from least to most safe practices and variation within individuals.

Cleland, Deren, Fuller, Blaney, McMahon, Tortu, Des Jarlais, and Vlahov. Syringe Disposal Among Injection Drug Users in Harlem and the Bronx During the New York State Expanded Syringe Access Demonstration Program. Health Educ Behav, 34(3), pp. 285-295, 2006.

Factors Associated with Buying and Selling Syringes among IDUs in a Setting of one of North America 's Largest Syringe Exchange Programs

Researchers performed analyses of syringe buying and syringe selling among Vancouver injection drug users, recruited from May 1996 and followed up between November 2002 and August 2003, in the context of one of North America's largest syringe exchange programs (SEPs). An interviewer-administered questionnaire, approximately 45 minutes in duration, was used to collect information regarding risk factors for HIV infection and sources of sterile syringes. Seventy participants (15%) reported syringe selling and 122 (26%) reported syringe buying. Syringe sellers were more likely to be female, reside in unstable housing, need help injecting, and have visited the SEP at least once weekly. Syringe buyers were more likely to need help injecting, have difficulty finding new syringes, have binged on drugs, and have visited the SEP at least once weekly. Syringe buying most frequently occurred when the SEP was closed. Kuyper, L., Kerr, T., Li, K., Hogg, R., Tyndall, M., Montaner, J., and Wood, E. Factors Associated with Buying and Selling Syringes Among Injection Drug Users in a Setting of one of North America's Largest Syringe Exchange Programs. Subst Use Misuse, 41(6-7), pp. 883-899, 2006.

Agreement in Reported Sexual Partnership Dates and Implications for Measuring Concurrency

This study describes the reliability of reported dates of first and last sexual exposure, as elicited from STD/HIV cases during routine contact investigation, and determines their adequacy for assessing concurrency. Contact tracing data from 5 studies were used in which both members of 774 dyads were interviewed and named each other as sex partners. Partners' agreement was assessed on the dates of first and last exposure as related to precision (to the day, month, or year) of reported dates and demographic and behavioral characteristics of the dyad. Simulations were then performed that introduced reporting error, based on observed data, to posit "true" temporal configurations of partnerships to assess the impact of unreliability in reporting on the measurement of concurrency. Thirty-two percent of dyads agreed on the exact date of first sexual exposure, and 36% did so for the date of last sexual exposure. Sixty-four percent agreed within 30 days on the date of first sexual exposure, and 81% did so for the date of last sexual exposure. The reliability of reported dates was positively related to the precision of the reports. Agreement on reported exposure dates was not meaningfully associated with any of the sociodemographic and behavioral variables available. Based on simulations, the positive predictive value of reported dates for estimating concurrency was approximately 80% over a wide range of conditions. These data suggest that the reliability of reported exposure dates is reasonably good but that estimating concurrency with reported dates is subject to some error. Data are needed to analyze the statistical and epidemiologic issues of assessing concurrency. Brewer, D., Rothenberg, R., Muth, S., Roberts, J., and Potterat, J. Agreement in Reported Sexual Partnership Dates and Implications for Measuring Concurrency. Sex Transm Dis, 33(5), pp. 277-283, 2006.

Social Context of Needle Selling in Baltimore, Maryland

Although much of the debate surrounding the distribution of sterile syringes to

IDUs has focused on needle exchange programs (NEPs), IDUs acquire their syringes from 3 major sources: NEPs, pharmacies, and secondary exchangers or needle sellers. The purpose of the present study is to examine types and frequencies of social interactions among drug injectors who sell needles, most of which come from NEPs, compared with individuals who do not sell needles. Specifically, this study compared engagement in drug-related behaviors, roles in the drug economy, and social network membership. Data were collected as part of the SHIELD study, an HIV prevention intervention targeted at drug users and their social networks (n=910) from February 2001 through September 2003 in Baltimore, Maryland (USA). In this sample, 56 participants reported selling needles. Needle sellers had higher levels of engagement in drug-related social interactions, including using drugs with others, giving or receiving drugs from others, and buying drugs with other users. Participants who sold needles had a significantly higher number of roles in the drug economy. Also, they had more social network members who were injectors, with whom they talked about risky drug behaviors, gave needles to, and shared cookers and bleach. Compared with non-selling injectors, needle sellers engage in HIV risk-related behaviors, such as injecting daily and sharing injection equipment, more frequently. The study's findings may be useful to determine whether secondary exchangers should be targeted for HIV prevention activities both to reduce their own risk and to diffuse risk reduction information throughout the drug using community. Latkin, C., Davey, M., and Hua, W. Social Context of Needle Selling in Baltimore, Maryland. Subst Use Misuse, 41(6-7), pp. 901-913, 2006.

The Dynamics of Injection Drug Users' Personal Networks and HIV Risk Behavior

While studies of the social networks of IDUs have provided insight into how the structures of interpersonal relationships among IDUs affect HIV risk behaviors, the majority of these studies have been cross-sectional. The present study examined the dynamics of IDUs' social networks and HIV risk behaviors over time. Using data from a longitudinal HIV-intervention study conducted in Baltimore, MD, this study assessed changes in the composition of the personal networks of 409 IDUs. A multi-nomial logistic regression analysis was used to assess the association between changes in network composition and simultaneous changes in levels of injection HIV risk behaviors. Using the regression parameters generated by the multi-nomial model, the predicted probability was estimated of being in each of four HIV risk behavior change groups. Compared to the base case, IDUs who reported an entirely new set of drug-using network contacts at follow-up were more than three times as likely to be in the increasing risk group. In contrast, those reporting all new non-drug-using contacts at follow-up had a greater likelihood of being in the stable low-risk group by nearly 50%. They also had a decreased probability of being in the consistently high-risk group by more than 70%. These findings show that, over and above IDUs' baseline characteristics, changes in their personal networks are associated with changes in individuals' risky injection behaviors. They also suggest that interventions aimed at reducing HIV risk among IDUs might benefit from increasing IDUs' social contacts with individuals who are not drug users. Costenbader, E., Astone, N., and Latkin, C. The Dynamics of Injection Drug Users' Personal Networks and HIV Risk Behaviors. Addiction, 101(7), pp. 1003-1013, 2006.

Factors Associated With Non-IDUs Having IDU Sex Partners

This study examined factors associated with non-injectors having 1 or more IDUs as sex partners. Data were collected as part of the Self-Help in Eliminating Life Threatening Diseases study, a network-oriented experimental HIV prevention intervention. All eligible participants were administered a detailed face-to-face interview on their socio-demographic background,

patterns of drug use, HIV prevention and risk behaviors, and social networks. The sample for these analyses consisted of 863 non-injectors, 97 of whom had 1 or more injection drug-using sex partners. The study found that the factors associated with an increased odds of having 1 or more IDU sex partners were long-term unemployment, increasing proportion of women in network (among male non-injectors), increasing number of recent sex partners (among former injectors), increasing number of injecting non-sex partners in the network, and increasing network size above 15. These findings indicate that there are specific network characteristics associated with non-injectors having injecting sex partners. Howard, D., and Latkin, C. A Bridge Over Troubled Waters: Factors Associated With Non-Injection Drug Users Having Injection Drug-using Sex Partners. J Acquir Immune Defic Syndr, 42(3), pp. 325-330, 2006.

Child, Peer, Parent, and School Predictors of Rebellious Behavior in Childhood

This study assesses the interrelationships among several sets of variables and rebellious behavior in a sample of Puerto Rican and African American elementary school-aged children. The independent sets of variables (domains) were child personality attributes, parental attributes, including parental marijuana use, peer factors, school environment, and ethnic identification and discrimination. The dependent or outcome variable was children's rebellious behavior. Children and their mothers were interviewed in their homes. Pearson correlations and hierarchical multiple regression analyses were used to assess the extent to which the independent variables were related to the children's rebellious behavior. Each of the domains was associated with children's rebellious behavior without control on the remaining domains. With control on the remaining domains, child personality accounted for the most variance in childhood rebellious behavior. With control on child personality, only the school environment remained significant. Children with personality traits that are associated with rebellious behavior may have parents who exhibit antisocial behavior and use marijuana. Furthermore, these children may be at risk for other problem behaviors, including legal drug use, and would benefit from interventions, which address primarily their personality characteristics, but also their school environments. Brook, J., Brook, D., Balka, E., and Rosenberg, G. Predictors of Rebellious Behavior in Childhood Parental Drug Use, Peers, School Environment, and Child Personality. J Addict Dis, 25(2), pp. 77-87, 2006.

Substance Use among Adolescent Children with Drug Abusing Fathers

This longitudinal study examined paternal, perceived maternal, and youth risk factors at Time 1 (T1) (e.g., substance use, violent victimization, parental rules) as predictors of the stage of substance use in the adolescent child at Time 2 (T2). Participants (N = 296) consisted of drug-abusing fathers and one of their adolescent children, aged 12 to 20 years. Fathers and youths were each administered structured interviews separately and in private. Adolescents were re-interviewed approximately one year later. Pearson correlation analyses showed that the paternal, perceived maternal, and youth risk factors were significantly related to adolescent stage of substance use at T2. With an increase in risk factors, there was an increase in T2 stage of substance use in the child. Findings imply that father-oriented treatment programs should focus on how paternal behaviors, such as illegal drug use, inadequate parenting skills, and a poor father-child relationship contribute to youth problem behaviors, including alcohol, tobacco, and illicit drug use. Castro, F., Brook, J., Brook, D., and Rubenstone, E. Paternal, Perceived Maternal, and Youth Risk Factors as Predictors of Youth Stage of Substance Use A Longitudinal Study. J Addict Dis, 25(2), pp. 65-75, 2006.

Parent Drug Use and Personality Attributes: Child Rearing in African-American and Puerto Rican Young Adults

This study assessed the effect of the interrelationship of mothers' and fathers' tobacco and marijuana use with their personality attributes on some of their child rearing behaviors. A longitudinal design was used to analyze the data of 258 males and females who were seen four times over a 13-year period from early adolescence through young adult parenthood. Thirty-one percent of the multiple regression analyses revealed significant interactions between the effect of tobacco or marijuana use and a personality attribute on child rearing. The majority of these significant interactions suggested that protective personality characteristics were offset by substance use risks resulting in less adequate child rearing. If these results are substantiated in an experimental intervention, it suggests that having resilient personality attributes does not protect against the negative effects of tobacco or marijuana use on child rearing. Brook, Balka, Fei, and Whiteman. The Effects of Parental Tobacco and Marijuana Use and Personality Attributes on Child Rearing in African-American and Puerto Rican Young Adults. J Child Fam Stud, 15(2), pp. 153-164, 2006.

Cigarette Smoking among Adolscents with Drug Abusing Fathers

This study examined the longitudinal predictors of cigarette smoking in a sample of at-risk adolescents whose fathers were drug abusers (N = 296). At time 1, structured interviews were administered, separately and in private, to male and female youth (X age = 16.3) and their fathers; adolescents were re-interviewed approximately 1 year later (at time 2). Structural equation modeling was used to examine the interrelationship of time 1 paternal tobacco and illicit drug use, father-child relations, adolescent psychological adjustment, and peer group factors and adolescent smoking at time 2. A supplementary analysis assessed the same model with control on the adolescent's age, gender, frequency of contact with the father, and the father's treatment status. The structural equation model showed a mediational pathway linking paternal tobacco and drug use to a weak and conflictual father-child relationship, which was associated with greater adolescent maladjustment, which in turn was related to deviant peer affiliations, which predicted adolescent smoking at time 2. There was also a direct path from paternal tobacco and drug use to adolescent time 2 smoking. The supplementary analysis found no significant differences between the models with and without control. Findings provide evidence of the mechanisms that underlie the association between paternal drug use characteristics and smoking in the adolescent child. Clinical implications suggest the importance of the father-child relationship to smoking prevention programs for at-risk youth. Brook, D., Brook, J., Rubenstone, E., Zhang, C., and Gerochi, C. Cigarette Smoking in the Adolescent Children of Drug-abusing Fathers. Pediatrics, 117(4), pp. 1339-1347, 2006.

Perceptions of People with Substance use Problems Returning Home from NY City Jails

Each year about 100,000 people return to New York City communities from municipal jails. Although about four-fifths report drug or alcohol problems, few have received any formal drug treatment while in jail. Researchers and practitioners have identified a number of policies related to corrections, income, housing, and drug treatment that may be harmful to the successful reintegration of people leaving jail. In order to explore the challenges to successful community reentry, six focus groups and one in-depth interview were conducted with 37 men and women who had been released from jail or prison in the last 12 months. Participants were asked to describe their experiences prior to and immediately following release from jail. Findings suggest that many people leaving jail are not prepared for release and, upon

release, face a myriad of obstacles to becoming healthy, productive members of their communities. Van Olphen, J., Freudenberg, N., Fortin, P., and Galea, S. Community Reentry: Perceptions of People with Substance use Problems Returning Home from NY City Jails. J Urban Health, 83(3), pp. 372-381, 2006.

Contextual Determinants of Condom Use Among Female Sex Exchangers in East Harlem, NYC: An Event Analysis

Recent studies have identified a variety of contexts involving HIV risk behaviors among women who exchange sex for money or drugs. Event analysis was used to identify the individual, relationship, and contextual factors that contribute to these high-risk sex exchange practices. Analyses were conducted on data obtained from 155 drug-using women who reported details of their most recent sex exchange event with male clients. The majority of sex exchange encounters (78%) involved consistent condom use. In multivariable analysis, protective behavior was associated primarily with situational and relationship variables, such as exchange location, substance use, sexual practices, and respondent/client discussion and control. To inform HIV prevention programs targeted to women sex exchangers, research should focus on the contextual determinants of risk, especially with regard to condom-use negotiation and factors involving substance use that adversely affect women's ability to manage protective behavior in the context of sex exchange. McMahon, Tortu, Pouget, Hamid, and Neaigus. Contextual Determinants of Condom Use Among Female Sex Exchangers in East Harlem, NYC: An Event Analysis. AIDS Behav, published online June 16, 2006.

Borderline Personality and Substance Use in Women

The association between borderline personality disorder (BPD) and substance use disorder (SUD) was examined in a predominantly psychiatric (77.6%) sample of 232 women. BPD proved to be a significant predictor of a lifetime diagnosis of SUD across four different categories: any SUD (including alcohol); alcohol use; drug use; and heroin, cocaine, or poly-substance use. BPD continued to be a predictor of SUD even when the effects of other cluster B and all cluster C PDs were controlled statistically. Antisocial personality disorder generally yielded larger odds ratios than BPD and emerged as a partial mediator of the relation between BPD and SUD. Histrionic PD was the only other PD that showed meaningful relations with SUD. Feske, U., Tarter, R., Kirisci, L., and Pilkonis, P. Borderline Personality and Substance Use in Women. Am J Addict, 15(2), pp. 131-137, 2006.

Strong HIV and Hepatitis Disclosure Norms and Frequent Risk Behaviors Among Hungarian Drug Injectors

Ethnographic interviews and focus groups were conducted between May 2003 and January 2004 among IDUs (n=29) in Budapest, Hungary, to assess knowledge related to HIV, hepatitis B (HBV), and hepatitis C (HCV) and norms, attitudes, and behaviors. Participants perceived themselves at low risk for infection with HIV but at high risk for hepatitis through injection but not sexual exposure. They reported strong disclosure norms for HIV and hepatitis infections, while sexual and injection risk behaviors were influenced by trust about partners' self-report of infection status. Injection networks were small, with infrequent syringe sharing among a few close friends. Cookers and drug filters often were shared, and filters were reused as a backup drug supply. Most sexual relationships were monogamous, and condoms were rarely used. Although participant norms supported HIV/HBV/HCV testing, there was no evidence that these norms influenced disclosure among injection and sex partners who are close friends. Network interventions among IDUs in Hungary should build on disclosure norms and trust to reduce injection and sex risk.

Testing services should also be expanded and access increased so that IDUs can act on and reinforce their norms for testing. Gyarmathy, V., Neaigus, A., Ujhelyi, E., Szabó, T., and Rácz, J. Strong HIV and Hepatitis Disclosure Norms and Frequent Risk Behaviors among Hungarian Drug Injectors. Drug Alcohol Depend, 82(1), pp. S65-S69, 2006.

Secondary Syringe Exchange as a Model for HIV Prevention Programs in the Russian Federation

Effective prevention of syringe-borne transmission of HIV and the hepatitis viruses can be undermined if contact between IDU and the staff of prevention programs is impeded by police harassment, limited program resources, and the absence of an open "drug scene." All these are commonplace in the Russian Federation. In response, "Project Renewal," a program of the AIDS Prevention and Control Center of the Tatarstan Ministry of Health in Kazan, has created a hybrid syringe exchange program that has its primary focus recruited and trained volunteers to provide secondary syringe exchange. To compensate for operational barriers, the program staff identified private venues and trained responsible individuals to work through their own and related networks of injectors to provide clean syringes, supplies, and educational materials, while facilitating the collection and removal of used and potentially contaminated syringes. Program staff developed a detailed set of tracking instruments to monitor, on a daily and weekly basis, the locations and types of contacts and the dissemination of trainings and materials to ensure that the secondary distribution network reaches its target audience. Data show that these secondary exchange sites have proven more productive than the primary mobile and fixed-site syringe exchanges in Kazan. Beginning in 2001, Project Renewal has trained other programs in the Russian Federation to use this model of reaching injectors, identifying and training volunteers, and monitoring results of secondary syringe exchange. Irwin, K., Karchevsky, E., Heimer, R., and Badrieva, L. Secondary Syringe Exchange as a Model for HIV Prevention Programs in the Russian Federation. Subst Use Misuse, 41(6-7), pp. 979-999, 2006.

Surveillance of HIV, Hepatitis B Virus, and Hepatitis C Virus in an Estonian Injection Drug-using Population: Sensitivity and Specificity of Testing Syringes for Public Health Surveillance

Surveillance of blood-borne infections among IDUs can be accomplished by determining the presence of pathogen markers in used syringes. Parallel testing of returned syringes and venous blood from IDUs was conducted to detect antibodies to human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Syringe surveillance for HIV yielded a sensitivity and specificity of 92% and 89%, respectively, and provided a reasonable estimate of the prevalence of HIV among participants. Because sensitivity for HBV (34%) and HCV (55%) was low, syringe testing appears to be more useful for surveillance of hepatitis over time and less so for estimation of prevalence. Uuskula, A., Heimer, R., Dehovitz, J., Fischer, K., and McNutt, L. Surveillance of HIV, Hepatitis B Virus, and Hepatitis C Virus in an Estonian Injection Drug-using Population: Sensitivity and Specificity of Testing Syringes for Public Health Surveillance. J Infect Dis, 193(3), pp. 455-457, 2006.

Traditional Activities and Spirituality have Positive Effects on Alcohol Cessation in Native Americans

The detrimental effects of alcohol misuse and dependence are well documented as an important public-health issue among American Indian adults. This preponderance of problem-centered research, however, has eclipsed some important resilience factors associated with life course patterns of American

Indian alcohol use. In this study, the researchers investigate the influence of enculturation, and each of the three component dimensions (traditional practices, traditional spirituality, and cultural identity) to provide a stringent evaluation of the specific mechanisms through which traditional culture affects alcohol cessation among American Indians. Data were collected as part of a 3-year lagged sequential study currently underway on four American Indian reservations in the upper Midwest and five Canadian First Nation reserves. The sample consisted of 980 Native American adults, with 71% women and 29% men who are parents or guardians of youth ages 10-12 years old. Logistic regression was used to assess the unique contribution of the indicators of alcohol cessation. Excluding adults who had no lifetime alcohol use, the total sample size for present analysis is 732 adult respondents. The findings show that older adults, women, and married adults were more likely to have quit using alcohol. When the researchers examined the individual components of enculturation, two of the three components (participation in traditional activities and traditional spirituality) had significantly positive effects on alcohol cessation. Although our findings provide empirical evidence that traditional practices and traditional spirituality play an important role in alcohol cessation, the data are cross-sectional and therefore do not indicate direction of effects. Longitudinal studies are warranted, in light of the work that concludes that cultural/spiritual issues may be more important in maintaining sobriety once it is established rather than initiating it. Stone, R., Whitbeck, L., Chen, X., Johnson, K., and Olson, D. Traditional Practices, Traditional Spirituality, and Alcohol Cessation Among American Indians. J Stud Alcohol, 67(2), pp. 236-244, 2006.

Needles in the Haystacks: The Social Context of Initiation to Heroin Injection in Rural Ohio

Although there has been much research on the social context of heroin injection, little has been reported outside of major urban areas. This article examines contextual factors associated with initiation to heroin injection in rural Ohio, based on semi-structured qualitative interviews and focus groups involving 25 recent heroin injectors (12 women, 13 men) recruited from three contiguous counties between June 2002 and February 2004. Curiosity about the drug's effects, the growing pressures of drug dependence and economic need, and the influence of intimate and group relations were all identified as factors that offset fears commonly associated with injection. This study complements other research on the social ecology of heroin injection and may contribute to improved services for injection drug users in rural areas and small communities. Draus, P., and Carlson, R. Needles in the Haystacks: the Social Context of Initiation to Heroin Injection in Rural Ohio. Subst Use Misuse, 41(8), pp. 1111-1124, 2006.

Marked Ethnic Differences in HIV Prevalence and Risk Behaviors Among Injection Drug Users in Dushanbe, Tajikistan, 2004

To examine differences by ethnicity of HIV prevalence and correlates among IDUs in Dushanbe, Tajikistan, researchers enrolled 489 active adult IDUs in a cross-sectional risk factor study of HIV infection. Participants were provided HIV pre-and posttest counseling and risk reduction counseling and answered an interviewer-administered questionnaire. HIV-1 status was determined with rapid tests and confirmed with ELISA. Participants included 204 Tajiks (49.1%), 145 Russians (29.7%), 58 Uzbeks (11.9%), and 46 participants of other nationalities (9.4%). Overall prevalence of HIV-1 infection was 12% and varied significantly by ethnicity: it was highest among ethnic Tajiks, at 19.2%; lowest among Russians and Uzbeks, at 3.4%; and 13% among other nationalities. Ethnic groups differed significantly in years injecting, receiving a needle from a needle exchange program (NEP), injecting in groups, having undergone drug treatment, reported condom use, and arrest history. Among

Tajiks, HIV infection was significantly associated with daily injecting (OR 2.16); reporting that narcotics were very easy to obtain (OR 2.46); having undergone drug treatment (OR 2.75), and injecting "alone" (OR 3.12). The findings indicate that ethnic differences were strongly associated with HIV prevalence and risk behaviors and suggest that prevention efforts might be most effective if they were targeted by ethnicity. Stachowiak, J., Tishkova, F., Strathdee, S., Stibich, M., Latypov, A., Mogilnii, V., and Beyrer, C. Marked Ethnic Differences in HIV Prevalence and Risk Behaviors among Injection Drug Users in Dushanbe, Tajikistan, 2004. Drug Alcohol Depend, 82(1), pp. 7-14, 2006.

Pathways to Risky Sexual Behavior Among South African Adolescents

This study tested a developmental model of pathways to risky sexual behavior among South African adolescents. Participants comprised 633 adolescents, 12-17 years old, recruited from households in Durban, South Africa. Data were collected using in-person interviews. Topics included adolescents' sexual behaviors, household poverty levels, vulnerable personality and behavioral attributes, parent-child relations, and deviant peers. Structural equation modeling was used to assess the pathways to risky sexual behavior among the adolescents. The goodness-of-fit index (GFI) was .93. One major pathway indicated that family poverty was associated with difficulty in the parent-child relationship. This was related to vulnerable personality and behavioral attributes and to association with deviant peers, which, in turn, were related to risky sexual behavior. Findings suggest that poverty, parent-child relations, personality and behavioral vulnerabilities, and peer influences should be among factors addressed by prevention and intervention programs to reduce sexual risk behaviors by South African adolescents. Brook, D., Morojele, N., Zhang, C., and Brook, J. South African Adolescents: Pathways to Risky Sexual Behavior.. AIDS Educ Prev, 18(3), pp. 259-272, 2006.

Prenatal Cocaine Exposure not Linked to Child Behavior Problems at Age 7

This study examined the relationship between prenatal cocaine exposure and parent-reported child behavior problems at age 7 years. Data were from 407 African-American children (210 cocaine-exposed, 197 non-cocaine-exposed) enrolled prospectively at birth in a longitudinal study on the neurodevelopmental consequences of in utero exposure to cocaine. Prenatal cocaine exposure was assessed at delivery through maternal self-report and bioassays (maternal and infant urine and infant meconium). The Achenbach Child Behavior Checklist (CBCL), a parent report measure of childhood externalizing and internalizing behavior problems, was completed by the child's current primary caregiver during an assessment visit scheduled when the child was seven years old. Structural equation and GLM/GEE models disclosed no association linking prenatal cocaine exposure status or level of cocaine exposure to child behavior (CBCL Externalizing and Internalizing scores or the eight CBCL subscale scores). This evidence, based on standardized ratings by the current primary caregiver, fails to support hypothesized cocaine-associated behavioral problems in school-aged children with in utero cocaine exposure. A next step in this line of research is to secure standardized ratings from other informants (e.g., teachers, youth self-report). Accornero, V., Anthony, J., Morrow, C., Xue, L., and Bandstra, E. Prenatal Cocaine Exposure: An Examination of Childhood Externalizing and Internalizing Behavior Problems at Age 7 Years. Epidemiol Psychiatr Soc, 15(1), pp. 20-29, 2006.

Psychiatric Disorders among Parents/Caretakers of American Indian Early Adolescents in the Midwest

This study reports prevalence and comorbidty of five DSM-III-R diagnoses (alcohol abuse, alcohol dependence, drug abuse, major depressive episode, and generalized anxiety disorder) among American Indian and Canadian First Nations parents/caretakers of children aged 10-12 years from the Northern Midwest United States and Canada. Lifetime prevalence rates were compared to adults in the National Comorbidity Survey (NCS) and Southwest and Northern Plains cultures from the AI-SUPERPFP study. Native interviewers used computer-assisted personal interviews to administer the University of Michigan Composite International Diagnostic Interview (UM-CIDI) to 861 tribally enrolled parents and caretakers (625 females; 236 males) of 741 tribally enrolled children aged 10-12 years. Fathers/male caretakers ranged in age from 21 years to 68 years with an average age of 41 years; mothers/female caretakers ranged in age from 17 years to 77 years with an average of 39 years. About three-fourths (74.6%) of the adults met lifetime criteria for one of the five disorders; approximately one-third (31.6%) met lifetime criteria for two or more of the five disorders. Prevalence of the substance use disorders was higher than those in the general population (NCS); prevalence of internalizing disorders (major depressive disorder and generalized anxiety disorder) was very similar to those in the general population. Prevalence rates for alcohol abuse among the Northern Midwest adults were higher than those reported for Southwest and Northern Plains Tribes, but rates of alcohol dependency were very similar across cultures. The higher prevalence rates for some mental disorders found for the Northern Midwest are discussed in terms of potential method variance. The Northern Midwest results reflect unique patterns of psychiatric disorders in the ubiquity of substance abuse disorders and the co-occurrence of substance abuse disorders with internalizing disorders. Reducing lifetime occurrences of substance abuse disorders would have an enormous positive impact on the mental health of this population. Whitbeck, Hoyt, Johnson, and Chen. Mental Disorders among Parents/caretakers of American Indian Early Adolescents in the Northern Midwest. Soc Psychiatry Psychiatr Epidemiol, 2006.

Drug Use Related to Suicide Ideation in Midwestern American Indian Youth

This study examined correlates of suicidal ideation among 212 American Indian youth who lived on or near three reservations in the upper Midwestern United States. The youths were, on average, 12 years old, and 9.5% reported current thoughts about killing themselves. Females were over 2 times more likely than males to think about suicide. Multivariate logistic regression results indicated that gender, enculturation, negative life events, perceived discrimination, self-esteem, and drug use were related to the likelihood of thinking about suicide. Drug use was the strongest correlate of suicidal ideation, and both enculturation and perceived discrimination emerged as important culturally specific variables. It was suggested that suicide prevention programs should draw on the strengths of American Indian culture. Yoder, K., Whitbeck, L., Hoyt, D., and Lafromboise, T. Suicidal Ideation among American Indian Youths. Arch Suicide Res, 10(2), pp. 177-190, 2006.

Alcohol, Drugs, and Substance Use among Asian-American College Students

Two hundred and forty eight self-identified Asian-American college students participated in this study that examined the prevalence rates and sociodemographic factors of substance use among Asian Americans in college. Using a Basic Demographic Questionnaire, Family of Origin Measure, Acculturation Lifestyle Survey, and Substance Use Checklist (all instruments were in English), prevalence rates were found to be comparable to or higher than a national sample: 94.5% lifetime prevalence and 78.6% current prevalence (past 30 days) of alcohol use; and higher current prevalence (past

30 days) of illicit drug use (9.5%) and of cigarette use (22.8%) than other Asians aged 12 and older (3.5% for illicit drugs and 17.7% for cigarettes) in a national survey. Male students and those who were employed were more likely to be current users (past 30 days) of drugs in general (15%) and marijuana (13.2%), and users of wine coolers (76.0%) and cigarettes (61.1%) in their lifetime. Being born overseas, years in the U.S., and preference for American TV/movies are associated with substance use. Asian Americans are not immune from substance use (or abuse) while in college. These findings point to the need for culture-specific prevention interventions for Asian Americans. So, D., and Wong, F. Alcohol, Drugs, and Substance use among Asian-American College Students. J Psychoactive Drugs, 38(1), pp. 35-42, 2006.

Rapid Assessment and Response Studies of Injection Drug Use: Knowledge Gain, Capacity Building, and Intervention Development in a Multi-site Study

Researchers evaluated the World Health Organization's rapid assessment and response (RAR) method of assessing IDU and its associated health problems, focusing on knowledge gain, capacity building, and whether RAR leads to the development of interventions reducing the health effects of injection drug use. Data were derived from RAR studies conducted in Beijing, China; Bogotá, Colombia; Greater Rosario, Argentina; Hanoi, Vietnam; Kharkiv, Ukraine; Minsk, Belarus; Nairobi, Kenya; Penang, Malaysia; St. Petersburg, Russia; and Tehran, Iran. Substantial gains in knowledge and response capacity were reported at all of the study sites. Before RAR initiation, prevention and intervention programs had been absent or inadequate at most of the sites. The RARs resulted in many new or modified interventions; 7 sites reported 24 health-related interventions that were subsequently developed and influenced by the RARs. RARs, which require relatively little external funding, appear to be effective in linking assessment to development of appropriate interventions. The present results add to the evidence that rapid assessment is an important public health tool. Stimson, G., Fitch, C., DesJarlais, D., Poznyak, V., Perlis, T., Oppenheimer, E., and Rhodes, T. Rapid Assessment and Response Studies of Injection Drug Use: Knowledge Gain, Capacity Building, and Intervention Development in a Multi-site Study. Am J Public Health, 96(2), pp. 288-295, 2006.

Getting Clean and Harm Reduction: Adversarial or Complementary Issues for Injection Drug Users

Many contemporary HIV prevention interventions targeting IDUs have been implemented using "Harm Reduction' as a theoretical framework. Among drug-using individuals, however, the abstinence-based "getting clean" models espoused by Narcotics Anonymous and other widely adopted approaches to drug treatment are often more readily accepted. This paper describes an ethnographic examination of the ideological dichotomy between Harm Reduction and abstinence-based "getting clean" treatment model which emerged during the piloting phase of an HIV prevention intervention in Baltimore City, Maryland, USA. It particularly focuses on how the conflict was identified and what changes were made to the intervention to help resolve participants' dichotomous thinking concerning their substance abuse issues. Peterson, J., Mitchell, S., Hong, Y., Agar, M., and Latkin, C. Getting Clean and Harm Reduction: Adversarial or Complementary Issues for Injection Drug Users. Cad Saude Publica, 22(4), pp. 733-740, 2006.

The Urban Environment and Sexual Risk Behavior among Men Who have Sex with Men

Researchers discuss the importance of considering how characteristics of the

urban environment can influence a wide variety of health behaviors and disease outcomes, including those related to drug abuse, but note that few studies have focused on the sexual risk behaviors of men who have sex with men (MSM). Many gay men reside in or move to urban areas, and sexual risk behaviors and associated outcomes have increased among some urban MSM in recent years. Moreover, as interventions aimed at changing individual-level risk behaviors have shown mainly short-term effects, it is apparent that consideration should now be given to broader environmental influences. Previous efforts to assess the influence of environmental characteristics on sexual behaviors and related health outcomes among the general population have generally applied three theories as explanatory models: physical disorder, social disorganization and social norms theories. In these models, the intervening mechanisms specified to link environmental characteristics to individual-level outcomes include stress, collective efficacy, and social influence processes, respectively. Further work is needed to determine whether these models can be empirically supported in generating inferences about the sexual behavior of urban MSM. Conceptualizing sexual risk among MSM to include social and physical environmental characteristics provides a basis for generating novel and holistic disease prevention and health promotion interventions. Frye, V., Latka, M., Koblin, B., Halkitis, P., Putnam, S., Galea, S., and Vlahov, D. The Urban Environment and Sexual Risk Behavior Among Men Who Have Sex with Men. J Urban Health, 83(2), pp. 308-324, 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Prevention Ressearch

Effects of a School-Based Drug Abuse Prevention Program for Adolescents on HIV Risk Behavior in Young Adulthood

Early onset of substance use among adolescents has been found to be associated with later risky sexual behaviors. This study examined long-term follow-up data from a large randomized school-based drug prevention trial to (1) investigate the long-term impact of the prevention program on drug use and sexual behaviors that put one at elevated risk for HIV infection; and (2) use growth modeling procedures to examine potential mechanisms of intervention effects. Self-report survey data were collected from students in the 7th grade, prior to the intervention in 1985, and in grades 8, 9, 10, and 12. Participants in the intervention condition received a 30-session drug prevention program in 7th through 9th grades. Follow-up surveys were completed by 2042 young adults (mean age = 24) in 1998. As young adults, participants were considered to be engaging in high-risk behavior for HIV infection if they reported having multiple sex partners, having intercourse when drunk or very high, and recent high-risk substance use. The intervention had a direct protective effect on HIV risk behavior in the overall sample in young adulthood. Furthermore, among participants receiving 60% or more of the prevention program, analyses showed that the intervention significantly reduced growth in alcohol and marijuana intoxication over the course of adolescence, which in turn was associated with a reduction in later HIV risk behavior. The behavioral effects of competence-enhancement drug prevention programs can extend to risk behaviors including those that put one at risk for HIV infection. Griffin, K., Botvin, G., and Nichols, T. Effects of a School-Based Drug Abuse Prevention Program for Adolescents on HIV Risk Behavior in Young Adulthood. Prev Sci, 7(1), pp. 103-112, 2006.

Neurocognitive Skills Moderate Responses to Preventive Intervention

The present experiment was designed to determine whether individual variation in neurobiological mechanisms associated with substance abuse risk moderated effects of a brief preventive intervention on social competency skills. This study was conducted in collaboration with the ongoing preventive intervention study at Johns Hopkins University Prevention Intervention Research Center (JHU PIRC) within the Baltimore City Public Schools. A sub-sample (N = 120) of male 9th grade students was recruited from the larger JHU study population. Approximately half of the participants had a current or lifetime diagnosis of CD while the other half had no diagnosis of CD or other reported problem behaviors. Measures of executive cognitive function (ECF), emotional perception and intelligence were administered. In a later session, participants were randomly assigned to either an experimental or control

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group. The experimental group underwent a facilitated session using excerpted materials from a model preventive intervention, Positive Adolescent Choices Training (PACT), and controls received no intervention. Outcomes (i.e., social competency skills) were assessed using virtual reality vignettes involving behavioral choices as well as three social cognition questionnaires. Poor cognitive and emotional performance and a diagnosis of CD predicted less favorable change in social competency skills in response to the prevention curriculum. This study provides evidence for the moderating effects of neurocognitive and emotional regulatory functions on ability of urban male youth to respond to preventive intervention materials. Fishbein, D.H., Hyde, C., Eldreth, D., Paschall, M.J., Hubal, R., Das, A., Tarter, R., Ialongo, N., Hubbard, S., and Yung, B. Neurocognitive Skills Moderate Urban Male Adolescents' Responses to Preventive Intervention Materials. Drug Alcohol Depend, 82(1), pp. 47-60, 2006.

Project TND Demonstrated Long-term Effects on Drug Use of High Risk Youth

Project Towards No Drug Abuse is a 9-session health motivation--social skills--decision-making curriculum, which was implemented in South Carolina during years 1994-1999. Twenty-one schools recruited were randomly assigned to standard care (control), classroom only, or a classroom plus semester-long school-as-community component. Last 30-day use of cigarettes, alcohol, marijuana, and hard drugs were assessed at three time intervals: short-term (year 1), middle-term (years 2 or 3), and long-term (years 4 or 5). Multilevel random coefficients modeling were employed to estimate the adjusted levels of substance use. Among 1578 baseline subjects, follow-up data were available for 68% (year 1), 66% (years 2 or 3), and 46% (years 4 or 5) of subjects, respectively. Results revealed significant positive long-term program effects for hard drug use at year 4 or 5 for the two program interventions ($P = 0.02$). Project TND reduced hard drug use in the 46% who were successfully followed. It is the first program to demonstrate long-term self-reported behavioral effects on hard drug use among high-risk youth by using a school-based, limited-session model. Sun, W., Skara, S., Sun, P., Dent, C., and Sussman, S. Project Towards No Drug Abuse: Long-term Substance Use Outcomes Evaluation. Prev Med, 42(3), pp. 188-192, 2006.

Group Chat About Anti-drug Ads Produced Pro-Marijuana Attitudes

One route to influence in mass communication campaigns to reduce risky behavior is through interpersonal discussion of the content of the campaign and other behaviors pertinent to those targeted by the campaign. The goal of this study was to test the effects of online group interaction among adolescents about anti-marijuana advertisements on relevant attitudes and behaviors. A between-subjects post-only experimental design was used to test two crossed factors, online chat and strength of arguments in anti-drug ads. A sample of 535 students (46% male; mean age 15.5 years) was randomly assigned to one of four conditions: chat and strong-argument ads, chat and weak-argument ads, no chat and strong-argument ads, and no chat and weak-argument ads. The group interactions about anti-drug ads led to negative effects such that those who chatted reported more pro-marijuana attitudes and subjective normative beliefs than those who just viewed the ads. No support was found for the hypothesis that strong-argument ads would result in more anti-drug beliefs relative to weak-argument ads in either the chat or the no-chat conditions. Overall, these findings suggest that viewing anti-drug ads and discussing them with peers may result in deleterious effects in adolescents. David, C., Cappell, J.N., and Martin, F. The Social Diffusion of Influence Among Adolescents: Group Interaction in a Chat Room Environment About Anti-drug Advertisements. Communication Theory, 16(1), pp. 118-140, 2006.

Publications

Staff Highlights

Grantee Honors

Two-year Effects of the Family Checkup Program on the Prevention of Early Conduct Problems

This randomized trial examined the two-year outcomes of an initial study implementing an early childhood version of the Family Check-Up (FCU) program with 120 high risk families participating in the Women, Infants and Children (WIC) Nutritional Supplement Program for low-income families. Families with two-year old boys, and one or more risk factors for child problem behaviors were recruited and randomized to either intervention or control, and followed up when the children were ages 3 and 4. The FCU intervention was associated with reductions in disruptive behavior and greater maternal involvement and was particularly effective for children at greater risk for a persistent trajectory of conduct problems. The results are discussed in relation to other preventive interventions for young children. Very few family-based preventive interventions for child problem behaviors are available for this age group. These initial results support the early identification of risk factors for conduct problems, which increase risk for drug abuse, and support the development of prevention strategies for early childhood. Shaw, D., Dishion, T., Supplee, L., Gardner, F., and Arnds, K. Randomized Trial of a Family-centered Approach to the Prevention of Early Conduct Problems: 2-year Effects of the Family Check-up in Early Childhood. J Consult Clin Psychol, 74(1), pp. 1-9, 2006.

Multi-component Drug Abuse Prevention Programs: Effects of a Parent Component on Adolescent Outcomes

The current study estimates the effects of the parent program component of an evidence-based multi-component drug abuse prevention program for adolescents, Project STAR, among 351 parents of middle school students, who had been assigned by school to a program or comparison condition (n = 8 schools). The study was originally conducted in 1986, and the other program components were at the level of teachers, community leaders, and policy makers. Parents completed self-report surveys at baseline and two years later. Analyses estimated effects of the overall parent program as well as its three key constituent activities (parent-school committee participation, parent skills training, and parent-child homework activities) on perceptions of parental influence over their children's substance use. Parents who participated in the overall parent program demonstrated greater perceptions of influence over their children's substance use at two-year follow-up. Furthermore, parents who participated in parent-school committees and homework sessions demonstrated greater perceptions of influence over their children's substance use than those who did not. Parent skills training did not have an effect on perceptions of youth substance use. This study supports the use of components analysis to examine the impact of different program components on prevention outcomes. Also, the findings suggest that parent interventions may increase self-efficacy in parent-child management and communication skills. Riggs, N., Elfenbaum, P., and Pentz, M. Parent Program Component Analysis in a Drug Abuse Prevention Trial. J Adolesc Health, 39(1), pp. 66-72, 2006.

Prevention Curriculum Video Exposure Predicts Changes in Drug Use

This study sought to determine if exposure to two communication-oriented activities, videotapes and public service announcements, account for changes in substance use among adolescents participating in the Drug Resistance Strategies Project's "keepin' it REAL" adolescent substance use prevention curriculum. Students from 35 middle-schools (n=4,734, 72% Latino) responded to questionnaires related to these analyses. An analysis of

covariance (ANCOVA) model was fit separately to six substance use outcomes. The results suggested that intervention students who saw four or five videos reported smaller increases in alcohol and marijuana use in the past month than did students who saw fewer videos. Having seen the PSAs one or more times did not predict the reported change in substance use. Warren, J.R., Hecht, M.L., Wagstaff, D.A., Elek, E., Ndiaye, K., Dustman, P., and Marsiglia, F.F. Communicating PreventionÉ Journal of Applied Communication Research, 34(2), pp. 209-227, 2006.

Exposure to Classroom Aggression Predicts Development of Aggression in Children

Prior research suggests that exposure to elementary classrooms characterized by high levels of student aggression may contribute to the development of child aggressive behavior problems. To explore this process in more detail, this study followed a longitudinal sample of 4,907 children. The children were participants in the control arm of the universal level of Fast Track, a multi-site study of the prevention of conduct problems. Demographic factors associated with exposure to high-aggression classrooms, including school context factors (school size, student poverty levels, and rural vs. urban location) and child ethnicity (African American, European American) were examined. The developmental impact of different temporal patterns of exposure (e.g., primacy, recency, chronicity) to high-aggression classrooms was evaluated on child aggression. Analyses revealed that African American children attending large, urban schools that served socio-economically disadvantaged students were more likely than other students to be exposed to high-aggressive classroom contexts. Hierarchical regressions demonstrated cumulative effects for temporal exposure, whereby children with multiple years of exposure showed higher levels of aggressive behavior after 3 years than children with primacy, less recent, and less chronic exposure, controlling for initial levels of aggression. The findings of this study have implications for developmental research and preventive interventions. Specifically, transactional models that account for individual, classroom, school contextual and socio-cultural factors on the development of aggression, and the development of ecological interventions are discussed. Dishion, T., and Bierman, K. The Impact of Classroom Aggression on the Development of Aggressive Behavior Problems in Children. Dev Psychopathol, 18(2), pp. 471-487, 2006.

It Matters Who Leads School-based Prevention Programs

Studies have shown that the effectiveness of programs or curricula may depend in part on who delivers the material. In adolescent health education programs, peer leaders are often recruited to implement programs because they are more persuasive to other adolescents than adults. Teachers also systematically vary how groups are constructed in school-based health education programs. This study compared the effects of three leader and group selection methods within the context of two tobacco prevention programs delivered in middle schools. Eight schools received a social influences program (Chips) and eight received a program with a multicultural emphasis (Flavor). Within these 16 schools 84 classrooms consisting of 1486 students were randomly assigned to one of three leader and group creation conditions: (i) leaders defined as those who received the most nominations by students and groups created randomly (random group), (ii) same as (i) but groups created by assigning students to the leaders they nominated (network), and (iii) leaders and groups created by teachers (teacher). One year follow-up data showed that main effects of the curriculum and network assignments were non-significant on smoking initiation when entered alone. Interaction terms of curriculum and assignment methods, however, were significant such that the network and teacher conditions were less effective than the random group condition with Chips, and more effective than random group condition with

Flavor. These data show that school-based prevention programs should be evaluated in light of who implements the program. Even a peer-led program will be differentially effective based on how leaders are selected and how groups are formed, and this effect may be curriculum dependent. Valente, T.W., Unger, J.B., Anamara, R., Cen, S.Y., and Johnson, C.A. The Interaction of Curriculum Type and Implementation Method on 1-year Smoking Outcomes in a School-based Prevention Program. Health Education Research, 21(3), pp. 315-324, 2006.

Ways to Say No to Smoking and Other High Risk Behaviors

This study examined associations among adolescents' generated verbal strategies (i.e., Simple No, Declarative Statements, Excuse, Alternatives) and underlying nonverbal assertiveness (e.g., having a firm, authoritative voice; using direct eye contact; having a serious and confident facial expression) in 2 refusal situations: smoking and shoplifting. It is the first study to examine refusal skills strategies with a non-drug use and delinquent behavior situation. 454 sixth-grade urban minority students participated in videotaped role-play assessments of peer refusal skills. Differences were found by situation with students demonstrating greater use of Simple No in the smoking refusal and Alternatives in the shoplifting refusal. Nonverbal assertiveness was similar across situations and was associated with Declarative Statements, but only in the smoking refusal. The findings from this study suggest that, in addition to general refusal skills, prevention programs should tailor refusal skills practice to cover specific peer pressure situations. Nichols, T., Graber, J., Brooks-Gunn, J., and Botvin, G. Ways to Say No: Refusal Skill Strategies Among Urban Adolescents. Am J Health Behav, 30(3), pp. 227-236, 2006.

Results of Two Methods of Delivery of Life Skills Training

The study reported here assessed two methods of delivery of a prevention program called Life Skills Training (LST), implemented in nine rural disadvantaged school districts. This study tested the effectiveness of both standard LST curriculum, which is usually taught by one or two teachers in classes dedicated to substance abuse prevention), and the infused LST (I-LST) condition, which integrates LST and alcohol, tobacco and other drug information into the existing grade-level subject curricula, taught by the regular teachers for these subject areas. The results indicate that neither standard LST nor an infused LST delivery methods were effective for the entire sample, although some encouraging results were found for the females in the study. This study, conducted by researchers independent of the original LST program, is useful for school decision makers in determining what programs are most effective with which groups. It included all students with parental permission, controlling for prior use levels, unlike some previous LST studies. The results of the program, as implemented by regular classroom teachers, reflect many issues relevant to recruitment, training, implementation, adaptation, and institutionalization of prevention programming. Vicary, J., Smith, E., Swisher, J., Hopkins, A., Elek, E., Bechtel, L., and Henry, K. Results of a 3-year Study of Two Methods of Delivery of Life Skills Training. Health Educ Behav, 33(3), pp. 325-339, 2006.

The Impact of Tailored Intervention on Child Outcomes

Although clinical judgment is often used in assessment and treatment planning, rarely has research examined its reliability, validity, or impact in practice settings. This study tailored the frequency of home visits in a prevention program for aggressive- disruptive children (n = 410; 56% minority) on the basis of 2 kinds of clinical judgment: ratings of parental functioning using a standardized multi-item scale and global assessments of family need for

services. Parents and children were participants in Fast Track, a multi-component, longitudinal intervention to prevent conduct problems and serious antisocial behavior. Stronger reliability and better concurrent and predictive validity emerged for ratings of parental functioning than for global assessments. Exploratory analyses suggested that using ratings of parental functioning to tailor treatment recommendations improved the impact of the intervention by the end of 3rd grade but using more global assessments of family need did not, and may lead to delivery of optimal intervention doses. Bierman, K., Nix, R., Maples, J., and Murphy, S. Examining Clinical Judgment in an Adaptive Intervention Design: The Fast Track Program. J Consult Clin Psychol, 74(3), pp. 468-481, 2006.

Fidelity of Implementation of a School-based Drug Abuse Prevention Program: Project Toward No Drug Abuse (TND)

This article provides an implementation fidelity evaluation of the fourth experimental trial of Project toward No Drug Abuse (TND). Two theoretical content components of TND were examined to increase our understanding of the active ingredients of successful drug abuse prevention programs. A total of 18 senior high schools were randomly assigned by block to receive one of three conditions: 1) cognitive perception information curriculum; 2) cognitive perception information + behavioral skills curriculum; or 3) standard care (control). These curricula were delivered to both regular and continuation high school students (n=2331) by trained health educators and regular classroom teachers. Across all program schools, the two different curricula were implemented as intended, were received favorably by students, and showed significant improvement in knowledge specific to the theoretical content being delivered. This pattern of results suggests that the experimental manipulations worked as intended, and thus, permitted the attribution of future behavioral outcome differences between conditions to differences in content of Project TND material provided rather than to differences in the fidelity of delivery. Further, findings indicate that Project TND can be implemented effectively with low and high-risk youth in a general environment as well as with high-risk youth in a more specialized environment. Skara, S., Rohrbach, L. A., Sun, P., and Sussman, S. An Evaluation of the Fidelity of Implementation of a School-based Drug Abuse Prevention Program: Project Toward No Drug Abuse (TND). J Drug Educ, 35(4), pp. 305-329, 2005.

Prenatal Care Providers' Role in Reducing Risk for Smoking, Alcohol Use, Illicit Drug Use and Domestic Violence During Pregnancy

This qualitative study explored prenatal care providers' methods for identifying and counseling pregnant women to reduce or stop 4 high risk behaviors: smoking, alcohol use, illicit drug use, and the risk of domestic violence. Six focus groups were conducted (five with OB/Gyn physicians, one with nurse practitioners and certified nurse midwives), with 49 care providers, using open-ended questions that assessed: providers' specific issues or interests in preventing the risk behaviors; providers'' reactions and opinions to ACOG recommendations for handling the risk behaviors and whether providers feel they can have a positive impact on the risk behaviors; providers' challenges with assessing and counseling patients; providers' opinions about whether pregnancy is an opportune time to effect behavior change; whether providers should counsel patients about risk behaviors; best ways for providers to ask about the risky behaviors; and specific strategies providers have found effective for the risky behaviors. Three major themes emerged: (1) specific risk-prevention tactics or strategies exist that are useful during pregnancy; (2) some providers address patients' isolation or depression; and (3) providers can adopt a policy of "just chipping away" at risks. Specific tactics included normalizing risk prevention, using specific assessment techniques and

counseling strategies, employing a patient-centered style of smoking reduction, and involving the family. Providers generally agreed that addressing behavioral risks in pregnant patients is challenging, and that patient-centered techniques and awareness of patients' social contexts help patients disclose and discuss risks. Herzig, K., Danley, D., Jackson, R., Petersen, R., Chamberlain, L., and Gerbert, B. Seizing the 9-month Moment: Addressing Behavioral Risks in Prenatal Patients. Patient Educ Couns, 61(2), pp. 228-235, 2006.

HIV Risk is Common Among Older (Age 49-60) Substance Users, Particularly Men

Gender differences and other factors associated with current heroin and cocaine use were assessed among middle-aged drug users in New York City . Baseline data were merged from 2 studies of men and women with or at risk for HIV infection, and those age 49-60 years who had ever used heroin or cocaine were selected for analysis. HIV-antibody status, drug-use history, and psychosocial and sociodemographic data were examined. Logistic regression models were used to assess factors independently associated with current heroin and cocaine use. Of 627 persons who ever had used heroin and/or cocaine, 250 (39.9%) reported using these drugs within 6 months of the study interview. Men were more likely to be using drugs currently, compared with women (42.3% vs. 28.2%; p = .007). In multivariate analysis, men, unemployed persons, and HIV-seronegative persons were more likely to be using heroin or cocaine at the time of the interview. In addition, current marijuana users, persons drinking alcohol on a daily basis, and persons who had been homeless in the 6 months before the interview were also more likely to be using these drugs. It appears that a relatively high proportion of middle-aged substance users with or at risk for HIV infection, especially men, may continue to use illicit drugs into the sixth decade of life. Special attention needs to be given to aging and gender issues in framing HIV-prevention and drug-treatment programs. Hartel, D.M., Schoenbaum, E.E., Lo, Y., and Klein, R.S. Gender Differences in Illicit Substance Use Among Middle-Aged Drug Users with or at Risk for HIV Infection. Clin Infect Dis, 43(4), pp. 525-531, 2006.

Saturated in Beer: Awareness of Beer Advertising in Late Childhood and Adolescence

The purpose of this study was to examine exposure, response to, and awareness of beer advertising in 2 age groups, including awareness of a Budweiser advertisement (ad) that portrayed lizards and an animated ferret. In the spring of 2000, 1,996 fourth graders and 1,525 ninth graders attending 1 of 60 South Dakota schools participated in an in-school survey. Several indicators of advertising awareness, exposure, and response were assessed: recognition, product naming, brand naming, and liking in response to stills drawn from 4 masked television beer ads, listing of beer brands, exposure, attention to, and skepticism toward television beer ads. Fourteen percent of 4th graders and 20% of 9th graders recognized at least 3 of 4 sample beer ads. Seventy-five percent of 4th graders and 87% of 9th graders recognized the Budweiser ferret ad; about one in three 4th graders could name the brand it advertised, whereas more than three in four 9th graders could do so. When asked to list as many beer brands as they could, almost 29% of 4th graders listed 3 or more beer brands and 82% of 9th graders did so. Ninth graders liked beer advertisements more and paid greater attention to them, but 4th graders were exposed to them more often. Television beer ads result in high levels of beer advertising awareness in children as young as age 9, and even higher awareness among 14-year-olds. Practices that expose or appeal to youth, including use of animated characters, should be avoided by beer advertisers. Collins, R., Ellickson, P., McCaffrey, D., and Hambarsoomians, K. Saturated in Beer: Awareness of Beer Advertising in Late Childhood and Adolescence. J Adolesc Health, 37(1), pp. 29-36, 2005.

Effects of Differential Family Acculturation on Latino Adolescent Substance Use

This study examined links between parent-youth differential acculturation and youth substance-use likelihood in a sample of 73 recently immigrated Latino families with middle-school-aged youth. Multiple agents were utilized to assess family functioning and youth outcomes. Findings suggested that a greater level of differential acculturation between parents and youth was associated with greater likelihood of future youth substance use. However, the relationship between differential acculturation and youth substance use was mediated by family stress processes and effective parenting practices. Differential acculturation was related to increases in family stress and decreases in effective parenting practices, and each of these, in turn, was related to increases in future substance-use likelihood among Latino youth. Findings implicate the need for advancing policies and practices that address acculturation as a family process, rather than as merely an individual psychological phenomenon. Martinez, C.R. Effects of Differential Family Acculturation on Latino Adolescent Substance Use. Family Relations, 55, pp. 306-317, 2006.

Social Competence Among Urban Minority Youth Entering Middle School: Relationship with Alcohol Use and Antisocial Behaviors

Social competence is increasingly multidimensional during adolescence as young people encounter a variety of new social situations and can respond with a broad range of appropriate behaviors. However, research on social competence has focused more on children than adolescents. The present study examined the relationships between components of social competence (e.g., assertiveness and social confidence) and adolescent problem behaviors including alcohol use and antisocial behaviors (e.g., aggression and delinquency). A survey was administered to 6th grade students (N=2411) entering 20 New York City public and parochial middle schools and again a year later in the 7th grade. Findings indicated that verbal aggression was reported most frequently among students (93%), followed by physical aggression (69%), delinquent behaviors (53%), and alcohol use (16%). Structural equation modeling indicated that while assertiveness was protective in terms of adolescent problem behaviors, social confidence--the level of confidence that students had in initiating social interactions including dating--was associated with greater alcohol use and antisocial behavior both cross-sectionally and longitudinally. Additional analyses revealed that social confidence related to the initiation of dating (e.g., asking someone out for a date or having a conversation with a member of the opposite sex) was most strongly correlated with each problem behavior outcome. These findings suggest that social confidence, particularly as it relates to precocious dating behavior during early adolescence, is a risk factor for the early initiation of alcohol use and antisocial behavior. Griffin, K., Nichols, T., Birnbaum, A., and Botvin, G. Social Competence Among Urban Minority Youth Entering Middle School: Relationships with Alcohol Use and Antisocial Behaviors. Int J Adolesc Med Health, 18(1), pp. 97-106, 2006.

In India Sixth Graders Use More Tobacco Than Eight Graders

The epidemic of tobacco use is shifting from developed to developing countries, including India, where increased use is expected to result in a large disease burden in the future. Changes in prevalence of tobacco use in adolescents are important to monitor, since increased use by young people might be a precursor to increased rates in the population. A survey of 11,642 students in the sixth and eighth grades in 32 schools in Delhi and Chennai, India about

their tobacco use and psychosocial factors related to onset of tobacco use was conducted. Schools were representative of the range of types of school in these cities. Students who were in government schools, male, older, and in sixth grade were more likely to use tobacco than students who were in private schools, female, younger, and in eighth grade. Students in sixth grade were, overall, two to four times more likely to use tobacco than those in eighth grade. 24.8% (1529 of 6165) of sixth-grade students and 9.3% (509 of 5477) of eighth-grade students had ever used tobacco; 6.7% (413 of 6165) and 2.9% (159 of 5477), respectively, were current users. Psychosocial risk factors were greater in sixth-grade than in eighth-grade students. The increase in tobacco use by age within each grade was larger in sixth grade than in eighth grade in government schools, with older sixth-grade students at especially high risk. The finding that sixth-grade students use significantly more tobacco than eighth-grade students is unusual, and might indicate a new wave of increased tobacco use in urban India that warrants confirmation and early intervention. Reddy, K., Perry, C., Stigler, M., and Arora, M. Differences in Tobacco use Among Young People in Urban India by Sex, Socioeconomic Status, Age, and School Grade: Assessment of Baseline Survey Data. Lancet, 367(9510), pp. 589-594, 2006.

Direct and Mediated Effects of Aggressive Marital Conflict on Child Aggressive-Disruptive Behavior

Direct associations between aggressive marital conflict and child aggressive-disruptive behavior at home and school were explored in this cross-sectional study of 360 kindergarten children. In addition, mediated pathways linking aggressive marital conflict to maternal harsh punishment to child aggressive-disruptive behavior were examined. Moderation analyses explored how the overall frequency of marital disagreement might buffer or exacerbate the impact of aggressive marital conflict on maternal harsh punishment and child aggressive-disruptive behavior. Participants were a sub-sample of the normative and high risk groups in the Fast Track Project, and were included in this analysis if the biological mother of the study child was married and living with a spouse, and if the mother completed the measure of aggressive marital conflict during the child's kindergarten year. The Hierarchical regressions revealed direct pathways linking aggressive marital conflict to child aggressive-disruptive behavior at home and school, and maternal harsh punishment partially mediated the pathway linking aggressive marital conflict to child aggressive-disruptive behavior at home. Further analyses revealed that rates of marital disagreement moderated the association between aggressive marital conflict and child aggressive-disruptive behavior at home, with an attenuated association at high rates of marital disagreement as compared with low rates of marital disagreement. These preliminary findings suggest that marital conflict may be another important target for the prevention of child conduct problems and related high-risk trajectories. Erath, S., Bierman, K., and Bierman, K.C. Aggressive Marital Conflict, Maternal Harsh Punishment, and Child Aggressive-disruptive Behavior: Evidence for Direct and Mediated Relations. J Fam Psychol, 20(2), pp. 217-226, 2006.

The Mutual Influence of Parenting and Boys' Externalizing Behavior Problems

The current study examined the mutual influence of parenting and boys' externalizing behavior from 4th to 8th grade, how these relationships change as children develop, and the stability of parenting and child behavior in a sample of 122 boys. Child behavior predicted poor parental monitoring at 6th and 7th grade and inconsistent discipline at all grade levels examined. Parenting behavior was not related to child behavior above and beyond the stability of child behavior. Stability of child behavior decreased from 5th to 6th grade and stability of parental monitoring decreased from 5th-6th and 6th-7th

grade, suggesting that 6th grade was an important transition point for both parenting and child behavior. Fite, P.J., Colder, C.R., Lochman, J.E., and Wells, K.C. The Mutual Influence of Parenting and Boys' Externalizing Behavior Problems. Journal of Applied Developmental Psychology, 27(2), pp. 151-164, 2006.

Influences of Social Norms on Early Adolescent Substance Use

Social norms play an important role in adolescent substance use. Norm focus theory (Cialdini et al., 1990) distinguishes three types of norms: injunctive, descriptive, and personal. This study examines the relative influence of these three norms, as well as the moderating effects of gender and ethnicity, on the concurrent substance use of 2,245 Mexican or Mexican-American students, 676 other Latino students, 756 non-Hispanic White students, and 353 African-American students. Personal norms appear to be the strongest significant predictor of substance use. Descriptive, parental injunctive, and friend injunctive norms also demonstrate significant, though weaker influences. Controlling for intentions reduces the predictive ability of each type of norm, especially personal norms. Gender moderates the relationship between norms and substance use with the relationships generally stronger for males. Personal norms act as stronger predictors of some types of substance use for Mexican/Mexican Americans. Elek, E., Miller-Day, M., and Hecht, M.L. Influences of Personal, Injunctive, and Descriptive Norms on Early Adolescent Substance Use. Journal of Drug Issues, 36(1), pp. 147-171, 2006.

Brief Motivational Interviewing for Drug Using Adolescents

This article reviews studies of brief motivational interviewing (MI) interventions applied to adolescents (ages 13 to 18 years) and young adults (ages 19 to 25 years) using alcohol or other psychoactive substances. An overview of the principles of MI is provided followed by a review of 17 clinical studies reported in the literature. This review revealed mixed findings for the efficacy of brief MI among these populations. However, in 29% of the studies (5 of 17), there was a clear advantage of the brief MI demonstrated compared to standard care or other programming. Components common to successful brief MI interventions included one-on-one sessions and feedback on substance use compared to norms. Interviewer empathy has been shown to be a key component in studies with adults, but this was not measured in a standardized manner across the current studies. The studies reviewed here indicate that brief MI might be effective among these populations, but the key components necessary for successful MI interventions have not been fully identified. Grenard, J., Ames, S., Pentz, M., and Sussman, S. Motivational Interviewing with Adolescents and Young Adults for Drug-related Problems. Int J Adolesc Med Health, 18(1), pp. 53-67, 2006.

Victimization and Health Among Indigent Young Women in the Transition to Adulthood: A Portrait of Need

To understand victimization by physical and sexual violence and its association with physical and behavioral health in a probability sample of sheltered homeless and low-income-housed young women in the transition to adulthood (ages 18 through 25). Participants were 224 women ages 18 through 25 who were selected by means of a stratified random sample from 51 temporary shelter facilities (N = 94) and 66 Section 8 private project-based Housing and Urban Development (HUD)-subsidized apartment buildings (N = 130) in Los Angeles County, California. Women completed structured interviews. Forty-one percent of the sample had been physically or sexually victimized as children and 51% had been victimized since turning 18. Young women who experienced victimization were significantly ($p < .05$) more likely than non-victimized

women to have a sexually-transmitted disease (STD) other than HIV/AIDS or Hepatitis B or C, vaginal discharge or bleeding and pelvic pain in the past 6 months, and past-12 month screening diagnoses of drug abuse/dependence and depression. Victimized women were also significantly more likely to use alcohol to intoxication and drugs, including crack and amphetamines, during the past 6 months, and to have experienced psychological distress and poor self-esteem. This study highlights striking rates of victimization and its association with physical and behavioral health problems among indigent young women during the period of emerging adulthood. This portrait of need communicates an urgency to develop multifaceted programs for such women to help them successfully navigate the transition to adulthood and realize their full potential as adults. Wenzel, S., Hambarsoomian, K., D 'Amico, E., Ellison, M., and Tucker, J. Victimization and Health Among Indigent Young Women in the Transition to Adulthood: A Portrait of Need. J Adolesc Health, 38(5), pp. 536-543, 2006.

HIV Infection is a Significant Risk Factor for Human Papillomavirus (HPV) Among Drug Using Women

A total of 230 female former and current drug users in New York City were prospectively studied at 6 month intervals. Each assessment included interviews, HIV testing, and cervicovaginal lavage sampling for human papillomavirus (HPV). Incidence rates of and factors associated with HPV infections of all types and high-risk types were analyzed. Baseline median age was 40 years (range 24-65); 62% of women were Hispanic, 20% black, and 16% white; 54 (24%) were HIV seropositive; 172 (75%) were without detectable HPV; 58 (25%) had only low-risk or untypeable HPV. The incidence rate for any HPV 9.5/100 person-years type and for high-risk types was 4.8/100 person-years. HIV-seropositive women had a significantly increased hazard rate for any HPV (HRadj: 3.4; 95% CI: 1.4 to 8.0) and for high-risk HPV (HRadj 3.0; 95% CI: 1.4 to 6.6), adjusted for race, sexual behaviors, condom use, and history of other sexually transmitted infections. HIV infection was independently associated with a substantial and significantly increased risk for any and for high-risk genital HPV infection and was the most important risk factor found. Dev, D., Lo, Y., Ho, G.Y., Burk, R.D., and Klein, R.S. Incidence of and Risk Factors for Genital Human Papillomavirus Infection in Women Drug Users. J Acquir Immune Defic Syndr, 41(4), pp. 527-529, 2006.

HIV Prevalence and Risk Behaviors Among Injection Drug Users Following Implementation of Cross-border HIV Prevention Interventions in Northern Vietnam and Southern China

In 2002, the researchers implemented a 4-year HIV prevention intervention for injection drug users (IDUs) in Lang Son Province, Vietnam, and Ning Ming County, Guangxi Province, China, a cross-border region seriously affected by inter-twined epidemics of heroin injection and HIV infection. The interventions involve peer education on HIV risk reduction and provision of new needles/syringes through direct distribution and pharmacy vouchers. The researchers consider this to be a structural intervention in which risk reduction information and sterile injection equipment are diffused through the IDU populations and not limited to those who actually interact with peer educators. The evaluation of structural interventions poses complex methodological challenges. The evaluation of our interventions relies primarily on cross-sectional surveys (interviews and HIV testing) of samples of IDUs selected using a combination of targeted cluster and snowball methods. The researchers consider this to be an appropriate, albeit imperfect, design given the study context. This paper presents analyses of data from the IDU surveys conducted just prior to implementation of the interventions and 24 months thereafter. The cross-border interventions have reached large proportions of the IDUs in the project sites, drug-related HIV risk behaviors have declined in frequency, and

HIV prevalence among IDUs has been stable in China and declined in Vietnam over the 24 months since the interventions were implemented. Attribution of these positive trends to the interventions must be qualified in light of possible sampling biases and the absence of control groups. However, the researchers believe that the structural interventions implemented by the cross-border project have played a role in stabilizing HIV prevalence among IDUs two years after they were initiated. Evidence of further diffusion of the interventions among IDUs and continued stability or decline of HIV prevalence would strengthen this case. Hammett, T., Kling, R., Johnston, P., Liu, W., Ngu, D., Friedmann, P., Binh, K., Dong, H., Van, L., Donghua, M., Chen, Y., Jarlais, D., and Jarlais, D. Patterns of HIV Prevalence and HIV Risk Behaviors Among Injection Drug Users Prior to and 24 Months Following Implementation of Cross-border HIV Prevention Interventions in Northern Vietnam and Southern China. AIDS Educ Prev, 18(2), pp. 97-115, 2006.

Condom Use Among Mexican Migrants

This study analyzed the association between condom use and migration to the United States (US) in two Mexican municipalities. A cross-sectional, non-probabilistic study of egocentric social networks was conducted in CuauhtŽmoc, Colima and Tonalá, Jalisco during the months of December 2003 and January 2004, in 354 male migrants (mean age 32.8 years old). Migration, sexual network, history and risk for sexually transmitted infections (STIs) characteristics were surveyed. Statistical analyses were conducted using logistic regression. Results indicated that increased migration travel to the US was significantly associated with consistent condom use for CuauhtŽmoc (OR: 3.87; $p < 0.05$) and Tonalá (OR: 4.12; $p < 0.05$) municipalities. Other significant predictors included: age, type of sex partner, and perceived monogamy. These data support the hypothesis that migration to the US is associated with condom use. Fosados, R., Caballero-Hoyos, R., Torres-López, T., and Valente, T. Condom Use and Migration in a Sample of Mexican Migrants: Potential for HIV/STI Transmission. Salud Publica Mex, 48(1), pp. 57-61, 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

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

Escalating Reinforcement Schedule with Resets Results in Faster Abstinence and More Resistance to Relapse in Methamphetamine Users

Dr. John Roll and others at Friends Research Institute examined five different schedules for delivering vouchers exchangeable for goods and services, contingent on providing a methamphetamine abstinent urine specimen within the context of a group outpatient behavioral treatment setting. Although the total monetary value for vouchers earned was approximately equal in all conditions, schedules differed in terms of whether the values escalated over time, remained stable or decreased over time, whether they reverted to baseline levels in response to a drug positive urine, and whether participants were offered bonus incentives for obtaining several drug free urine tests in a row. Reinforcement schedules differed in terms of the speed at which participants initiated abstinence. The schedule which provided a stable reinforcement value of $25.00 per abstinence episode, along with a $50.00 bonus for three consecutive drug negative urines, resulted in 50% fewer participants obtaining a 4 week long period of abstinence. Additionally, the schedule, which began at $2.50 for first negative specimen increased the abstinence contingency by $1.25 for each consecutive drug abstinent specimen provided, gave a $10.00 bonus for each block of three consecutive drug free urines, and which reset the voucher value to the previously earned level for any drug positive urine, produced the most resistance to relapse. The total amount of reinforcement available under this schedule was $997.50 for 12 weeks of treatment if a participant remained 100% abstinent. These findings are significant because they underscore the value of providing contingent reinforcement for abstinence as a component of methamphetamine treatment. Additionally they demonstrate that using the escalating schedule with a reset contingency for drug use can substantially improve outcomes beyond what can be obtained for the same amount of money distributed without such contingencies. Roll, J. M., Huber, A.M., Sodano, R., Chudzynski, J.E., Moynier, E. and Shoptaw, S. The Psychological Record, 56, pp. 67-81, 2006.

Comparing Intervention Outcomes in Smokers Treated for Single Versus Multiple Behavioral Risks

Investigators conducted this study to determine whether smoking cessation outcome differed in smokers at risk and treated for smoking only versus those at risk and treated for one or two additional risk behaviors (high fat diets and high-risk sun exposure). The sample consisted of participants from three population-based studies (N=2,326). In each trial, participants were randomized to one of two groups: an expert system intervention or an

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assessment-only control condition. The stage-based expert system used tailored communications for treating the cancer-related risk behaviors of cigarette smoking, high-fat diet, or high-risk sun exposure. Findings indicate that there was no reduction in smoking cessation success when additional behavioral risks were treated. The smoking cessation expert system intervention resulted in significantly enhanced abstinence rates at long-term follow-up, with similar treatment effects among individuals at risk and treated only for smoking compared with persons at risk and treated for smoking plus one or two additional risk behaviors. The current findings support the strategy of treating multiple rather than single behaviors within individuals and populations that have multiple risks. Prochaska, J.J., Velicer, W.F., Prochaska, J.O., Delucchi, K., and Hall, S.M. Health Psychology, 25, pp. 380-388, 2006.

Do Smokers with Alcohol Problems have More Difficulty Quitting?

This paper reviews studies comparing smokers with and without alcohol problems on their nicotine dependence, ability to quit on a given quit attempt, whether they ever quit (lifetime quitting), and number of quit attempts. Almost all studies found that smokers with current and past alcohol problems were more nicotine dependent than smokers with no alcohol problems. Smokers with past alcohol problems were as likely to stop smoking on a given quit attempt as smokers with no problems, despite their increased nicotine dependence. It is hypothesized that this may be because smokers with past alcohol problems learned certain motivational and coping skills during alcohol recovery that helped them stop smoking and this counteracted the effect of greater nicotine dependence. Smokers with current or past alcohol problems appear to be less likely to quit in their lifetime. Given their equal ability to quit on a given attempt, this could be due to fewer quit attempts; however, whether this is actually so is unclear. The finding that smokers with past alcohol problems can quit as easily as those without alcohol problems suggests that smokers with past alcohol problems may respond to minimal treatments to stop smoking and may not necessarily need specialized treatment. Hughes, J.R., and Kalman, D. Drug and Alcohol Dependence, 82, pp. 91-102, 2006.

Characterizing Nicotine Withdrawal in Pregnant Cigarette Smokers

The aim of this study was to characterize nicotine withdrawal and craving in pregnant cigarette smokers. These data were collected as part of prospective clinical trials assessing the efficacy of voucher-based incentives to promote abstinence from cigarette smoking during pregnancy and postpartum. Results from 27 abstainers and 21 smokers during the first 5 days of a cessation attempt were examined. Abstinent pregnant smokers reported more impatience, anger and difficulty concentrating than did smokers. The results also suggest that pregnant smokers generally may have elevated baseline levels of withdrawal, which need to be considered in the design and analysis of future studies. Heil, S.H., Higgins, S.T., Mongeon, J.A., Badger, G.J., and Bernstein, I.M. Experimental and Clinical Psychopharmacology, 14, pp. 165-170, 2006.

A Comparison Between Low-Magnitude Voucher and Buprenorphine Medication Contingencies in Promoting Abstinence from Opioids and Cocaine

Investigators conducted this study to determine the relative efficacy of low-magnitude, contingency monetary vouchers, contingent buprenorphine medication, and standard counseling in promoting abstinence from illicit opioids and cocaine among opioid dependent adults. Following an 8 week baseline period during which participants received buprenorphine maintenance

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treatment with no contingencies in place, 60 participants were randomly assigned to one of 3 treatment groups for 12 weeks: 1) participants in the voucher group earned vouchers for each opioid and cocaine negative urine sample, in accordance with an escalating schedule. Continuous abstinence resulted in voucher earnings equivalent to a total of $269, which participants could exchange for material reinforcers of their choice. 2) Participants in the medication contingency group received half of their scheduled buprenorphine dose for clinic attendance and the other half for remaining abstinent from opiates and cocaine. 3) Participants in the standard counseling group did not receive programmed consequences contingent on urinalysis results. All participants were maintained on buprenorphine according to a 3 times per week dosing regimen and participated in behavioral drug counseling. Retention rates did not differ significantly across groups; however, participants in the medication contingency group achieved significantly more weeks of continuous abstinence from opiates and cocaine compared with participants in the voucher group. Results suggest that the use of medication-based contingencies in combination with behavioral therapy may have clinical utility in promoting abstinence. Gross, A., Marsch, L.A., Badger, G.J., and Bickel, W.K. Experimental and Clinical Psychopharmacology, 14 (2), pp. 148-156, May 2006.

Randomized, Placebo Controlled Trial of Sertraline and Contingency Manangement for the Treatment of Methamphetamine Dependence

Investigators evaluated the efficacy of sertraline (50mg twice a day) and contingency management for the treatment of methamphetamine dependence. In this randomized, placebo-controlled, double-blind trial, participants completed a 2 week non medication baseline and were randomized to one of four conditions for 12 weeks: sertraline plus contingency management (n=61); sertraline only (n=59); matching placebo plus contingency management (n=54); or matching placebo only (n=55). All participants attended clinic three times per week for data collection, medication dispensing, and relapse prevention groups. Outcomes included methamphetamine use (urine drug screening and self reported days of use), retention (length of stay), drug craving (visual analogue scale), and mood symptoms (Beck Depression Inventory). Study findings showed no statistically significant main or interaction effects for sertraline or contingency management in reducing methamphetamine use using a generalized estimating equation, although post hoc analyses showed the sertraline only condition had significantly poorer retention than the other conditions. Sertraline conditions produced significantly more adverse events than placebo conditions. A significantly higher proportion of participants in contingency management conditions achieved three consecutive weeks of methamphetamine abstinence than those in the non-contingency management conditions. These data do not demonstrate improved outcomes for sertraline versus placebo for treatment of methamphetamine dependence and suggest that sertraline may be contraindicated for methamphetamine dependence. However, the findings provide support for the use of contingency management in the treatment of methamphetamine dependence. Shoptaw, S., Huber, H., Peck, J., Yang, X., Liu, J., Dang, J., Roll, J., Shapiro, B., Rotheram-Fuller, E., and Ling, W. Drug and Alcohol Dependence, April 2006.

The Role of Homework in Cognitive-Behavioral Therapy for Cocaine Dependence

This study examined the effects of homework compliance on treatment outcome in 123 participants receiving cognitive behavioral therapy for cocaine dependence. Regression analyses revealed a significant relationship between homework compliance and cocaine use that was moderated by readiness to

change. Homework compliance predicted less cocaine use during treatment but only for participants higher in readiness to change. For those lower in readiness to change, homework compliance was not associated with cocaine use during treatment. Homework compliance early in therapy was associated with better retention in treatment. Homework compliance was not predicted by participants' level of education or readiness to change. These findings support the use of homework during cognitive behavioral therapy for substance use disorders. Gonzales, V.M., Schmitz, J.M., and Delaune, K.A. J. Consulting and Clinical Psychology, 74(3), pp. 633-637, June 2006.

Recommendations for Managing Analytic Complexities Associated with Group Therapy for Substance Abuse Treatment

Using state-of-the-science group therapy studies as examples, Drs. Antonio Morgan-Lopez and William Fals-Stewart, of the Research Triangle Institute, highlight the logistical, methodological, and analytic complexities of group therapy research and provide clarifying recommendations. Complexities discussed include whether to constitute "closed" groups with fairly stable group membership, or "rolling" groups with frequently changing membership; the interdependence of group participants, and changes in group membership; and assuming group data is hierarchical, with group members fully nested within a group. Recommendations include matching the analytic approach to the study goals, working toward development of new statistical approaches, and collecting time series data to inform these new approaches. Given that the vast majority of substance abuse treatment is delivered in group settings, and the tremendous complexity of evaluating group therapy data, this sort of guidance to investigators is sorely needed to advance the field of treatment research. Morgan-Lopez, A. A., and Fals-Stewart, W. Experimental and Clinical Psychopharmacology, 14, pp. 265-273, 2006.

Making Sense of Therapeutic Alliance as a Mechanism in Adolescent Substance Abuse Treatment: Not All Behavior Change in Treatment Can be Explained by Therapeutic Alliance

Dr. Aaron Hogue and colleagues at the National Center on Addiction and Substance Abuse at Columbia University, Dr. John Cecero of Fordham University, and Dr. Howard Liddle of the University of Miami conducted a secondary analysis study of the role of therapeutic alliance in treatment success for adolescent substance abusers. In general, therapeutic alliance is conceptualized as the degree to which a therapist and client(s) develop a positive, collaborative relationship, and the strength of this relationship is thought by some to be one of the key ingredients in therapy success. But others have argued that therapeutic alliance is not sufficient to produce change, that alliance is a product of success rather than a cause of it, and that the role of alliance may differ depending on the therapy model and the developmental stage of the patient. This groundbreaking study tested the role of therapeutic alliance for adolescents in treatment, and compared the role of alliance in two different therapy models (individual-based cognitive-behavioral therapy, or CBT, vs. family-based Multi-Dimensional Family Therapy, or MDFT). Overall, the investigators found that therapeutic alliance was not a significant predictor of treatment outcome for adolescents in CBT, but both parent and adolescent alliance predicted outcome for MDFT. Importantly, while stronger parent-therapist alliances predicted better outcomes in MDFT, stronger adolescent-therapist outcomes predicted worse outcomes in MDFT, based on parent reports of their teens' externalizing behavior. The results of this study caution against a simple alliance explanation for therapeutic success, and suggest that a simple focus on the therapeutic relationship or on the therapy technique alone is likely to be an inadequate explanation of complex behavior change. Hogue, A., Dauber, S., Stambaugh, L. F., Cecero, J. J., and Liddle, H. A. Journal of Consulting and Clinical Psychology, 74, pp. 121-129, 2006.

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Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Research on Pharmacotherapies for Drug Abuse

Aripiprazole Attenuates the Discriminative-Stimulus and Subject-Rated Effects of D-Amphetamine in Humans

Studies of aripiprazole in animals suggest that partial agonists at the D2 receptors may be an effective strategy for the treatment of stimulant dependence. Aripiprazole is an atypical antipsychotic that has partial D2 agonist activity. In this study, seven participants with a history of stimulant abuse learned to discriminate 15 mg oral d-amphetamine, after which the effects of a range of doses of d-amphetamine (0, 2.5, 5, 10 and 15 mg) , alone and in combination with aripiprazole (0 and 20 mg) were assessed. Administration of aripiprazole significantly attenuated the discriminative-stimulus and cardiovascular effects of d-amphetamine, as well as some of the subject-rated drug effects. Lile, J.A., Stoops, W.W., Vansickel, A.R., Glaser, P.E.A., Hays, L.R. and Rush, C.R. Neuropsychopharmacology, 30, pp. 2103-2114, 2005.

Safety and Immunogenicity of a Nicotine Conjugate Vaccine in Current Smokers

This study in 68 smokers was carried out to assess the safety and immunogenicity of a nicotine conjugate vaccine, NicVAX, and its effects on smoking behavior. Participants were assigned to 1 of 3 doses of NicVAX (50, 100 or 200 µg) or placebo. They were injected on days 0, 28, 56, and 182 and monitored for 38 weeks. Results showed that NicVAX was safe and well tolerated. Vaccine immunogenicity was dose-related (P<.001) with the highest dose eliciting antibody concentrations within the anticipated range of efficacy. The 30-day abstinence rate was significantly different across the 4 doses (P=.02) with the highest rate of abstinence occurring with 200 µg. Hatsukami, D.K., Rennard, S., Jorenby, D., Fiore, M., Koopmeiners, J., de Vos, A., Horwith, G. and Pentel, P.R. Clin. Pharmacol. Ther., 79, pp. 456-467, 2005.

Cognitive Deficits Predict Low Treatment Retention in Cocaine Dependent Patients

Impaired cognition predicted treatment dropout from cognitive behavioral therapy (CBT) in a small sample of cocaine dependent patients. To further address the role of impaired cognition in retention and treatment outcome of cocaine-dependent patients in CBT, the P.I. expanded a previous investigation to a larger sample, added depressed cocaine patients, and added an additional cognitive assessment. Fifty-six cocaine dependent patients receiving CBT in outpatient clinical trials were assessed for cognitive performance at treatment

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entry with the computerized MicroCog (MC) and the Wisconsin Card Sort Test (WCST). Treatment completion was defined as 12 or more weeks. Treatment dropouts had significantly lower MC scores (poorer cognitive functioning) than completers on attention, memory, spatial ability, speed, accuracy, global functioning, and cognitive proficiency, with effect sizes in the moderate to large range. These findings were not affected by depression, demographics (age, gender, race, sex, marital status) or drug use (years of cocaine use or average weekly cocaine expenditure in the prior 30 days). In contrast, patients' performance on the WCST was in the average or near-average range, and WCST scores did not differentiate between completers and dropouts. Consistent with previous research, results suggest that mild cognitive impairments (< or =1 S.D. below the mean) negatively affect retention in outpatient CBT treatment for cocaine dependence. Future studies should examine whether there are specific effects of different executive functioning abilities on treatment outcome. Modified behavioral and pharmacologic interventions should be considered to target mild cognitive impairments to improve substance treatment outcome. Aharonovich, E., Hasin, D. S., Brooks, A. C., Liu, X., Bisaga, A., & Nunes, E. V. Cognitive Deficits Predict Low Treatment Retention in Cocaine Dependent Patients. Drug Alcohol Depend., 81, pp. 313-322, 2006.

Clozapine Use and Relapses of Substance Use Disorder Among Patients With Co-occurring Schizophrenia and Substance Use Disorders

Previous correlational research with schizophrenic patients has suggested that the second-generation antipsychotic medication clozapine helps to induce remissions of substance use disorder in patients with co-occurring psychosis and substance abuse. This research, however, could be biased by selection factors. Studying patients who are currently in substance abuse remission could control for level of motivation to stop using substances and other methodological confounds.To test whether clozapine was associated with prevention of substance abuse relapses, the P.I. examined patients with schizophrenia or schizoaffective disorder who were in their first 6-month remission of substance use disorder during a prospective 10-year follow-up study. All patients received yearly multimodal assessments of substance use. Antipsychotic medications were prescribed by community doctors as part of usual clinical care. Patients using clozapine at the first 6-month period of substance abuse remission (n = 25) were much less likely to relapse over the next year compared with those on other antipsychotic medications (n = 70): 8.0% vs 40.0%, chi(2) = 8.73 (df = 1), P = .003. Although medication assignment was not randomized, several potential confounders were similar between the groups. In conclusion, clozapine should be considered for the treatment of patients with schizophrenia and co-occurring substance use disorder to prevent relapses to substance abuse. Brunette, M.F., Drake, R.E., Xie, H., McHugo, G.J., and Green, A.I. Clozapine Use and Relapses of Substance Use Disorder Among Patients With Co-occurring Schizophrenia and Substance Use Disorders. Schizophr. Bull, 2006 (EPub ahead of print).

Drug Stroop Performance: Relationships With Primary Substance of Use and Treatment Outcome in a Drug-Dependent Outpatient Sample

A modified Stroop protocol was administered to a sample of 80 dependent drug users (62 males, 18 females) prior to beginning a time-limited outpatient treatment study combining pharmacotherapy and cognitive-behavioral coping skills therapy for cocaine, marijuana, or heroin dependence. Results indicated that cocaine-dependent participants responded more slowly than marijuana-dependent participants to all stimulus words. Cocaine words yielded slower

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reaction times than neutral words across all treatment groups. The heroin- and cocaine-dependent groups' overall performance did not differ. There was no treatment group by drug word interaction. For cocaine-dependent participants, Stroop performance in the presence of cocaine stimuli was associated with worse treatment outcome. In conclusion, Stroop performance may have prognostic utility among drug-dependent patients in a cognitive-behavioral coping skills intervention and may highlight the mechanisms associated with changing substance use in this treatment modality. Carpenter, K. M., Schreiber, E., Church, S., and McDowell, D. Drug Stroop Performance: Relationships with Primary Substance of Use and Treatment Outcome in a Drug-dependent Outpatient Sample. Addict. Behav., 31, pp. 174-181, 2006.

Response to Cocaine, Alone and in Combination with Methylphenidate, in Cocaine Abusers with ADHD

Attention deficit hyperactivity disorder (ADHD) is prevalent in adult cocaine abusers. Yet, it remains to be determined how the response to cocaine differs in cocaine abusers with ADHD compared to cocaine abusers without ADHD. Further, since ADHD is commonly treated with stimulants, such as methylphenidate (MPH), it is important to examine whether MPH maintenance alters the response to cocaine in cocaine abusers with ADHD. Thus, the first phase of this study compared the response to cocaine in adult cocaine abusers with ADHD to those without ADHD. The second phase assessed the effects of oral sustained-release methylphenidate (MPH-SR) maintenance (40 and 60 mg) on the response to cocaine only in those with ADHD. Cocaine abusers with ADHD (N=7) and without ADHD (N=7) who were not seeking treatment remained inpatient initially for 1 week, when the effects of cocaine alone were tested (Phase 1). Cocaine abusers with ADHD remained inpatient for an additional 3 weeks, during which the effects of cocaine during oral MPH-SR maintenance were tested (Phase 2). During cocaine fixed dosing sessions, participants received four injections of i.v. cocaine (0, 16 or 48 mg/70 kg), spaced 14 min apart. During cocaine choice sessions, participants had a choice between receiving i.v. cocaine (16 or 48 mg/70 kg) or two tokens, each exchangeable for 2 US dollars. Subjective effects related to ADHD symptoms (e.g. ratings of "Able to Concentrate") were significantly lower in cocaine abusers with ADHD compared to those without ADHD when placebo cocaine was administered. Active cocaine produced similar increases in cardiovascular and positive subjective effects in both groups and there was no difference in cocaine choice between the two groups. These data suggest that the response to cocaine is not different between cocaine abusers with ADHD compared to those without ADHD. When the cocaine abusers with ADHD were maintained on MPH-SR, cardiovascular effects were increased, however, this did not warrant termination of any test session. Maintenance on MPH-SR decreased some of the positive subjective effects of cocaine. Further, maintenance on a high dose of MPH-SR decreased cocaine choice. Thus, oral MPH-SR is safe in combination with repeated cocaine doses and decreases some of the positive and reinforcing effects of cocaine in cocaine abusers with ADHD. Collins, S.L., Levin, F.R., Foltin, R.W., Kleber, H.D., and Evans, S.M. Response to Cocaine, Alone and in Combination with Methylphenidate, in Cocaine Abusers with ADHD. Drug Alcohol Depend., 82, pp. 158-167, 2006.

Buprenorphine/Naloxone Reduces the Reinforcing and Subjective Effects of Heroin in Heroin-dependent Volunteers

Although buprenorphine is effective in treating opioid dependence, optimal maintenance doses of buprenorphine or the buprenorphine/naloxone combination have not yet been established. The present study was designed to evaluate the effects of buprenorphine/naloxone maintenance (2/0.5, 8/2, 32/8 mg sublingual) on the reinforcing and subjective effects of heroin (0, 12.5, 25, 50, and 100 mg intranasal) in heroin-dependent individuals. During test weeks,

participants (N=7) first sampled a dose of heroin and 20 dollars. During subsequent choice sessions, participants could choose to self-administer heroin and/or money. Participants responded under a modified progressive-ratio schedule (PR 50, ..., 2,800) during a ten-trial self-administration task. Heroin break point values and subjective responses were significantly lower under 8/2 and 32/8 mg buprenorphine/naloxone compared to 2/0.5 mg. The self-administration and subjective effects data for heroin in the presence of buprenorphine/naloxone were compared to a separate control group of recently detoxified participants (N=8) in order to obtain estimates for the apparent in vivo dissociation constant (K(A)), the efficacy estimate (tau), and the estimated fraction of receptors remaining after buprenorphine/naloxone treatment (q). The apparent in vivo dissociation constant for heroin ranged from 50 to 126 mg (K(A)) and the efficacy estimate ranged from 13 to 20 (tau). In addition, 2/0.5, 8/2, and 32/8 mg buprenorphine/naloxone dose-dependently reduced the receptor population by 74, 83, and 91%, respectively. These data demonstrate that both 8/2 and 32/8 mg buprenorphine/naloxone were well tolerated and effective in reducing the reinforcing and subjective effects of heroin, relative to the 2/0.5-mg dose. The data also show for the first time in humans that it is possible to quantify the efficacy and affinity of heroin for mu opioid receptors, and that 80-90% of mu receptors need to be inactivated in order to obtain significant reductions in heroin-induced effects. These results have important implications for future studies in which it will be possible to obtain estimates of relative affinity and efficacy of different agonists at mu opioid receptors. Comer, S.D., Walker, E.A., and Collins, E.D. Buprenorphine/Naloxone Reduces the Reinforcing and Subjective Effects of Heroin in Heroin-dependent Volunteers. Psychopharmacology (Berl), 181, pp. 664-675, 2006.

Analysis of Variations in the Tryptophan Hydroxylase-2 (TPH2) Gene in Cocaine Dependence

While the exact physiological mechanisms underlying cocaine dependence remain unclear, a growing body of evidence indicates a role for the serotonergic neurotransmitter system in the pathology of this substance use disorder. The focus of the present study is to determine whether genetic variation in the tryptophan hydroxylase-2 (TPH2) gene, which encodes the enzyme responsible for synthesis of the majority of the serotonin contained in neurons of the central nervous system, contributes to the pathophysiology of cocaine dependence. To examine this hypothesis, the investigators used a case-control study design in which the genotype and allele distributions for six single nucleotide polymorphisms (SNPs) in the TPH2 gene were compared between cocaine-dependent (n = 299) and control individuals (n = 208) of African descent. The results indicate that none of the SNPs in the TPH2 gene examined in this study associate with the cocaine-dependent phenotype. This work suggests that variations in the TPH2 gene are not a risk factor for the development of cocaine dependence, but these findings require confirmation in larger, independent samples of cocaine-dependent and control subjects. Dahl, J.P., Cubells, J.F., Ray, R., Weller, A.E., Lohoff, F.W., Ferraro, T.N. et al.. Analysis of Variations in the Tryptophan Hydroxylase-2 (TPH2) Gene in Cocaine Dependence. Addict. Biol., 11, pp. 76-83, 2006.

Interaction Between Variation in the D2 Dopamine Receptor (DRD2) and the Neuronal Calcium Sensor-1 (FREQ) Genes in Predicting Response to Nicotine Replacement Therapy for Tobacco Dependence

It has been demonstrated that a functional dopamine D2 receptor promoter variant (DRD2 -141 Ins/Del) predicts response to nicotine replacement therapy (NRT). The present study extends this finding in the same population of 363 NRT-treated subjects, by examining variation in the gene encoding the

neuronal calcium sensor-1 protein (FREQ), which functions to regulate D2 receptor desensitization. The results indicate a statistically significant interaction effect of DRD2-141 and FREQ genotypes on abstinence at the end of the NRT treatment phase; 62% of the smokers with at least one copy of the DRD2 -141 Del allele and two copies of the FREQ rs1054879 A allele were abstinent from smoking, compared to 29-38% abstinence rates for other smokers in the trial. This result suggests that the interaction between variation in the DRD2 and FREQ genes, which both encode components of the D2 dopamine receptor signal transduction pathway, impacts the efficacy of NRT. Dahl, J. P., Jepson, C., Levenson, R., Wileyto, E. P., Patterson, F., Berrettini, W.H. et al.. Interaction Between Variation in the D2 Dopamine Receptor (DRD2) and the Neuronal Calcium Sensor-1 (FREQ) Genes in Predicting Response to Nicotine Replacement Therapy for Tobacco Dependence. Pharmacogenomics. J., 6, pp. 194-199, 2006.

Modafinil Attenuates Disruptions in Cognitive Performance During Simulated Night-Shift Work

Common complaints among shift workers are sleep disruptions and increased sleepiness while working, which may contribute to shift workers being more susceptible to diminished performance and work-related accidents. The purpose of this double-blind, within-participant study was to examine the effects of the alerting agent modafinil on cognitive/psychomotor performance, mood, and measures of sleep during simulated shift work. In all, 11 participants completed this 23-day residential laboratory study. They received a single oral modafinil dose (0, 200, 400 mg) 1 h after waking for three consecutive days under two shift conditions: day shift and night shift. Shifts alternated three times during the study, and shift conditions were separated by an 'off' day. When participants received placebo, cognitive performance and subjective ratings of mood were disrupted during the night shift, relative to the day shift. Objective and subjective measures of sleep were also disrupted, but to a lesser extent. Modafinil reversed disruptions in cognitive performance and mood during the night shift. While modafinil produced few effects on sleep measures during the night shift, the largest dose produced several sleep alterations during the day shift. These data demonstrate that abrupt shift changes produced cognitive performance impairments and mood disruptions during night shift work. Therapeutic doses of modafinil attenuated night-shift-associated disruptions, but the larger dose produced some sleep impairments when administered during day-shift work. Hart, C.L., Haney, M., Vosburg, S.K., Comer, S.D., Gunderson, E., and Foltin, R.W. Modafinil Attenuates Disruptions in Cognitive Performance During Simulated Night-Shift Work. Neuropsychopharmacology, 31, pp. 1526-1536, 2006.

Biomarkers to Assess the Utility of Potential Reduced Exposure Tobacco Products

To date, there are no valid biomarkers that serve as proxies for tobacco-related disease to test potential reduced exposure products. This paper represents the deliberations of four workgroups that focused on four tobacco-related heath outcomes: Cancer, nonmalignant pulmonary disease, cardiovascular disease, and fetal toxicity. The goal of these workgroups was to identify biomarkers that offer some promise as measures of exposure or toxicity and ultimately may serve as indicators for future disease risk. Recommendations were based on the relationship of the biomarker to what is known about mechanisms of tobacco-related pathogenesis, the extent to which the biomarker differs among smokers and nonsmokers, and the sensitivity of the biomarker to changes in smoking status. Other promising biomarkers were discussed. No existing biomarkers have been demonstrated to be predictive of tobacco-related disease, which highlights the importance and urgency of conducting research in this area. Hatsukami, D.K., Benowitz, N.L., Rennard, S.I., Oncken, C., and

Hecht, S.S. Biomarkers to Assess the Utility of Potential Reduced Exposure Tobacco Products. Nicotine.Tob.Res., 8, pp. 169-191, 2006.

A Double-blind, Placebo-Controlled Trial of Amantadine, Propranolol, and Their Combination for the Treatment of Cocaine Dependence in Patients with Severe Cocaine Withdrawal Symptoms

This trial evaluated the efficacy of amantadine, propranolol and their combination in cocaine dependent patients with severe cocaine withdrawal symptoms. Cocaine withdrawal symptom severity was measured by the cocaine selective severity assessment (CSSA). One hundred and ninety-nine patients with high scores on the CSSA participated in a 10-week double-blind trial. Patients were randomly assigned to receive amantadine (300mg/day), propranolol (100mg/day), a combination of amantadine (300mg/day) and propranolol (100mg/day) or matching placebo capsules. The primary outcome measure was cocaine abstinence. In the intent-to-treat sample, there were no significant differences between the four medication groups in treatment retention. The odds of cocaine abstinence showed a marginally significant increase over time in the propranolol group ($p=0.06$) but not in the other three groups. In highly medication-adherent patients, treatment retention was significantly better in the propranolol group compared to the placebo group ($p=0.01$) and the odds of cocaine abstinence increased significantly over time in the propranolol group but not in the other three groups. In the intent-to-treat sample, none of the three active treatments (propranolol, amantadine or their combination) was significantly more effective than placebo in promoting abstinence from cocaine among patients who entered treatment with more severe cocaine withdrawal symptoms. Among patients highly adherent to study medication, propranolol treatment was associated with better treatment retention and higher rates of cocaine abstinence compared to placebo.
Kampman, K.M., Dackis, C., Lynch, K.G., Pettinati, H., Tirado, C., Gariti, P. et al. A Double-blind, Placebo-Controlled Trial of Amantadine, Propranolol, and Their Combination for the Treatment of Cocaine Dependence in Patients with Severe Cocaine Withdrawal Symptoms. Drug Alcohol Depend. 2006 (epub ahead of print).

Severity of Dependence and Motivation for Treatment: Comparison of Marijuana- and Cocaine-Dependent Treatment Seekers

Although marijuana dependence is prevalent, most individuals with marijuana dependence do not seek treatment. There are few data characterizing treatment seeking marijuana-dependent patients compared to patients presenting for treatment of other drugs regarding the severity of illness and motivation for treatment. Forty-two marijuana-dependent individuals were compared to 58 cocaine-dependent individuals seeking treatment. Compared to cocaine-dependent patients, those with marijuana dependence were younger and less likely to be dependent on alcohol or other drugs. Both groups had similar rates of comorbid anxiety and affective disorders. Marijuana-dependent individuals had lower total number of dependence symptoms but had a higher percentage of individuals endorsing withdrawal symptoms. Although marijuana-dependent individuals had less outpatient treatment exposure, the difference between the two groups was not significant and motivation for change, based on the University of Rhode Island Change Assessment, was similar for both groups of treatment seekers. However, the Circumstances, Motivation, Readiness for Treatment Scale suggested that cocaine-dependent individuals were more motivated for treatment. Taken together, these data suggest that treatment seeking marijuana-dependent individuals have substantial withdrawal dependence symptomatology although it is less clear if

they are as motivated to seek out treatment as cocaine-dependent treatment seekers. Levin, F.R., Brooks, D.J., Bisaga, A., Raby, W., Rubin, E., Aharonovich, E. et al. Severity of Dependence and Motivation for Treatment: Comparison of Marijuana- and Cocaine-Dependent Treatment Seekers. J. Addict. Dis., 25, pp. 33-41, 2006.

A Randomized, Open-Label, Controlled Trial of Gabapentin and Phenobarbital in the Treatment of Alcohol Withdrawal

Gabapentin was compared with phenobarbital for the treatment of alcohol withdrawal in a randomized, open-label, controlled trial in 27 inpatients. There were no significant differences in the proportion of treatment completers between treatment groups or the proportion of patients in each group requiring rescue medication for breakthrough signs and symptoms of alcohol withdrawal. There were no significant treatment differences in withdrawal symptoms or psychological distress, nor were there serious adverse events. These findings suggest that gabapentin may be as effective as phenobarbital in the treatment of alcohol withdrawal. Given gabapentin's favorable pharmacokinetic profile, further study of its effectiveness in treating alcohol withdrawal is warranted. Mariani, J.J., Rosenthal, R.N., Tross, S., Singh, P., and Anand, O.P. A Randomized, Open-Label, Controlled Trial of Gabapentin and Phenobarbital in the Treatment of Alcohol Withdrawal. Am. J. Addict., 15, pp. 76-84, 2006.

Preliminary Observations of Paranoia in a Human Laboratory Study of Cocaine

Cocaine-induced paranoia (CIP) has recently shown a relationship to genetic factors that may moderate disulfiram treatment response in cocaine-dependent individuals. However, little research has examined CIP under controlled laboratory conditions. This study examined subjective and physiological responses to a 0.4 mg/kg dose of smoked cocaine in a human laboratory setting with 23 male and 21 female cocaine users. Twenty-nine of 44 participants (67%) reported feeling Paranoid/Suspicious in response to cocaine. Those who reported feeling Paranoid/Suspicious were more likely to be older and male. Further studies are warranted to investigate the mechanisms of gender influence on CIP, and CIP in pharmacotherapy development for cocaine-dependent individuals. Mooney, M., Sofuoglu, M., Dudish-Poulsen, S., and Hatsukami, D.K. Preliminary Observations of Paranoia in a Human Laboratory Study of Cocaine. Addict. Behav., 31, pp. 1245-1251, 2006.

Attitudes and Knowledge about Nicotine and Nicotine Replacement Therapy

Nicotine replacement therapies (NRTs) represent an effective means of promoting smoking cessation, but they remain underutilized. Negative attitudes and false beliefs about nicotine and nicotine replacement may cause NRT underutilization. In a randomized, controlled, single-blind study of nicotine gum, 97 smokers were assessed on their attitudes and knowledge about nicotine, nicotine replacement, and smoking cessation therapy. Information from these self-report measures was used in an intervention that provided tailored, brief feedback to promote positive attitudes and accurate knowledge about NRT. Considerable variability in pretreatment attitudes and knowledge was observed across individuals. Moreover, attitudes and knowledge showed a consistent pattern of intercorrelation and were systematically related to smoking characteristics (e.g., prior use of NRT, nicotine dependence, treatment completion). The brief feedback intervention led to a significant global elevation in attitudes about nicotine, NRT, and assisted cessation but not knowledge about nicotine. Changes in attitudes and knowledge were not significantly related to gum use or smoking cessation. Recommendations for the

appropriate application of brief feedback are offered. Mooney, M.E., Leventhal, A.M., and Hatsukami, D.K.. Attitudes and Knowledge about Nicotine and Nicotine Replacement Therapy. Nicotine. Tob. Res., 8, pp. 435-446, 2006.

Tobacco-Specific Nitrosamines in New Tobacco Products

New tobacco products, designed to attract consumers who are concerned about the health effects of tobacco, have been appearing on the market. Objective evaluation of these products requires, as a first step, data on their potentially toxic constituents. Tobacco-specific nitrosamines (TSNAs) are an important class of carcinogens in tobacco products, but virtually no data were available on their levels in these products. In the present study, the investigators analyzed several new products-Ariva, Stonewall, Exalt, Revel, Smokey Mountain, and Quest-for TSNAs and compared their TSNA levels with those in nicotine replacement products and conventional smokeless tobacco and cigarette brands. TSNAs were not detected in Smokey Mountain, which is a tobacco-free snuff product. The lowest levels among the new products containing tobacco were in Ariva and Stonewall (0.26-0.28 microg/g wet weight of product). The highest levels in the new products were found in Exalt (3.3 microg/g tobacco), whereas Revel and Quest had intermediate amounts. Only trace amounts were found in nicotine replacement products, and conventional brands had levels consistent with those reported in the literature. These results demonstrate that TSNA levels in new tobacco products range from relatively low to comparable with those found in some conventional brands. Stepanov, I., Jensen, J., Hatsukami, D., and Hecht, S.S. Tobacco-Specific Nitrosamines in New Tobacco Products. Nicotine. Tob. Res., 8, pp. 309-313, 2006.

The Status of Disulfiram: A Half of a Century Later

For more than 55 years, disulfiram has been approved by the Food and Drug Administration for the treatment of alcohol dependence. It is a unique medication that relies on "psychological threat" to avoid disulfiram-ethanol reactions. This paper reviews the history of disulfiram treatment, the current status of disulfiram treatment, the ensuing developments in disulfiram use in treating various addictions, and future directions. Clinical trials using disulfiram for the treatment of alcohol, cocaine, or co-occurring alcohol + cocaine dependence were included in this review. Disulfiram efficacy studies focusing on supervised, implant, and combination pharmacotherapies were also examined. In clinical trials, disulfiram has demonstrated inconsistent results in helping patients to abstain from alcohol, and patients poorly adhere to a disulfiram-treatment regimen. This has raised questions about disulfiram's practicality in the treatment of alcohol dependence. Recently, however, disulfiram has gained attention as a complementary agent to newer pharmacological medications, such as an opiate antagonist that specifically reduces alcohol craving. One hypothesis is that disulfiram would assist patients in gaining psychological control over drinking when given in conjunction with an opiate antagonist that would act directly on reducing alcohol craving. Preliminary evidence also suggests that disulfiram treatment could be a viable treatment for cocaine dependence because it was shown to reduce cocaine use among nonalcoholic, cocaine-dependent patients. Suh, J. J., Pettinati, H.M., Kampman, K.M., and O'Brien, C.P. The Status of Disulfiram: A Half of a Century Later. J. Clin. Psychopharmacol., 26, pp. 290-302, 2006.

Interaction of Amphetamines and Related Compounds at the Vesicular Monoamine Transporter

Amphetamine-type agents interact with the vesicular monoamine transporter (VMAT2), promoting the release of intravesicular neurotransmitter and an

increase in cytoplasmic neurotransmitter. Some compounds, like reserpine, "release" neurotransmitter by inhibiting the ability of VMAT2 to accumulate neurotransmitter in the vesicle, while other types of compounds can release neurotransmitter via a carrier-mediated exchange mechanism. The purpose of this study was to determine, for 42 mostly amphetamine-related compounds, their mode of interaction with the VMAT2. Authors used a crude vesicular fraction prepared from rat caudate to assay VMAT2 activity. Test compounds were assessed in several assays including: a) inhibition of [(3)H]dihydro tetrabenazine binding, b) inhibition of vesicular [(3)H]dopamine uptake, and c) release of pre-loaded [(3)H]dopamine and [(3)H]tyramine. Several important findings derive from this comprehensive study. First, this work indicates that most agents are VMAT2 substrates. Two, these data strongly suggest that amphetamine-type agents deplete vesicular neurotransmitter via a carrier-mediated exchange mechanism rather than via a free-base effect, although this conclusion needs to be confirmed via direct measurement of vesicular pH. Three, these data fail to reveal differential VMAT2 interactions among agents which do and do not produce long-term 5-HT depletion. Four, the data reported revealed the presence of two pools of [(3)H]amine within the vesicle, that which is free, and that which is tightly associated with the ATP/protein complex that helps store amine. Finally, the VMAT2 assays the authors have developed should prove useful for guiding the synthesis and evaluation of novel VMAT2 agents as possible treatment agents for addictive disorders. Partilla, J.S., Dempsey, A.G., Nagpal, A.S., Blough, B.E., Baumann, M.H., Rothman, R.B., J Pharmacol Exp Ther. July 11, 2006 [Epub ahead of print].

A Novel Nicotinic Acetylcholine Receptor Antagonist Radioligand for PET Studies

Using positron emission tomography (PET) with a specific and selective radioligand targeting nicotinic acetylcholine receptor (nAChR) would allow us to better understand various nAChR related CNS disorders. The use of radiolabeled nAChR antagonists would provide a much safer pharmacological profile, avoiding most peripheral side effects that might be generated from radiolabeled nAChR agonists even at the tracer level; thus, PET imaging with nAChR antagonists would facilitate clinical application. A potent and selective nAChR antagonist was labeled and characterized with PET in non-human primates. Its high brain uptake, high signal-to-noise ratio, and high specific binding strongly suggest a great potential to carry out imaging studies in humans. In addition, the use of a C-11 radiotracer would allow us to perform multiple PET studies in the same individual within a short time frame. The presence of an iodine atom in the molecule also allows the possibility to label with radioiodine for SPECT studies. Ding, Y.S., Kil, K.E., Lin, K.S., Ma, W., Yokota, Y., and Carroll, I.F., Bioorg Med Chem Lett. 16(4), pp. 1049-1053, February 15, 2006.

Recent Advances in the Treatment of Cocaine Abuse: Central Nervous System Immunopharmacotherapy

Cocaine addiction continues to be a major health and societal problem in spite of governmental efforts devoted toward educating the public of the dangers of illicit drug use. A variety of pharmacotherapies and psychosocial programs have been proposed in an effort to provide a method for alleviation of the physical and psychological symptoms of cocaine abuse. Unfortunately, these methods have been met with limited success, illustrating a critical need for new effective approaches for the treatment of cocaine addiction. Recently an alternative cocaine abuse treatment strategy was proposed using intranasal administration of an engineered filamentous bacteriophage displaying cocaine-sequestering antibodies on its surface. These phage particles are an effective vector for CNS penetration and are capable of binding cocaine, thereby blocking its behavioral effects in a rodent model. The convergence of phage

display and immunopharmacotherapy has allowed for an investigation of the efficacy of protein-based therapeutics acting within the CNS on the effects of cocaine in animal models and has uncovered a new tool in the battle against cocaine addiction. Dickerson, T.J., and Janda, K.D. AAPS J. 7(3):E579-586, October 19, 2005.

Development of New Brain Imaging Agents Based Upon Nocaine-Modafinil Hybrid Monoamine Transporter Inhibitors

11C-labeled(+)-trans-2-[[(3R,4S)-4-(4-chlorophenyl)-1-methylpiperidin -3-yl]methylsulfanyl]ethanol ([11C]5) and (+)-trans-2-[[(3R,4S)-4-(4-chlorophenyl) -1-methylpiperidin-3-yl]methylsulfanyl]-1-(piperidin-1-yl)ethanone ([11C]6) were synthesized and evaluated as new imaging agents for the norepinephrine transporter (NET). [11C]5 and [11C]6 display high affinity for the NET in vitro (Ki = 0.94 and 0.68 nM, respectively) and significant selectivity over the dopamine (DAT) and serotonin transporters (SERT). Because of their high affinity and favorable transporter selectivities authors speculated that these ligands might serve as useful PET agents for imaging NET in vivo. Contrary to our expectations, both of these ligands provided brain images that were more typical of those shown by agents binding to the DAT. Musachio, J.L., Hong, J., Ichise, M., Seneca, N., Brown, A.K., Liow, J.S., Halldin, C., Innis, R.B., Pike, V.W., He, R., Zhou, J., and Kozikowski, A.P. Bioorg Med Chem Lett. 16(12), pp. 3101-3104, June 15, 2006.

Dopamine Transporter (DAT) Inhibitors Alleviate Specific Parkinsonian Deficits in Monkeys: Association with DAT Occupancy In Vivo

This study was undertaken to test the hypothesis that viable dopamine neurons in Parkinson's disease express the dopamine transporter (DAT) and release dopamine (DA). Authors postulated that potent DAT inhibitors, with low affinity for the serotonin transporter (SERT), may elevate endogenously released extracellular dopamine levels to provide therapeutic benefit. General methods: The therapeutic potential of eight DAT inhibitors was investigated in MPTP-treated (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) cynomolgus monkeys (Macaca fasicularis), with efficacy correlated with DAT occupancy as determined by PET imaging in striatum. Four potent DAT inhibitors, with relatively high norepinephrine transporter, but low SERT affinities, that occupied the DAT improved activity in parkinsonian monkeys, whereas three high affinity DAT inhibitors with low DAT occupancy did not. O-1163 occupied the DAT but had short-lived pharmacological effects. The benztropine analog difluoropine increased general activity, improved posture, reduced body freeze, and produced disturbances at high doses. O-1369 alleviated parkinsonian signs in advanced parkinsonian monkeys, by increasing general activity, improving posture, reducing body freeze and sedation, but not significantly reducing bradykinesia or increasing locomotor activity. In comparison with the D2-D3-DA receptor agonist quinelorane, O-1369 elicited oro-facial dyskinesias, whereas quinelorane did not improve posture or reduce balance and promoted stereotypy. Authors conclude that DAT inhibitors with therapeutic potential combine high DAT affinity in vitro, high DAT occupancy of brain striatum in vivo, with enduring daytime effects that do not extend into the nighttime. Advanced parkinsonian monkeys (80% DAT loss) respond more effectively to DAT inhibitors than mild parkinsonian monkeys (46% DAT loss). The therapeutic potential of dopamine transport inhibitors for Parkinson's disease warrants preclinical investigation. Madras, B.K., Fahey, M.A., Goulet, M., Lin, Z., Bendor, J., Goodrich, C., Meltzer, P.C., Elmaleh, D.R., Livni, E., Bonab, A.A., and Fischman, A.J. J Pharmacol Exp Ther. August 2, 2006 [Epub ahead of print].

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Research on Medical Consequences of Drug Abuse and Infections

Abnormal Glucose Metabolism Among Older Men with or at Risk of HIV Infection

The aim of this study was to determine factors associated with diabetes, insulin resistance, and abnormal glucose tolerance in older men with or at risk of HIV infection. Diabetes was assessed by self-report in 643 men >/=49 years old with or at risk of HIV infection. In a subset of 216 men without previously diagnosed diabetes [including 90 HIV-uninfected men, 28 HIV-infected, antiretroviral- naive men, 28 HIV-infected men taking non-protease inhibitor (PI)-containing highly active antiretroviral therapy (HAART), and 70 HIV-infected men taking PI-containing HAART], an oral glucose tolerance test with insulin levels was performed. HIV serology, CD4 cell count, weight, height and waist circumference were measured. Antiretroviral use, drug use, family history of diabetes, physical activity and sociodemographic data were obtained using standardized interviews. Of 643 participants, 116 (18%) had previously diagnosed diabetes. With the oral glucose tolerance test, 15 of 216 men (7%) were found to have undiagnosed diabetes and 40 (18%) impaired glucose tolerance. Factors independently associated with previously diagnosed diabetes included use of non-PI-containing HAART, methadone treatment, positive CAGE test for alcoholism, obesity and family history of diabetes. Factors independently associated with greater insulin resistance included waist circumference and heroin use. Factors independently associated with abnormal glucose tolerance (impaired glucose tolerance or diabetes) included age >/=55 years and Hispanic ethnicity. HIV-infected men with diabetes risk factors should undergo screening for diabetes regardless of HAART use. Interventions targeting modifiable risk factors, including overweight and physical inactivity, are warranted. The potential impact of opiate and alcohol abuse on glucose metabolism should be recognized in clinical care, and addressed in future research studies of HIV-infected persons. Howard, A., Floris-Moore, M., Lo, Y., Arnsten, J., Fleischer, N., Klein, R., HIV Med. 7(6), pp. 389-396, September 2006.

Neurocognitive Aspects of Medication Adherence in HIV-positive Injecting Drug Users

Cognitive deficits are associated with nonadherence to HIV medications. HIV-positive injecting drug users (IDUs) are at particular risk for nonadherence and cognitive barriers to adherence specific to this population should therefore be identified. The present study assessed the relation of three domains of cognitive functioning, executive functions, memory, and psychomotor speed, to self-reported antiretroviral adherence in a sample of HIV-positive IDUs. Depression, use of alcohol, heroin, cocaine/crack, or marijuana in the last week

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were also included in the models. Logistic regression analyses showed that only psychomotor slowing was significantly associated with nonadherence. Executive functions, memory, depression, and active alcohol and substance use were unrelated to adherence. No other studies to date have exclusively linked psychomotor slowing to nonadherence in HIV infection. Psychomotor slowing among our study sample was severe and suggests that when evident, such slowing may be a valuable determinant for antiretroviral adherence among IDUs. Waldrop-Valverde, D., Ownby, R.L., Wilkie, F.L., Mack, A., Kumar, M., and Metsch, L., AIDS Behav. 10(3), pp. 287-297, May 2006.

Resistance to HIV Infection

The biological correlates of an effective immune response that could contain or prevent HIV infection remain elusive despite substantial scientific accomplishments in understanding the interactions among the virus, the individual and the community. The observation that some individuals appear to possess resistance to HIV infection or its consequences has generated a host of epidemiologic investigations to identify biological or behavioral characteristics of these individuals. These data might hold the keys to developing appropriate strategies for mimicking the effective responses of those who appear immune. In this paper authors review genetic mechanisms including the role of chemokines and their receptors, cytokines, host genetic immune response to HIV infection, local immune response correlating with behavioral variables, co-infection and immune based mechanisms that have been elucidated so far. The authors offer suggestions for how to use these observations as platforms for future research to further understand natural resistance to HIV infection through cohort studies, population genotype sampling, mathematical modeling of virus-host interactions and behavioral analyses. Marmor, M., Hertzmark, K., Thomas, S.M., Halkitis, P.N., and Vogler, M., J Urban Health. 83(1), pp. 5-17, January 2006.

Methamphetamine Modulates Gene Expression Patterns in Monocyte Derived Mature Dendritic Cells: Implications for HIV-1 Pathogenesis

The US is currently experiencing a grave epidemic of methamphetamine use as a recreational drug, and the risk for HIV-1 infection attributable to methamphetamine use continues to increase. Recent studies show a high prevalence of HIV infection among methamphetamine users. Dendritic cells (DCs) are potent antigen presenting cells that are the initial line of defense against HIV-1 infection. In addition, DCs also serve as reservoirs for HIV-1 and function at the interface between the adaptive and the innate immune systems, which recognize and internalize pathogens and subsequently activate T cells. Exposure to methamphetamine results in modulation of immune functional parameters that are necessary for host defense. Chronic methamphetamine use can cause psychiatric co-morbidity, neurological complications, and can alter normal biological processes and immune functions. Limited information is available on the mechanisms by which methamphetamine may influence immune function. This study explores the effect of methamphetamine on a specific array of genes that may modulate immune function. Authors hypothesize that methamphetamine treatment results in the immunomodulation of DC functions, leading to dysregulation of the immune system of the infected host. This suggests that methamphetamine has a role as a cofactor in the pathogenesis of HIV-1. Authors used the high-throughput technology of gene microarray analysis to understand the molecular mechanisms underlying the genomic changes that alter normal biological processes when DCs are treated with methamphetamine. Additionally, they validated the results obtained from microarray experiments using a combination of quantitative real-time PCR and Western blot analysis. These data are the first evidence that methamphetamine modulates DC expression of

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several genes. Methamphetamine treatment alters categories of genes that are associated with chemokine regulation, cytokinesis, signal transduction mechanisms, apoptosis, and cell cycle regulation. This report focuses on a selected group of genes that are significantly modulated by methamphetamine treatment and that have been associated with HIV-1 pathogenesis. The purpose of this study was to identify genes that are unique and/or specific to the complex immunomodulatory mechanisms that are altered as a result of methamphetamine abuse in HIV-1-infected patients. These studies will help to identify the molecular mechanisms that underlie methamphetamine toxicity, and several functionally important classes of genes have emerged as targets in methamphetamine-mediated immunopathogenesis of HIV-1. Identification of novel DC-specific and methamphetamine-responsive genes that modulate several biological, molecular, and signal transduction functions may serve as methamphetamine- and/or HIV-1-specific drug targets. Mahajan, S.D., Hu, Z., Reynolds, J.L., Aalinkeel, R., Schwartz, S.A., and Nair, M.P., Mol Diagn Ther. 10(4), pp. 257-269, 2006.

Pharmacokinetic Drug Interactions Between Opioid Agonist Therapy and Antiretroviral Medications: Implications and Management for Clinical Practice

Opioid dependence and HIV/AIDS are 2 of the most serious yet treatable diseases worldwide. Global access to opioid agonist therapy and HIV treatment is expanding but when concurrently used, problematic pharmacokinetic drug interactions can occur. Authors reviewed English, Spanish, French, and Italian language articles from 1966 to 2005 in Medline using the following keywords: HIV, AIDS, HIV therapy, antiretroviral therapy, HAART, drug interactions, methadone, and buprenorphine. Additionally, authors reviewed abstracts from national and international meetings and conference proceedings. Selected references from these articles were reviewed as well. Clinical case series and carefully controlled pharmacokinetic interaction studies have been conducted between methadone and most approved antiretroviral therapies. Important pharmacokinetic drug interactions have been demonstrated within each class of agents, affecting either methadone or antiretroviral agents. Few studies, however, have been conducted with buprenorphine. The metabolism of both therapies, description of the known interactions, and clinical implications and management of these interactions are reviewed. Authors conclude that certain interactions between methadone and antiretroviral medications are known and may have important clinical consequences. To optimize care, clinicians must be alert to these interactions and have a basic knowledge regarding their management. Bruce, R.D., Altice, F.L., Gourevitch, M.N., and Friedland, G.H., J Acquir Immune Defic Syndr. 41(5), pp. 563-572, April 2006.

Models for Integrating Buprenorphine Therapy into the Primary HIV Care Setting

Opiate dependence among human immunodeficiency virus (HIV)-infected patients has been associated with negative clinical outcomes, yet few affected patients receive appropriate and coordinated treatment for both conditions. The introduction of buprenorphine maintenance therapy into HIV care settings provides an opportunity for providers to integrate treatment for opiate dependence into their practices. Buprenorphine maintenance therapy has been associated with reductions in opiate use, increased social stability, improved adherence to antiretroviral therapy, and lowered rates of injection drug use. Authors describe the following 4 models for the integration of buprenorphine maintenance therapy into HIV care: (1) a primary care model, in which the highly active antiretroviral therapy-administering clinician also prescribes buprenorphine; (2) a model that relies on an on-site specialist in addiction medicine or psychiatry to prescribe the buprenorphine; (3) a hybrid model, in which an on-site specialist provides the induction (with or without stabilization

phases) and the HIV care provider provides the maintenance phase; and (4) a drug treatment model that provides buprenorphine maintenance therapy services with HIV services in the substance abuse clinic setting. The key barriers against effective integration of buprenorphine maintenance therapy and primary HIV services are discussed, and we suggest several mechanisms to overcome such obstacles. Basu, S., Smith-Rohrberg, D., Bruce, R.D., and Altice, F.L., Clin Infect Dis. 42(5), pp. 716-721, March 1, 2006.

Predictors of Hepatitis C Virus RNA Levels in a Prospective Cohort Study of Drug Users

High levels of hepatitis C virus (HCV) RNA are associated with a poor response to treatment of chronic hepatitis C, and a substantial reduction in HCV RNA levels predicts a favorable treatment response. Authors prospectively studied time-dependent and time-independent predictors of HCV RNA levels in 264 drug users with chronic HCV infection. Interviews on medical history and high-risk behaviors, phlebotomy for HIV viral load, serum HCV RNA levels as measured by the COBAS Amplicor HCV Monitor (Roche Diagnostics, Branchburg, NJ), and a lymphocyte subset assay were performed. Factors associated with HCV RNA levels over time were analyzed using a linear mixed model. Nearly 70% of the participants were men, two thirds were Hispanic, and the mean age was 46 years. HCV RNA levels increased over time. Older age ($P < 0.001$), HIV seropositivity ($P = 0.03$), and HCV nongenotype 1 ($P = 0.05$) were predictors of higher HCV RNA levels on multivariate analysis. Among 142 HIV-seropositive participants, a detectable HIV-1 viral load ($P < 0.001$) and recent alcohol use ($P = 0.02$) were predictors of higher HCV RNA levels. The predictors of higher HCV RNA levels found in this longitudinal study are consistent with those of prior cross-sectional studies. Further studies are warranted to determine if treatment of alcohol use affects HCV RNA levels. Fishbein, D.A., Lo, Y., Netski, D., Thomas, D.L., Klein, R.S., J Acquir Immune Defic Syndr. 41(4), pp. 471-476, April 1, 2006.

Identification of a Specific Gene Expression Pattern Associated with HCV-Induced

Pathogenesis in HCV- and HCV/HIV-Infected Individuals Gene expression profiling was performed on liver biopsies from 28 patients (12 HCV and 16 HCV/HIV infected) in an attempt to understand the mechanisms of HCV liver disease in the presence and absence of HIV coinfection. The data were compared with clinical observations and a gene expression database obtained for transplant HCV-infected samples. This is the first report of functional genomics being used to compare intrahepatic gene expression profiles of HCV- and HCV/HIV-infected individuals. Significantly, the intrahepatic global gene expression profiles do not differ between HCV- and HCV/HIV-infected individuals. However, a subset of patients was identified who share a specific pattern of gene expression, termed the enhanced gene expression (EGE) pattern. Specifically, the EGE (+) patients show a dramatic decreased expression of multiple genes associated with the FAS-apoptosis pathway and increased expression of lymphocyte adhesion molecules and lymphocyte-specific genes. The EGE (+) patients also have partially impaired Type I and II IFN-mediated antiviral responses, including a lack of induction of the anti-fibrogenic cytokine IFN-gamma. Importantly, the pattern of gene expression observed in EGE (+) patients has similarities to patients who developed fibrosis within 1 year of receiving a liver transplant. Walters, K.A., Smith, M.W., Pal, S., Thompson, J.C., Thomas, M.J., Yeh, M.M., Thomas, D.L., Fitzgibbon, M,, Proll, S., Fausto, N., Gretch, D.R., Carithers, R.L. Jr., Shuhart, M.C., and Katze, M.G., Virology. 350(2), pp.453-464. Epub 2006 Mar 30, July 5, 2006.

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

Coinfected Subjects

True treatment rates and the impact of comorbidities on treatment rates for hepatitis C virus in the HCV-HIV-coinfected subjects are unknown. The aim of this study was to quantify the rates of treatment prescription and the effect of comorbidities on hepatitis C virus treatment rates in HCV-HIV-coinfected veterans. The Veterans Affairs National Patient Care Database was used to identify all hepatitis C virus-infected subjects between 1999 and 2003 using ICD-9 codes. Demographics, comorbidities and pharmacy data were retrieved. Authors used logistic regression to compare the predictors of hepatitis C virus treatment in hepatitis C virus-monoinfected and HCV-HIV-coinfected subjects. Authors identified 120,507 hepatitis C virus-infected subjects, of which 6502 were HIV coinfected. 12% of the hepatitis C virus-monoinfected and 7% of the -coinfected subjects were prescribed hepatitis C virus treatment ($P < 0.0001$). Those not prescribed treatment were older (48.6 years vs. 47.7 years, $P = 0.007$) and more likely to be black (52% vs. 32%, $P < 0.0001$). HIV coinfected was less likely to be prescribed hepatitis C virus treatment (OR 0.74, 95% CI: 0.67-0.82). Among the coinfected subjects, the following were associated with non-treatment (OR, 95% CI): black race (0.45, 0.35-0.57); Hispanic race (0.56, 0.38-0.82); drug use (0.68, 0.53-0.88); anaemia (0.17, 0.11-0.26); bipolar disorder (0.63, 0.40-0.99); major depression (0.72, 0.53-0.99); mild depression (0.47, 0.35-0.62). Authors conclude that a small number of HCV-HIV-coinfected veterans are prescribed treatment for hepatitis C virus. Non-treatment is associated with increasing age, minority race, drug use and psychiatric illness. Further studies are needed to determine the eligibility for treatment and reasons for non-treatment for hepatitis C virus. Butt, A.A., Justice, A.C., Skanderson, M., Good, C., and Kwoh, C.K. Aliment Pharmacol Ther. 24(4), pp. 585-591, August 15, 2006.

Tenofovir for Chronic Hepatitis B Virus Infection in HIV-Coinfected Patients

Tenofovir has significant activity against hepatitis B virus (HBV), but clinical data about its utility for treatment of hepatitis B in patients coinfected with HBV and HIV are limited. Authors report the long-term safety and efficacy of tenofovir in 6 HBV-HIV-coinfected persons who received tenofovir as part of their antiretroviral regimen and were followed up for an average of 26.8 months (range, 19 to 33 months). Four of 6 patients were positive for hepatitis B e antigen (HBeAg), and all 6 had initial HBV DNA levels greater than 7 log10 copies/mL. HBV DNA levels dropped by a mean (median) of 2.83 (3.40) and 3.92 (4.63) log10 after 12 and 24 months of treatment, respectively. After 24 months, 3 patients had HBV DNA levels below the limit of detection and 5 had HIV RNA levels below the limit of detection (less than 400 copies/mL). The sixth patient had stopped treatment and had a 0.14-log10 decrease in HIV RNA level at 36 months of follow-up. The CD4+ lymphocyte count increased by a mean (median) value of 47/microL (177/microL). No significant adverse events attributable to tenofovir therapy were reported. Butt, A.A. AIDS Read. 16(4), pp. 219-222, April 2006.

Comorbid Medical and Psychiatric Conditions and Substance Abuse in HCV Infected Persons on Dialysis

The burden of comorbidity in the Hepatitis C virus (HCV) infected persons on dialysis is unknown. Authors identified all HCV infected and uninfected subjects in the United States Renal Data System in the years 1997-1998 using ICD-9 codes. Controls were matched on the date of first dialysis. ICD-9 codes and claims data was used to identify medical and psychiatric comorbidities. Authors identified 5,737 HCV infected persons and 11,228 HCV uninfected subjects. HCV infected subjects were younger, more likely to be black race and male and

more likely to have the following comorbidities: hypertension; hepatitis B; cirrhosis; wasting; anemia; human immunodeficiency virus (HIV) infection; major depression; mild depression; bipolar disorder; schizophrenia; post-traumatic stress disorder; drug use; alcohol use; smoking and less likely to have the following comorbidities: coronary artery disease; stroke; peripheral vascular disease; diabetes; cancer; erythropoietin use. After adjusting for age, gender and race, HCV infected subjects were more likely to have hypertension, hepatitis B, cirrhosis, wasting, anemia and HIV infection and less likely to have coronary artery disease and stroke. Authors concluded that HCV infected persons on dialysis are more likely to have psychiatric comorbidities and substance abuse, as well as certain medical comorbidities. These factors should be considered when developing future intervention strategies. Butt, A.A., Evans, R., Skanderson, M., and Shakil, A.O. J Hepatol. 44(5), pp. 864-868, May 2006.

HIV/Hepatitis C Virus-Coinfected Patients with Normal Alanine Aminotransferase Levels

The significance of normal alanine aminotransferase (ALT) levels in patients with HIV/hepatitis C virus (HCV) coinfection is not well understood. Authors performed a cross-sectional retrospective analysis on consecutive HIV/HCV-coinfected patients (n = 89) who underwent a liver biopsy during a 2-year period. Similar data were also collected on HCV-monoinfected patients (n = 117). Mean ALT levels and the percentage of patients with normal ALT (< or =40 U/L) levels were similar in HIV/HCV-coinfected (mean +/-SD, 81.7 +/-56.1 U/L; 21%) and HCV-monoinfected patients (97.3 +/- 100.7 U/L; 18%; P = 0.19 and 0.54, respectively). Coinfected patients, however, had significantly advanced necroinflammation (P= 0.001) and fibrosis (P = 0.02) compared with monoinfected patients. The percentage of patients with advanced necroinflammation (grades 3 or 4) was lower in HCV-monoinfected patients with normal ALT levels compared with those with elevated ALT (5% vs 20%, respectively). In contrast, the percentage of coinfected patients with advanced necroinflammation was similar whether the patient had normal or elevated ALT levels (32% vs 37%, respectively). In coinfected patients, normal ALT levels are not an indicator of mild necroinflammation and may not portend a more benign disease course. Gonzalez, S.A., Liu, R.C., Edlin, B.R., Jacobson, I.M., and Talal, A.H. J Acquir Immune Defic Syndr. 41(5), pp. 582-589, April 15, 2006.

Neurocognitive Consequences of HIV in Southern India: A Preliminary Study of Clade C Virus

The neurocognitive impact of the clade C viral strain of human immunodeficiency virus (HIV) has not been determined. The purpose of this study was to examine neurocognitive function in southern India among individuals with the clade C virus with advanced HIV. A battery of cognitive tasks sensitive to the effects of HIV on brain function was translated and administered in Tamil and Telegu, two widely spoken languages in southern India. A sample of 30 treatment-naïve HIV-positive individuals with a median CD4 cell count of 97, and 30 age and education matched healthy controls obtained from the same region of India, were included in the study. Results revealed significant differences on most cognitive tests, with lower performances obtained by the HIV-positive individuals. These results suggest that cognitive difficulties are present among individuals with the clade C virus in India, with as many as 56% of the patients with advanced HIV meeting the criterion for impairment in two cognitive domains. Additional study is needed to determine if clade C HIV infection is more or less prone to cause neurocognitive deficit than the clade B virus. Furthermore, the impact of antiretroviral therapy on neurocognitive dysfunction in clade C virual infection needs to be determined. Yepthomi, T., Paul, R., Vallabhaneni, S., Kumarasamy, N., Tate,

D.F., Solomon, S., and Flanigan, T. J Int Neuropsychol Soc.12(3), pp. 424-430, May 2006.

(C2) Saliva, Breast Milk, and Mucosal Fluids in HIV Transmission

The oral environment has received various amounts of attention in association with HIV infection and pathogenesis. Since HIV infection occurs through mucosal tissue, oral factors-including tissue, fluids, and compartments-are of interest in furthering our understanding of the diagnosis, infectivity, transmission, and pathogenesis of disease. This report reviews: (1) HIV testing and diagnoses with oral fluids; (2) post-natal acquisition of HIV in association with breast-feeding from HIV-positive mothers; and (3) oral sex and HIV transmission. In the first, authors examine how oral fluids are used to detect HIV infection and review current consensus on the role of salivary molecules as markers for immunosuppression. Second, lactation-associated HIV acquisition is reviewed, with special consideration of emerging issues associated with the impact of anti-retroviral therapies. Last, authors consider current data on the risk of HIV infection in association with oral sex. Investigation of these diverse topics has a common goal: understanding how HIV presents in the oral environment, with an aim to rapid and accessible HIV diagnosis, and improved prevention and treatment of infection. Page-Shafer, K., Sweet, S., Kassaye, S., and Ssali, C. Adv Dent Res. 19(1), pp. 152-157, April 1, 2006.

Commercial Sex Work and Risk of HIV Infection Among Young Drug-Injecting Men Who Have Sex with Men in San Francisco

The objective of this study was to investigate the relationship between sex work and HIV infection among young injection drug-using men who have sex with men (MSM-IDU). This study was a cross-sectional analysis of behavioral and serologic data collected from 227 street-recruited MSM-IDU in San Francisco, California, between January 2000 and November 2001. Sixty-eight percent of participants reported being paid by another man for sex. HIV prevalence was 12% (95% confidence interval, 8-16%); 42% of seropositive participants were unaware of their infection. HIV was independently associated with higher number of paying male partners and history of gonorrhea and inversely associated with number of female partners, education, and syringe-sharing. Consistent condom use overall was 41%, but varied significantly by type of partner. Among MSM-IDU in San Francisco, sex work with men is strongly associated with HIV infection and the prevalence of condom use is low. HIV prevention among MSM-IDU must be tailored to address the excess risk associated with sex work. Bacon, O., Lum, P., Hahn, J., Evans, J., Davidson, P., Moss, A., Page-Shafer, K. Sex Transm Dis. 33(4), pp. 228-234, April 2006.

Treatment Algorithm for the Management of Hepatitis C in HIV-Coinfected Persons

In the era of highly effective antiretroviral therapy (ART), HCV-related liver disease has emerged as a significant cause of morbidity and mortality. Accordingly, expert panels have recommend that coinfected patients undergo medical evaluation for HCV-related liver disease, consideration for HCV treatment and, if indicated, orthotopic liver transplantation. While the treatment of such patients is complicated by medical, and psychiatric comorbidities, HIV disease, and concurrent antiretroviral therapy, randomized controlled trials support the safety, tolerability and efficacy of HCV treatment with peginterferon alfa (PEG-IFN) plus ribavirin (RBV) in HIV-infected persons. Although, the available data has led to consensus among experts regarding the need to medically manage HCV disease in HIV-infected persons, uncertainty remains regarding the best treatment algorithm for coinfected patients. Sulkowski, M.S. J Hepatol.44(1 Suppl):S49-55, 2006.

Progression of Liver Fibrosis Among Injection Drug Users with Chronic Hepatitis C

Although most hepatitis C virus (HCV) infections are acquired by injection drug use, prospective data on the progression of liver fibrosis are sparse. Baseline liver biopsies were obtained (1996-1998) on a random sample of 210 out of 1667 HCV-positive injection drug users (IDUs). Subjects were followed biannually, with a second biopsy offered to those eligible. Paired biopsies were scored 0 to 6 (modified Ishak score), significant fibrosis was defined as score 3 or greater, and progression of fibrosis was defined as an increase 2 or more units or clinical evidence of end-stage liver disease. Predictive values of blood markers [FibroSURE, aspartate aminotransferase-to-platelet-ratio index (APRI) and alanine aminotransferase (ALT)] were assessed for detection of contemporaneous and future liver fibrosis. Among 119 prospectively followed IDUs, 96% were African American; 97% HCV genotype 1a/b; 27% HIV-infected, and median age was 42 years. Most (90.7%) did not have significant liver fibrosis at first biopsy. Although predictive value for detecting insignificant fibrosis at first biopsy was greater than 95% for FibroSURE, APRI, and ALT, specificities were 88.9%, 72.7%, and 72.7%, respectively. After 4.2 years median follow-up, 21% had progression of fibrosis, which was significantly associated with serum level of HCV RNA and ALT. No serological test had predictive value greater than 40% for contemporaneous or future significant fibrosis. Even initial biopsy result had only a 30.4% value for predicting future significant fibrosis. In conclusion, significant liver fibrosis and progression were detected in some, but not most, IDUs in this cohort. In this setting with low fibrosis prevalence, FibroSURE, ALT, and APRI tests predict insignificant fibrosis; however, further work is needed to find noninvasive markers of significant liver fibrosis. Wilson, L.E., Torbenson, M., Astemborski, J., Faruki, H., Spoler, C., Rai, R., Mehta, S., Kirk, G.D., Nelson, K., Afdhal, N., and Thomas, D.L. Hepatology. 43(4), pp. 788-795, April 2006.

The Cannabis Withdrawal Syndrome

The demand for treatment for cannabis dependence has grown dramatically. The majority of the people who enter treatment have difficulty in achieving and maintaining abstinence from cannabis. Understanding the impact of cannabis withdrawal syndrome on quit attempts is of obvious importance. Cannabis, however, has long been considered a 'soft' drug, and many continue to question whether one can truly become dependent on cannabis. Skepticism is typically focused on whether cannabis use can result in 'physiological' dependence or withdrawal, and whether withdrawal is of clinical importance. The neurobiological basis for cannabis withdrawal has been established via discovery of an endogenous cannabinoid system, identification of cannabinoid receptors, and demonstrations of precipitated withdrawal with cannabinoid receptor antagonists. Laboratory studies have established the reliability, validity, and time course of a cannabis withdrawal syndrome and have begun to explore the effect of various medications on such withdrawal. Reports from clinical samples indicate that the syndrome is common among treatment seekers. In summary, a clinically important withdrawal syndrome associated with cannabis dependence has been established. Additional research must determine how cannabis withdrawal affects cessation attempts and the best way to treat its symptoms. Budney, A.J. and Hughes, J.R., Curr Opin Psychiatry. 19(3), pp. 233-238, May 2006.

Oral Delta-9-tetrahydrocannabinol Suppresses Cannabis Withdrawal Symptoms

This study assessed whether oral administration of delta-9-tetrahydrocannbinol (THC) effectively suppressed cannabis withdrawal in an outpatient

environment. The primary aims were to establish the pharmacological specificity of the withdrawal syndrome and to obtain information relevant to determining the potential use of THC to assist in the treatment of cannabis dependence. Eight adult, daily cannabis users who were not seeking treatment participated in a 40-day, within-subject ABACAD study. Participants administered daily doses of placebo, 30mg (10mg/tid), or 90mg (30mg/tid) oral THC during three, 5-day periods of abstinence from cannabis use separated by 7-9 periods of smoking cannabis as usual. Comparison of withdrawal symptoms across conditions indicated that (1) the lower dose of THC reduced withdrawal discomfort, and (2) the higher dose produced additional suppression in withdrawal symptoms such that symptom ratings did not differ from the smoking-as-usual conditions. Minimal adverse effects were associated with either active dose of THC. This demonstration of dose-responsivity replicates and extends prior findings of the pharmacological specificity of the cannabis withdrawal syndrome. The efficacy of these doses for suppressing cannabis withdrawal suggests oral THC might be used as an intervention to aid cannabis cessation attempts. Budney, A.J., Vandrey, R.G., Hughes, J.R., Moore, B.A., Bahrenburg, B., Drug Alcohol Depend., June 10, 2006.

Clinical Trial of Abstinence-based Vouchers and Cognitive-Behavioral Therapy for Cannabis Dependence

Ninety cannabis-dependent adults seeking treatment were randomly assigned to receive cognitive-behavioral therapy, abstinence-based voucher incentives, or their combination. Treatment duration was 14 weeks, and outcomes were assessed for 12 months posttreatment. Findings suggest that (a) abstinence-based vouchers were effective for engendering extended periods of continuous marijuana abstinence during treatment, (b) cognitive-behavioral therapy did not add to this during-treatment effect, and (c) cognitive-behavioral therapy enhanced the posttreatment maintenance of the initial positive effect of vouchers on abstinence. This study extends the literature on cannabis dependence, indicating that a program of abstinence-based vouchers is a potent treatment option. Discussion focuses on the strengths of each intervention, the clinical significance of the findings, and the need to continue efforts toward development of effective interventions. Budney, A.J., Moore, B.A., Rocha, H.L., and Higgins, S.T. J Consult Clin Psychol. 74(2), pp. 307-316, April 2006.

Ritonavir has Minimal Impact on the Pharmacokinetic Disposition of a Single Dose of Bupropion Administered to HumanVolunteers

A drug-drug interaction study was conducted to determine whether ritonavir (200 mg; 4 doses over 2 days) alters the pharmacokinetic disposition of bupropion (75 mg; once) coadministered to 7 healthy volunteers in a placebo-controlled 2-way crossover study. Serum samples collected from 0 to 24 hours after bupropion administration were assayed for concentrations of bupropion and metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion). Derived pharmacokinetic parameters were compared between placebo/bupropion and ritonavir/bupropion trials by paired t test. The effect of ritonavir on most pharmacokinetic parameters was minimal (<20% mean change). The only parameters that showed a statistically significant effect were threohydrobupropion area under the blood concentration curve (14% +/- 5% decrease, mean +/- SE; P = .04) and erythrohydrobupropion time-to-maximal serum concentration (161% +/- 92% increase, P = .03), suggesting that ritonavir may inhibit the carbonyl reductase enzyme responsible for formation of these metabolites. These findings indicate that short-term ritonavir dosing has only minimal impact on the pharmacokinetic disposition of a single dose of bupropion in healthy volunteers. Hesse, L.M., Greenblatt, D.J., von Moltke, L.L., Court, M.H., J Clin Pharmacol. 46(5), pp.

567-576, May 2006.

Cardiovascular Function in Multi-Ethnic Study of Atherosclerosis: Normal Values by Age, Sex, and Ethnicity

MRI provides accurate and high-resolution measurements of cardiac anatomy and function. The purpose of this study was to describe the imaging protocol and normal values of left ventricular (LV) function and mass in the Multi-Ethnic Study of Atherosclerosis (MESA). Eight hundred participants (400 men, 400 women) in four age strata (45-54, 55-64, 65-74, 75-84 years) were chosen at random. Participants with the following known cardiovascular risk factors were excluded: current smoker, systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, fasting glucose > 110 mg/dL, total cholesterol > 240 mg/dL, and high-density lipoprotein (HDL) cholesterol < 40 mg/dL. Cardiac MR images were analyzed using MASS software (version 4.2). Mean values, SDs, and correlation coefficients in relationship to patient age were calculated. There were significant differences in LV volumes and mass between men and women. LV volumes were inversely associated with age ($p < 0.05$) for both sexes except for the LV end-systolic volume index. For men, LV mass was inversely associated with age (slope = -0.72 g/year, $p = 0.0021$), but LV mass index was not associated with age (slope = -0.179 g/m2/year, $p = 0.075$). For women, LV mass (slope = -0.15 g/year, $p = 0.30$) and LV mass index (slope = 0.0044 g/m2/year, $p = 0.95$) were not associated with age. LV mass was the largest in the African-American group (men, 181.6 +/- 35.8 [SD] g; women, 128.8 +/- 28.1 g) and was smallest in the Asian-American group (men, 129.1 +/- 20.0 g; women, 89.4 +/- 13.3 g). The normal LV differs in volume and mass between sexes and among certain ethnic groups. When indexed by body surface area, LV mass was independent of age for both sexes. Studies that assess cardiovascular risk factors in relationship to cardiac function and structure need to account for these normal variations in the population. Natori, S., Lai, S., Finn, J.P., Gomes, A.S., Hundley, W.G., Jerosch-Herold, M., Pearson, G., Sinha, S., Arai, A., Lima, J.A., and Bluemke, D.A., AJR Am J Roentgenol. 186(6 Suppl 2):S357-365, June 2006.

Hypertension and Smoking are Associated with Reduced Regional Left Ventricular

Function in Asymptomatic: Individuals the Multi-Ethnic Study of Atherosclerosis This study sought to test the hypothesis that reduced regional left ventricular (LV) function is associated with traditional risk factors including hypertension, hypercholesterolemia, and smoking in asymptomatic individuals. Coronary artery disease is the main etiology of congestive heart failure in the U.S. and Europe. However, the relationship between risk factors for coronary artery disease and decreased myocardial function has not been studied systematically in asymptomatic individuals. The Multi-Ethnic Study of Atherosclerosis (MESA) is a cohort study designed to investigate the nature of atherosclerosis in asymptomatic individuals. A total of 1,184 participants (45 to 84 years old) underwent tagged cardiac magnetic resonance imaging. Regional LV function was quantified by analyzing peak systolic circumferential strain (Ecc) in regions corresponding to the left anterior descending (LAD), circumflex (LCX), and right coronary (RCA) territories. The association between risk factors and strains was studied using multiple linear regression. Higher diastolic blood pressure (DBP) was associated with lower Ecc ($p <$ or $= 0.002$). The Ecc's in the LAD territory of participants with DBP <80, 80 to 84, 85 to 89, and > or =90 mm Hg were -15.6%, -14.8%, -14.2%, and -13.7%, respectively ($p <$ 0.001). Similar results were documented in other territories and after multivariable analysis. Smokers had lower Ecc in the LAD and RCA regions compared with nonsmokers. Furthermore, dose response relationship between cigarette consumption measured in pack-years and regional LV dysfunction by Ecc was noted ($p <$ or $= 0.01$ in LAD and RCA territories). Finally, combined

diastolic hypertension and smoking was associated with a greater reduction of regional LV function. Authors conclude that higher diastolic blood pressure and smoking are associated with decreased regional LV function in asymptomatic individuals. Rosen, B.D., Saad, M.F., Shea, S., Nasir, K., Edvardsen, T., Burke, G., Jerosch-Herold, M., Arnett, D.K., Lai, S., Bluemke, D.A., and Lima, J.A., J Am Coll Cardiol. 47(6), pp. 1150-1158, March 26, 2006.

Caffeine Metabolites in Umbilical Cord Blood, Cytochrome P-450 1A2 Activity, and Intrauterine Growth Restriction

Studies investigating antenatal caffeine consumption and reproductive outcomes show conflicting results, and most studies have used maternal self-reported caffeine consumption to estimate fetal exposure. This study (n=1,606) was specifically designed to test the association of caffeine and its primary metabolites in umbilical cord blood with intrauterine growth restriction (IUGR). Pregnant women were recruited from 56 obstetric practices and 15 clinics affiliated with six hospitals in Connecticut and Massachusetts between September 1996 and January 2000. In an adjusted model including caffeine only, levels in all quartiles were associated with reduced risk of IUGR. In adjusted analyses including paraxanthine and caffeine, serum paraxanthine levels in the highest quartile were associated with increased risk of IUGR (adjusted odds ratio=3.29, 95% confidence interval: 1.17, 9.22); caffeine remained protective. These conflicting findings suggest that cytochrome P-450 1A2 (CYP1A2) metabolic activity may be associated with IUGR, so the ratio of paraxanthine to caffeine was then modeled. The likelihood of IUGR increased 21% for every one standard deviation change in the ratio (adjusted odds ratio=1.21, 95% confidence interval: 1.07, 1.37), suggesting that CYP1A2 activity, and not the absolute levels of paraxanthine, influences fetal growth. No associations were observed between caffeine or any metabolites and preterm delivery. Grosso, L.M., Triche, E.W., Belanger, K., Benowitz, N.L., Holford, T.R., and Bracken, M.B. Am J Epidemiol. 163(11), pp. 1035-1041, June 1, 2006.

Caffeine Metabolism, Genetics, and Perinatal Outcomes: A Review of Exposure Assessment Considerations During Pregnancy

The purpose of this study was to review the methodologic issues complicating caffeine exposure assessment during pregnancy; to discuss maternal and fetal caffeine metabolism, including genetic polymorphisms affecting caffeine metabolism; and to discuss the endogenous and exogenous risk factors known to influence caffeine metabolism. Methods consisted of a review of the relevant literature. Results indicated that there is wide inter-individual variation in caffeine metabolism, primarily due to variations in CYP1A2 enzyme activity. Some variability in CYP1A2 activity is due to genetic polymorphisms in the CYP1A2 gene that can cause increased or decreased inducibility of the enzyme. Considerable evidence exists that maternal caffeine metabolism is influenced by a variety of endogenous and exogenous factors and studying the genetic polymorphisms may improve understanding of the potential effects of caffeine and its metabolites on perinatal outcomes. There is substantial evidence that measurement of maternal, fetal, and neonatal caffeine metabolites may allow for a more precise measure of fetal caffeine exposure. Authors conclude that research on the genetic polymorphisms affecting caffeine metabolism may further explain the potential effects of caffeine and its metabolites on perinatal outcomes. Grosso, L.M. and Bracken, M.B. Ann Epidemiol. 15(6), pp. 460-466, July 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Services Research

Efficacious Treatment of Opioid Dependence in a Primary Care, Office-based Setting

The optimal level of counseling and frequency of attendance for medication distribution had not been established for the primary care, office-based buprenorphine-naloxone treatment of opioid dependence. This study from David A. Fiellin and colleagues from Yale University shows that once-weekly doses of buprenorphine and naloxone, combined with psychotherapy and delivered in a doctor's office, were just as effective in treating opiate addiction as thrice-weekly doses and extended weekly counseling. The authors conducted a 24-week randomized, controlled clinical trial with 166 patients assigned to one of three treatments: standard medical management and either once-weekly or thrice-weekly medication dispensing or enhanced medical management and thrice-weekly medication dispensing. Standard medical management was brief, manual-guided, medically focused counseling; enhanced management was similar, but each session was extended. The primary outcomes were the self-reported frequency of illicit opioid use, the percentage of opioid-negative urine specimens, and the maximum number of consecutive weeks of abstinence from illicit opioids. The three treatments had similar efficacies with respect to the mean percentage of opioid-negative urine specimens (standard medical management and once-weekly medication dispensing, 44 percent; standard medical management and thrice-weekly medication dispensing, 40 percent; and enhanced medical management and thrice-weekly medication dispensing, 40 percent; P=0.82) and the maximum number of consecutive weeks during which patients were abstinent from illicit opioids. All three treatments were associated with significant reductions from baseline in the frequency of illicit opioid use, but there were no significant differences among the treatments. The proportion of patients remaining in the study at 24 weeks did not differ significantly among the patients receiving standard medical management and once-weekly medication dispensing (48 percent) or thrice-weekly medication dispensing (43 percent) or enhanced medical management and thrice-weekly medication dispensing (39 percent) (P=0.64). Adherence to buprenorphine-naloxone treatment varied; increased adherence was associated with improved treatment outcomes. Patient satisfaction was significantly higher with once-weekly than with thrice-weekly medication dispensing, although this may represent a chance finding. This study further confirms that many patients can receive efficacious care for opioid dependence in a primary care, office-based setting. Furthermore, it establishes the level of care required to achieve optimal results and to most efficiently treat the increasing number of patients that have been attracted to this medical service. Fiellin, D.A., et al. Counseling Plus Buprenorphine-Naloxone Maintenance Therapy for Opioid Dependence. New England Journal of Medicine, 355(4), pp. 365-374, 2006.

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Survival Benefits of AIDS Treatment

As widespread adoption of potent combination antiretroviral therapy (ART) reaches its tenth year, the objective of this study was to quantify the cumulative survival benefits of acquired immunodeficiency syndrome (AIDS) care in the United States. Eras were defined that corresponded to advances in standards of human immunodeficiency virus (HIV) disease care, including opportunistic infection prophylaxis, treatment with ART, and the prevention of mother-to-child transmission (pMTCT) of HIV. Per-person survival benefits for each era were determined using a mathematical simulation model. Published estimates provided the number of adult patients with new diagnoses of AIDS who were receiving care in the United States from 1989 to 2003. Compared with survival associated with untreated HIV disease, per-person survival increased 0.26 years with Pneumocystis jiroveci pneumonia prophylaxis alone. Four eras of increasingly effective ART in addition to prophylaxis resulted in per-person survival increases of 7.81, 11.05, 11.57, and 13.33 years, compared with the absence of treatment. Treatment for patients with AIDS in care in the United States since 1989 yielded a total survival benefit of 2.8 million years. pMTCT averted nearly 2900 infant infections, equivalent to 137,000 additional years of survival benefit. In conclusion, at least 3.0 million years of life have been saved in the United States as a direct result of care of patients with AIDS, highlighting the significant advances made in HIV disease treatment. Walensky, R., Paltiel, A., Losina, E., Mercincavage, L., Schackman, B., Sax, P., Weinstein, M., and Freedberg, K. The Survival Benefits of AIDS Treatment in the United States. J Infect Dis, 194(1), pp. 11-19, 2006.

DAART in Methadone Clinics Associated with Improved HIV Treatment Outcomes

Directly administered antiretroviral therapy (DAART) in methadone clinics has the potential to improve treatment outcomes for human immunodeficiency virus (HIV)-infected injection drug users (IDUs). DAART was provided at 3 urban methadone clinics. Eighty-two participants who were initiating or reinitiating highly active antiretroviral therapy (HAART) received supervised doses of therapy at the clinic on the mornings on which they received methadone. Treatment outcomes in the DAART group were compared with outcomes in 3 groups of concurrent comparison patients, who were drawn from the Johns Hopkins HIV Cohort. The concurrent comparison patients were taking HAART on a self-administered basis. The 3 groups of concurrent comparison patients were as follows: patients with a history of IDU who were receiving methadone at the time HAART was used (the IDU-methadone group; 75 patients), patients with a history of IDU who were not receiving methadone at the time that HAART was used (the IDU-non-methadone group; 244 patients), and patients with no history of IDU (the non-IDU group; 490 patients). At 12 months, 56% of DAART participants achieved an HIV type 1 RNA level <400 copies/mL, compared with 32% of participants in the IDU-methadone group (P=.009), 33% of those in the IDU-non-methadone group (P=.001), and 44% of those in the non-IDU group (P=.077). The DAART group experienced a median increase in the CD4 cell count of 74 cells/mm3, compared with 21 cells/mm3 in the IDU-methadone group (P=.04), 33 cells/mm3 in the IDU-non-methadone group (P=.09), and 84 cells/mm3 in the non-IDU group (P=.98). After adjustment for other covariates in a logistic regression model, DAART participants were significantly more likely to achieve viral suppression than were patients in each of the 3 comparison groups. These results suggest that methadone clinic-based DAART has the potential to provide substantial clinical benefit for HIV-infected IDUs. Lucas, G., Mullen, B., Weidle, P., Hader, S., McCaul, M., and Moore, R. Directly Administered Antiretroviral Therapy in Methadone Clinics is Associated with Improved HIV Treatment Outcomes, Compared with Outcomes among Concurrent Comparison Groups. Clin Infect

Dis, 42(11), pp. 1628-1635, 2006.

Medicaid Coverage and Access to Publicly Funded Opiate Treatment

Numerous studies have established the efficacy of methadone maintenance programs for treatment of opiate addiction. Participation in methadone treatment is associated with decreases in heroin use, criminal activity, and HIV risky behaviors. Moreover, methadone maintenance programs are considered to be a cost-effective form of treatment for opiate addiction costing approximately $13 per day. In this observational, longitudinally based study of 555 individuals, the changes in access to methadone maintenance treatment following Oregon's decision to remove substance abuse treatment from the Medicaid program was examined. Access was compared before and after the benefit change for two cohorts of adults addicted to opiates presenting for publicly funded treatment. Propensity score analysis was used to model some of the selective dis-enrollment from Medicaid that occurred after the benefit change. Logistic regression was used to compare access to methadone by cohort, controlling for client characteristics. Opiate users presenting for publicly funded treatment after the change were less than half as likely (OR = 0.40) to be placed in an opiate treatment program compared to the prior year. Further analysis revealed that those with no recent treatment history were less likely to present for treatment after the benefit change. These results have implications for states considering Medicaid cuts, especially if the anticipated increases in illegal activity, emergency room utilization, unemployment, and mortality can be demonstrated. Deck, D., Wiitala, W., and Laws, K. Medicaid Coverage and Access to Publicly Funded Opiate Treatment. J Behav Health Serv Res, 33(3), pp. 324-334, 2006.

Outreach Recovery Management Checkups Can Shorten the Cycle of Relapse, Treatment Reentry, and Recovery

A growing body of evidence suggests that a subset of drug-dependent substance users suffer from a severely chronic relapsing condition, whereby they may cycle repeatedly through periods of relapse, treatment reentry, incarceration, and recovery, over a course of many years. Eight quarterly interviews were conducted on 448 participants in both residential (60%) and outpatient (40%) drug abuse treatment programs randomly assigned to either an assessment-only condition or to a Recovery Management Checkup (RMC) condition in which outreach workers interviewed patients to assess their need for re-treatment. The sample was 85% African American, most (47%) were between 30 and 40 years of age, and about 60% were females. The intervention utilized motivational interviewing techniques to: (1) provide personalized feedback to participants about their substance use and related problems, (2) help the participant recognize their substance use problem and consider returning to treatment, (3) address existing barriers to treatment, and (4) schedule an assessment and facilitate reentry (reminder calls, transportation). The frequency, type, and predictors of transitions between points in the relapse, treatment reentry, and recovery cycle were measured. Results indicated that about one-third of the participants transitioned from one point in the cycle to another each quarter; 82% transitioned at least once, 62% multiple times. People assigned to RMC were significantly more likely to return to treatment sooner and receive more treatment. The probability of transitioning to recovery was related to the severity, problem orientation, desire for help, self-efficacy, self-help involvement, and recovery environment at the beginning of the quarter and the amount of treatment received during the quarter. These findings support the characterizations of addiction as a chronic condition, and demonstrate the need and effectiveness of post-discharge monitoring and checkups. The methods in this study also provide a simple but replicable method for learning more about the multiple pathways

that individuals travel along before achieving a prolonged state of recovery. Scott, C.K., Dennis, K.L., and Foss, M.A. Utilizing Recovery Management Checkups to Shorten the Cycle of Relapse, Treatment Reentry, and Recovery. Drug Alcohol Depend. 78, pp. 325-338, 2005.

Clinical Significance of Tobacco Withdrawal

Determination of the clinical significance of tobacco withdrawal is important for several reasons. First, the diagnosis of nicotine withdrawal and all disorders in the American Psychiatric Association's Diagnostic and Statistical Manual requires the syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. Second, several countries have approved the use of nicotine replacement therapy solely for relief of withdrawal symptoms. This indication implies tobacco withdrawal produces clinically significant distress. Third, some have stated tobacco withdrawal is not clinically significant. To estimate the clinical significance of tobacco withdrawal, this review located six experimental studies that reported Profile of Mood States (POMS) scores after stopping smoking in untreated smokers and compared them with scores in psychiatric outpatients. The pre-cessation POMS Total Mood Disturbance scores (median = 13.6) were similar to adult norms (mean, M = 17.8) but during abstinence (M = 5 days), the scores had increased (M = 27.4) to be similar to that of psychiatric outpatient norms (M = 25.1). These results and others, suggest stopping smoking causes clinically significant distress. By demonstrating that tobacco withdrawal can produce clinically significant distress, this paper suggests tobacco withdrawal itself is a disorder worthy of intervention. In addition, it suggests that claims by the tobacco industry and others that tobacco withdrawal is insignificant are untrue. Hughes, J. Clinical Significance of Tobacco Withdrawal. Nicotine Tob Res, 8(2), pp. 153-156, 2006.

Juvenile Drug Court: Enhancing Outcomes by Integrating Evidence-Based Treatments

This study evaluated the effectiveness of juvenile drug court for 161 juvenile offenders meeting diagnostic criteria for substance abuse or dependence and determined whether the integration of evidence-based practices enhanced the outcomes of juvenile drug court. Over a 1-year period, a four-condition randomized design evaluated outcomes for family drug court with usual community services, juvenile drug court with usual community services, drug court with multi-systemic therapy, and drug court with multi-systemic therapy enhanced with contingency management for adolescent substance use, criminal behavior, symptomatology, and days in out-of-home placement. In general, findings supported the view that drug court was more effective than family court services in decreasing rates of adolescent substance use and criminal behavior. Possibly due to the greatly increased surveillance of youth in drug court, however, these relative reductions in antisocial behavior did not translate to corresponding decreases in re-arrest or incarceration. In addition, findings supported the view that the use of evidence-based treatments within the drug court context improved youth substance-related outcomes. Clinical and policy implications are discussed. Henggeler, S.W., Halliday-Boykins, C.A., Cunningham, P.B., Randall, J., Shapior, S.B., and Chapman, J.E. Juvenile Drug Court: Enhancing Outcomes by Integrating Evidence-Based Treatments. J Consult Clin Psychol, 74(1), pp. 42-54, 2006.

Prevalence of DSM/ICD-Defined Nicotine Dependence

In this study techniques of systematic review were used to estimate for adults (1) the lifetime and current prevalence of DSM/ICD-defined nicotine dependence and (2) the prevalence of individual DSM/ICD dependence criteria.

Systematic computer searches and other methods located eleven population-based surveys of adults (>/=18 year olds) and two of young adults (18-30 year olds). In the USA and Germany, about 25% of adults had been dependent on nicotine in their lifetime, including 15% who were currently dependent. Similar or higher rates were seen in Asian men but <5% of Asian women had been dependent. About a third of ever-smokers and half of current smokers either had been or were currently dependent on nicotine and this did not consistently differ by age, country or sex. Impaired control over tobacco use was the most commonly endorsed criteria and giving up activities to use and spending lots of time with nicotine were the least commonly endorsed. This study is consistent with others that show that nicotine dependence is one of the most common mental disorders; however, about half of current smokers do not meet DSM/ICD dependence criterion, perhaps because they have not tried to stop, nicotine is more legal than other drugs of dependence, and nicotine causes fewer behavioral disturbances than other drugs of abuse. However none of these possible explanations have been empirically tested as yet. Hughes, Helzer, and Lindberg. Prevalence of DSM/ICD-defined Nicotine Dependence. Drug Alcohol Depend, available onlinw May 15, 2006.

Sanctions and Rewards in Drug Court Programs

This article documents the specific behaviors that are sanctioned and rewarded, and the sanctions and rewards used, perceptions of the efficacy of sanctions, level of standardization in the application of sanctions and rewards, participants' understanding of the sanctioning system, and the decision-making process regarding sanctioning in 5 judicial circuits in Florida. Using qualitative data gathered from interviews with 86 key stakeholders and analyzed using NUD*IST software, the authors compared responses between drug courts and traditional courts, as well as by respondent role (staff vs. offender). Main findings include: many more sanctions were used and more behaviors identified as being likely to result in a sanction in drug courts as compared to traditional courts, sanctions used in drug courts were more treatment oriented than in traditional courts, and drug courts appeared to emphasize tailoring sanctions to the individual participant rather than applying sanctions in a standardized manner. Applications to drug court practice and directions for future research are discussed. Lindquist, C.H., Krebes, C.P., and Lattimore, P.K. Sanctions and Rewards in Drug Court Programs. Implementation, Perceived Efficacy, and Decision Making. Journal of Drug Issues, 36(1), pp. 119-146, 2006.

Substance Abuse Treatment Duration for Medicaid versus HMO's

As Medicaid clients have come to be enrolled in managed care, concerns have arisen about the ability of private sector systems to meet the needs of enrollees with substance abuse problems. This paper describes treatment initiation and duration for Medicaid and commercial substance abuse treatment clients in a large HMO. This study was a prospective secondary analysis of information from HMO databases. Subjects included 641 adult Medicaid clients who contacted the HMO's addiction medicine department in 1996-1997 and 447 commercial HMO addiction medicine patients during that same time. Chief dependent variables were initiation and duration of substance abuse treatment after the index event. Logistic regression showed that longer HMO enrollment predicted treatment initiation after substance abuse assessment, but Medicaid status was not a significant predictor. A competing risks analysis using Cox proportional hazards models indicated that once subjects had initiated, Medicaid was not significantly related to exit from substance abuse treatment. Analysis of health plan dis-enrollment by Medicaid clients indicated that the most common reason was loss of Medicaid eligibility. The investigators conclude that these results raise the possibility that state Medicaid policies may make it difficult for clients to obtain suitable chemical dependency treatment

services. McFarland, B.H., Lynch, F.L., Freeborn, D.K., Green, C.A., Polen, M.R., Deck, D.D., and Dickinson, D.M. Substance Abuse Treatment Duration for Medicaid Versus Commercial Clients in a Health Maintenance Organization. Med Care, 44(6), pp. 601-606, 2006.

Adoption of Buprenorphine is Contingent Upon Profit Status As Well As Client and Staff Characteristics

The recent approval of buprenorphine for the treatment of opiate dependence offers an opportunity to analyze innovation adoption in community-based treatment. Using data collected from national samples of 299 privately funded and 277 publicly funded treatment centers, this research examined buprenorphine adoption using baseline data collected between 2002 and 2004 as well as follow-up data collected 12 months later. Private centers were significantly more likely than public centers to report current use of buprenorphine. The baseline data indicated that early adoption was positively associated with center accreditation, physician services, availability of detoxification services, current use of naltrexone, and the percentage of opiate-dependent clients. Multivariate analyses of follow-up data suggest that adoption was greater in accredited centers, for-profit facilities, organizations offering detoxification services, and naltrexone-using centers. Future research should continue to monitor the extent to which buprenorphine is adopted in these settings. Knudsen, H., Ducharme, L., and Roman, P. Early Adoption of Buprenorphine in Substance Abuse Treatment Centers: Data from the Private and Public Sectors. J Subst Abuse Treat, 30(4), pp. 363-373, 2006.

Treatment Barriers at Centralized Intake

The 59-item Barriers to Treatment Inventory (BTI) was administered to 312 substance abusers at a centralized intake unit following assessment but before treatment entry to assess their views on barriers to treatment. Factor analysis identified 25 items in 7 well-defined latent constructs: Absence of Problem, Negative Social Support, Fear of Treatment, Privacy Concerns, Time Conflict, Poor Treatment Availability, and Admission Difficulty. The factorial structure of the barriers is consistent with the findings of other studies that asked substance abusers about barriers to treatment and is conceptually compatible with Andersen's model of health care utilization. Factors were moderately to highly correlated, suggesting that they interact with one another. Selected characteristics were generally not predictive of barrier factors. Overall, results indicate that the BTI has good content validity and is a reliable instrument for assessing barriers to drug treatment. Rapp, R., Xu, J., Carr, C., Lane, D., Wang, J., and Carlson, R. Treatment Barriers Identified by Substance Abusers Assessed at a Centralized Intake Unit. J Subst Abuse Treat, 30(3), pp. 227-235, 2006.

Over Half of Male Cocaine Addicts Were Able to Sustain Abstinence Exceeding Five Years

The study examined long-term outcomes (mortality, substance use, mental health, employment, criminal involvement) among a cocaine dependent sample. This 12-year follow-up study, conducted in 2002-2003, updates information obtained at intake and two face-to-face interviews conducted in 1990-1991 and 1991-1992 among 321 male cocaine-dependent veterans admitted to drug treatment in 1988-1989. At the 2002-2003 follow-up, 28 had died (consistent with death rates for non drug abusing males) and 266 were interviewed. A mixed model examining the longitudinal relationships demonstrated that treatment was associated with lower levels of cocaine use over the 12-year follow-up period after entry into the index treatment and more stable recovery (i.e., 52% continuously abstinent from cocaine for at

least 5 years). Only two measures at intake predicted stable recovery at follow-up: only ethnicity (being White) and having greater confidence in one's ability to avoid cocaine use in high-risk situations. Individuals achieving stable recovery reported less psychiatric symptoms, criminal involvement, and unemployment during the year prior to the interview. Hser, Y., Stark, M.E., Paredes, A., Huang, D., Anglin, M.D., and Rawson, R. A 12-year Follow-up of a Treated Cocaine-dependent Sample. J Subst Abuse Treat, 30 pp. 219-226, 2006.

Utilization of Medicaid Substance Abuse Services Among Adolescents

This study examined race and gender disparities in utilization of substance abuse treatment among adolescents enrolled in Medicaid in Tennessee. By using Medicaid enrollment, encounter, and claims data, utilization of substance abuse services for the population of adolescents enrolled in TennCare was examined in two ways. The first utilization measure considered annual utilization rates and probability of use of substance abuse services for the statewide population of enrolled adolescents (approximately 170,000 per year). The second examined the age at which the first substance abuse service was received for the 8,473 youths who had that service paid for by TennCare during state fiscal years 1997 to 2001. Proportionally, among adolescents, more whites than blacks and more males than females used substance abuse services. The disparities were greater than differences in prevalence rates explain. Black females had the greatest disparity in service utilization. Whites and females received their first substance abuse service at a younger age than blacks or males in this Medicaid population. However, the age difference may not be clinically significant. The low utilization rates, in general, and the disparities in service use by race and gender raise questions about the identification of substance use problems at both provider and system levels. Heflinger, C., Chatman, J., and Saunders, R. Racial and Gender Differences in Utilization of Medicaid Substance Abuse Services among Adolescents. Psychiatr Serv, 57(4), pp. 504-511, 2006.

Episodic Homelessness and Health Care Utilization

The authors examined whether episodes of homelessness are associated with sub optimal medical utilization even when accounting for concurrent addiction severity and depression. They used data from a 30-month cohort of patients with HIV/AIDS and alcohol problems. Housing status, medical service utilization, addiction severity, and depressive symptoms were assessed at biannual standardized research interviews. Utilization outcomes included ambulatory visits, emergency department (ED) visits, and hospitalizations. The main independent variable, homelessness, was defined as spending >1 night in a shelter or on the street in the past 6 months. Separate multivariable longitudinal regression models for each outcome calculated incidence rate ratios (IRR) comparing utilization rates during 6-month intervals, homeless versus housed. Additional models assessed whether addiction severity and depressive symptoms accounted for utilization differences. Of the 349 subjects, 139 (39%) reported homelessness at least once during the study period. Among those reporting homelessness, the median number of nights homeless was 30 per 6-month observation period. Homelessness was associated with higher ED utilization (IRR=2.17; 95% CI=1.72-2.74) and hospitalizations (IRR=2.30; 1.70-3.12), despite no difference in ambulatory care utilization (IRR=1.09; 0.89-1.33). These utilization findings attenuated but remained significant when adjusting for addiction severity and depressive symptoms. The authors conclude that expanded access to addiction, psychiatric and ambulatory medical care alone without consideration of housing stability may not be sufficient to mitigate intensive medical utilization patterns among HIV-infected patients with alcohol problems. Kim, Kertesz, Horton, Tibbetts, and

Samet. Episodic Homelessness and Health Care Utilization in a Prospective cohort of HIV-infected Persons with Alcohol Problems. BMC Health Serv Res, 6(1), pp. 19-19, 2006.

Using Cell Phones with Cocaine-Addicted Homeless Patients in Treatment

This is the first study to examine whether cell phones could be used to collect ecological momentary assessment (EMA) data with homeless crack cocaine-addicted adults in treatment. The study adapted an EMA method to examine behavior in real time using cell phones and computer-automated telephone interviewing. Participants treated in an intensive outpatient treatment program were given cell phones for a 2-week period to record current states of cocaine craving and using episodes. Results showed cell phone technology could reliably deliver a computerized survey. This homeless population used a cell phone to report craving and using episodes. Drug use reported via EMA was in agreement with urine toxicology results for 73% of participants. Of 30 participants, 24 (80%) completed the full 2-week protocol. Participants indicated the survey made them more aware of phenomena leading to cravings and use, suggesting the usefulness of EMA as a potential intervention. Freedman, M.J., Lester, K.M., McNamara, C., Milby, J.B., and Schumacher, J.E. Cell Phones for Ecological Momentary Assessment With Cocaine-addicted Homeless Patients in Treatment. J Subst Abuse Treat, 30(2), pp. 105-111, 2006.

Self-report Measures are Superior to Biological Measures of Use for Quantifying Problem Severity

Structural equation modeling was used to demonstrate that multiple self-report and biological measures are influenced by the same underlying factor (substance use) and that no single measure is without error. The archival sample used included data from 337 adults (59% female; 85% African American; age normally distributed) with substance dependence. Individual measures and several possible combinations of them (including one based on the latent factors and another based on the Global Appraisal of Individual Needs (GAIN) Substance Frequency Scale was used to examine how well each measure predicted a wide range of substance-related problems. The measure with the highest construct validity in these analyses varied by drug and problem. Despite their advantages for detection, biometric measures were frequently less sensitive to the severity of other problems. Composite measures based on the substance-specific latent factors performed better than simple combinations of the biometric and psychometric measures. The Substance Frequency Scale from the GAIN performed as well as or better than all measures across problem areas, including the latent factor for any use. While the research was limited in some ways, it has important implications for the ongoing debate about the proper way to combine biometric and psychometric data. Lennox, R., Dennis, M.L., Scott, C.K., and Funk, R. Combining Psychometric and Biometric Measures of Substance Use. Drug Alcohol Depend, 83 pp. 95-103, 2006.

Self-rated Health Status Among HIV+ Patients

The purpose of the study was to assess how patients with HIV who are enrolled in a clinical trials cohort rate their health and to compare their ratings with those of patients with HIV from 2 other cohorts: the HIV Cost and Services Utilization Study (HCSUS), and Adult AIDS Clinical Trials Group protocol 320 (ACTG 320). Baseline information was analyzed for the 1649 subjects enrolled in the Adult AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) study prior to March 2002 who had self-rated health data available.

Those results were compared with results from 2 other groups: 1) HCSUS, the only nationally representative sample of people in care for HIV in the U.S., which conducted baseline interviews in 1996 and 1997, and 2) ACTG 320, a randomized, double-blinded, placebo-controlled trial comparing a 3-drug antiretroviral regimen with a 2-drug combination, which enrolled subjects in the same general time frame as HCSUS. T tests, Pearson correlations, and linear regression were used to determine factors associated with self-rated health and z scores were used to compare results between cohorts. The mean (SD) rating scale value on a 0-100 scale for ALLRT participants was 79.8 (16.8). Values were significantly lower for subjects who were older, had a history of injection drug use, had lower CD4 cell counts, or were beginning salvage antiretroviral therapy. Subjects in ALLRT reported significantly better self-rated health at baseline than those in HCSUS or ACTG 320 (11-12% higher rating scale values in ALLRT; $p<0.05$). When cohort differences were accounted for through regression and stratification, the differences in scores between subjects in ALLRT and HCSUS increased and the differences in scores between subjects in ALLRT and ACTG 320 diminished. Self-rated health varied significantly by age, CD4 count, injection drug use history, and salvage therapy status. Differences in self-rated health for clinical trials and non-clinical trials samples appear to be substantial and should be considered when applying trial results to clinical populations. Mrus, J., Schackman, B., Wu, A., Freedberg, K., Tsevat, J., Yi, M., and Zackin, R. Variations in Self-rated Health among Patients with HIV Infection. Qual Life Res, 15(3), pp. 503-514, 2006.

An Employment Framework for Justifying Increase Substance Abuse Spending

A large number of studies examining the cost of substance abuse often ignore indirect costs. This article argues that lost productivity (un/under-employment) is a substantial and restorable cost of substance abuse. The authors offer a framework for estimating the cost of substance abuse in terms of lost productivity, arguing that it makes sense to argue in favor or appropriate levels of spending by the states to restore substance abusers to full productivity in society. The authors acknowledge that criminal justice costs are another important social cost, however, a major advantage of employment is that full recovery makes a positive contribution to society, whereas not committing a crime does not. In addition, employment reduces the likelihood of relapse. Authors conclude by indicating the importance of including the relative effectiveness of treatments in the framework, as treatments vary widely in efficacy and the fidelity with which they are delivered. Meara, E., and Frank, R.G. Spending on Substance Abuse Treatment: How Much is Enough? Addiction, 100 pp. 1240-1248, 2005.

Reducing Shame May Reduce Substance Abuse

The current analyses sought to clarify the relations of shame-proneness and guilt-proneness to addictive behaviors in three studies drawing from two very different populations—college students and incarcerated jail inmates. Previous research has demonstrated that shame-proneness (the tendency to feel bad about the self) relates to a variety of life problems, whereas guilt-proneness (the tendency to feel bad about a specific behavior) is more likely to be adaptive. Thus the authors hypothesized that across all three samples, shame-proneness would be positively correlated with alcohol and drug problems and guilt-proneness would be inversely or unrelated to alcohol and drug problems. First, responses to the drug and alcohol scales of the Millon Clinical Multiaxial Inventory-II were compared to results of Tangney's 15-item, scenario-based Test of Self-Conscious Affect (TOSCA) using semi-partial correlations that eliminate shared variance between guilt and shame scores in two separate studies involving college undergraduates (Study 1 N =235, Study 2 N =249). Consistent with hypotheses, shame scores were positively correlated with both

alcohol and drug abuse scores, whereas guilt scores were negatively related to alcohol and drug abuse scores. Focusing in on a population in which substance abuse has been shown to be above average, a third study focused on jail inmates (Study 3 N =332). The Texas Christian University Correctional: Residential Treatment Form, Initial Assessment (TCU-CRTF) in addition to the Alcohol Problems (12 items) and Drug Problems (12 items) scales from Morey's Personality Assessment Inventory (PAI) were used to measure alcohol and drug abuse. Tangney's 19-item TOSCA for Socially Deviant Populations was used to measure shame and guilt. Results for the CRTF and PAI scores reflected the same pattern of results as for college students. However, though consistent with hypotheses, some guilt semi-partial correlations were non-significant. Though results were not causal in nature, they support the use of shame-reduction interventions for problem substance abuse populations. Dearing, R.L., Stuewig, J., and Tangney, J.P. On the Importance of Distinguishing Shame from Guilt: Relations to Problematic Alcohol and Drug Use. Addict Behav. 30, pp. 1392-1404, 2006.

Predicting Unmet Health Services Needs among Incarcerated Substance Users

Negative health consequences of illicit drug use, such as cardiovascular complications and infectious diseases, increase the likelihood of the need for health care. Evidence suggests, with the exception of emergency services, drug users generally are medically underserved. In addition, the effect of illicit drug use on health care utilization is becoming important for the criminal justice system. This study examined data for 661 incarcerated men in the Kentucky prison system focused on predictors of unmet physical, behavioral, and overall health care needs among chronic substance users. Analyses revealed that White incarcerated drug users were more likely to report unmet physical and overall health care needs than non-Whites and those with high school education or above were more likely to report unmet physical, behavioral, and overall health care needs. In addition, more episodes of serious illness, more mental health problems, and poorer self-rated health were predictive of all three types of unmet health care needs. A longer career of drug use emerged as a significant predictor of unmet behavioral health care needs, whereas more frequent drug use in the year before incarceration predicted unmet physical health care needs. Further research directions and implications for in-prison health care planning are discussed. Narevic, E., Garrity, T.F., Schoenberg, N.E., Hiller, M.L., Webster, J.M., Leukefeld, C.G., and Tindall, M.S. Factors Predicting Unmet Health Services Needs among Incarcerated Substance Users. Subst Use Misuse, 41, pp. 1077-1094, 2006.

Heroin Dependence and HIV Infection In Malaysia

Malaysia is experiencing severe problems with heroin dependence and HIV infection. This study of one hundred seventy seven (n=177) heroin-dependent subjects enrolled in a heroin-treatment program in Muar, Malaysia explored the association of heroin dependence and other HIV risk behaviors, to the prevalence of HIV and other infectious diseases. Subjects were evaluated with the AIDS Risk Inventory; serological tests for HIV, hepatitis B, and hepatitis C; and chest X-ray. It was found that all of the subjects were male; 67.8% were Malays, 28.8% Chinese, and 2.3%. Indian. Subjects had a mean (SD) age of 37.2 (9.1) years and 14.4 (8.5) years of using heroin; 76.3% reported lifetime injection drug use (IDU), and 41.5% reported current IDU. Test results showed 30 of 156 (19.2%) tested HIV positive, 143 of 159 (89.9%) tested hepatitis C positive, and 25 of 159 (15.7%) had radiological evidence of pulmonary tuberculosis. Malay subjects had a significantly higher prevalence of current IDU, needle sharing ($p<0.01$), and HIV infection ($p<0.05$) compared with Chinese subjects. Lifetime IDU, needle sharing, lack of consistent condom use, and Malay ethnicity were significantly associated with HIV infection. This study

demonstrates the high prevalence of HIV infection among heroin-dependent individuals in Malaysia, and supports the importance of interventions to reduce the major risk factors for HIV, including IDU, needle sharing, and unprotected sex. Chawarski, M., Mazlan, M., and Schottenfeld, R. Heroin Dependence And HIV Infection In Malaysia. Drug Alcohol Depend, 82(1), pp. S39-S42, 2006.

Gender Differences in the Prediction of Condom Use Among Incarcerated Juvenile Offenders

This study seeks to predict condom-protected vaginal intercourse among incarcerated youth using the Information-Motivation-Behavioral skills (IMB) model as the theoretical framework. The IMB model is a three-factor conceptualization of HIV preventive behavior including information on HIV/AIDS transmission and prevention methods, motivation to act on the knowledge and change risky behavior, and behavioral skills in performing the specific prevention act. Data was collected from youth held in a detention center located in a Southern city. Adolescents 13 years of age or older and recently incarcerated (within 3 days of booking) were eligible for the study. The study sample included 523 adolescents (328 male and 195 female. Participants were predominately African-American (90%), with an average age of 15, and average level of highest education was 9th grade. Survey data was collected for a self-report measure of AIDS knowledge, pre-condom peer influence, risk perception, condom attitudes, condom use self-efficacy, frequency of vaginal intercourse, and frequency of condom-protected vaginal intercourse. Results revealed that being male, peer influence, positive condom attitudes, and condom self-efficacy significantly predicted condom use. Separate gender analyses revealed that condom use among males was predicted by peer influence and positive condom attitudes, whereas condom use among females was predicted by peer influence, self-efficacy, and condom attitudes. Compared with males, females reported significantly greater knowledge, less peer influence, higher perceived risk for infection, more positive condom attitudes, and more self-efficacy. Despite these findings, females reported less condom use than males. The authors conclude that females find it difficult to use condoms consistently despite their awareness. They suggest that power imbalances and other dynamics operating within relationships between boys and girls need to be explored further in developing effective HIV prevention interventions. Robertson, A.A., Stein, J.A., and Baird-Thomas, C. Gender Differences in the Reduction of Condom Use among Incarcerated Juvenile Offenders: Testing the Information-motivation-behavior Skills (IMB) Model. J Adolesc Health, 38(2006), pp. 18-25, 2006.

Pregnant Women Treated in Women-only Versus Mixed-gender Programs Receive More Services

This study-compared characteristics of pregnant women treated in women-only (WO) and mixed-gender (MG) substance abuse treatment programs and compared services provided by these two types of programs. Participants were 407 pregnant women who were admitted to 7 WO programs and 29 MG programs in 13 counties across California during 2000-2002. Pregnant women treated in WO programs demonstrated greater severity in drug use, legal problems, and psychiatric problems than those treated in the MG programs. They were also less likely to be employed and more likely to be homeless. Women-only programs were more likely to offer childcare, children's psychological services, and HIV testing. The greater problem severity of pregnant women treated in WO programs suggests that these specialized services are filling an important gap in addiction services, although further expansion is warranted in psychiatric, legal, and employment services. Hser, Y., and Niv, N. Pregnant Women in Women-Only and Mixed-Gender Substance Abuse Treatment Programs: A Comparison of Client Characteristics and Program Services. J Behav Health Serv Res, 4(On-Line), pp. 1-12, 2006.

Participation by TC Staff Members in Methadone Sensitivity Training was Associated with a Lower Abstinence Orientation and Higher Knowledge of Methadone Treatment

This study examined a residential therapeutic community (TC) treatment program that began allowing clients to enroll in methadone maintenance. 104 staff members with patient contact in four TC facilities were invited to participate on a voluntary basis, and 46 women and 41 men (84%) agreed. Staff self-report measures included the 14-item Abstinence Orientation Scale (AOS), the 12-item Methadone Knowledge Scale (MKS), and the 6-item Disapproval of Drug Use Scale (DDU). Staff members who affirmed participation in addiction treatment themselves had greater methadone knowledge than those who had not. Staff members (N=40) who participated in a 2-hour methadone sensitivity training course had significantly greater methadone knowledge and lower abstinence orientation than those (N=45) who did not attend the training ($p<.001$). The TC staff in this study had stronger abstinence orientation (M=3.22) than found in prior studies of methadone clinic staff in New York (M=2.67) and Australia (2.95), which may represent a barrier to methadone in residential settings. Nevertheless, the TC sample did not differ on MHS scores from prior studies of methadone clinic staff. Results suggest that staff experience is correlated with attitudes and knowledge about methadone and that staff training is associated with changing attitudes and knowledge about methadone. Andrews, S., Sorensen, J. L., Guydish, J., Delucchi, K., and Greenberg, B. Knowledge and Attitudes About Methadone Maintenance Among Staff Working in a Therapeutic Community. Journal of Maintenance in the Addictions, 3(1), pp. 47-59, 2005.

Exposure to Transphobia and HIV Risk Behavior Among Transgendered Women

This study examined the relationship between exposure to transphobia -- societal discrimination and stigma of individuals who do not conform to traditional notions of gender -- and risk for engaging in unprotected receptive anal intercourse (URAI) among 327 transgendered women of color. Overall, 24% of participants had engaged in URAI at least once in the past 30 days. Individuals who self-identified as pre-operative transsexual/transgendered women were significantly more likely than self-identified females to have engaged in URAI. Although exposure to transphobia was not independently related to URAI, an interaction between age and experiencing discrimination was observed. Among transgendered women 18-25 years old, those reporting higher levels of exposure to transphobia had a 3.2 times higher risk for engaging in URAI compared to those reporting lower levels. Findings from this study corroborate the importance of exposure to transphobia on HIV risk, particularly among transgendered young adults. Sugano, E., Nemoto, T., and Operario, D. The Impact of Exposure to Transphobia on HIV Risk Behavior in a Sample of Transgendered Women of Color in San Francisco. AIDS Behav, 10(2), pp. 217-225, 2006.

Performance Measures for Alcohol and Other Drug Services

Performance measures, which evaluate how well health care practitioners' actions conform to practice guidelines, medical review criteria, or standards of quality, can be used to improve access to treatment and the quality of treatment for people with alcohol and other drug problems. This article examines different types of quality measures, how they fit within the continuum of care, and the types of data that can be used to arrive at these measures. The Washington Circle measures--identification, initiation of treatment, and treatment engagement--are a widely used set of performance

measures. Garnick, D., Horgan, C., and Chalk, M. Performance Measures for Alcohol and other Drug Services. Alcohol Res Health, 29(1), pp. 19-26, 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Clinical Trials Network Research

Investigación Y Prática En Colaboración: La Red De Ensayos Clinicos Del NIDA. [Research and Practice Together: The NIDA Clinical Trials Network]

This article, published from the SW Node, describes, in Spanish and English, the structure, functions, and unique contributions of the CTN, as well as its past, current, and planned protocols. Miller, W.R., Bogenschutz, M., and Villarreal, M.I. Investigación Y Prática En Colaboración: La Red De Ensayos Clinicos Del NIDA. [Research and Practice Together: The NIDA Clinical Trials Network] Adicciones, 18(1), pp.11-22, 2006.

Characteristics of Substance Abuse Treatment Programs Providing Services for HIV/AIDS, Hepatitis C Virus Infection, and Sexually Transmitted Infections: The National Drug Abuse Treatment Clinical Trials Network

Illicit drug users sustain the epidemics of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), hepatitis C (HCV), and sexually transmitted infections (STIs). Substance abuse treatment programs present a major intervention point in stemming these epidemics. As a part of the "Infections and Substance Abuse" study, established by the National Drug Abuse Treatment Clinical Trials Network, sponsored by National Institute on Drug Abuse, three surveys were developed; for treatment program administrators, for clinicians, and for state and District of Columbia health and substance abuse department administrators, capturing service availability, government mandates, funding, and other key elements related to the three infection groups. Treatment programs varied in corporate structure, source of revenue, patient census, and medical and non-medical staffing; medical services, counseling services, and staff education targeted HIV/AIDS more often than HCV or STIs. The results from this study have the potential to generate hypotheses for further health services research to inform public policy. Brown, L.S., Jr, Kritz, S.A., Goldsmith, R.J., Bini, E.J., Rotrosen, J., Baker, S., Robinson, J., McAuliffe, P. Characteristics of Substance Abuse Treatment Programs Providing Services for HIV/AIDS, Hepatitis C Virus Infection, and Sexually Transmitted Infections: The National Drug Abuse Treatment Clinical Trials Network. J Subst Abuse Treat, 30(4), pp. 315-321, June 2006.

Reasons Why Successful Clinical Trials Are Not Adopted by the Sites in Which They are Conducted

The National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) is

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intended to test promising drug abuse treatment models in multi-site clinical trial. Staff members from 8 CTN clinics (19 men and 23 women) representing various roles in their organization were interviewed regarding how the technology of multi-site clinical trials might be modified to better support adoption of tested interventions considering that only 1 of the 8 clinics actually adopted the tested intervention after the trial ended. Interview content analysis revealed four conceptual themes associated with adoption: a) researchers giving the impression of being concerned about the clinic and not just in gathering data, b) successful integration of the trial protocol with existing clinic practices, c) timely post-trial feedback on success, and d) planning within the clinic to adopt trial procedures before or during the trial. Guydish, J., Manser, S. T., Jessup, M., Tajima, B., Sears, C., and Montini, T. Multi-Level Assessment Protocol (MAP) for Adoption in Multisite Clinical Trials. Journal of Drug Issues, 35(3), pp. 529-646, 2005.

Publications

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Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Intranigral Transplants of Immortalized GABAergic Cells Decrease the Expression of Kainic Acid-Induced Seizures in the Rat Repeated systemic administration of low doses of kainic acid (KA) induces spontaneous convulsive seizures [Hellier et al., Epilepsy Res 31, pp. 73-84, 1998]. In this study, male Sprague-Dawley animals received intranigral transplants of a control cell line M213-2O, or a cell line transfected with human GAD67 cDNA (M213-2O CL4) [Conejero-Goldberg, C., Exp Neurol.161, pp. 453-461, 2000], or no transplant. Eight weeks after transplantation surgery, KA was administered (5 mg/kg/h) until animals reached stage V seizures as described by Racine [Racine, R.J., Electroencephalogr Clin Neurophysiol. 32, pp. 281-294, 1972]. The group transplanted with CL4 required a larger dose of KA and a longer latency to reach a stage V seizure. In addition, this group exhibited significantly fewer stage III and IV seizures. These results indicate that intranigral transplants of a GABA-producing cell line can decrease the number of kainic acid-induced seizures. Castillo, C.G., Mendoza, S., Freed, W.J., and Giordano, M. Behavioural Brain Research, 171(1), pp. 109-115, 2006.

GABAergic Lineage Differentiation of AF5 Neural Progenitor Cells In Vitro IRP scientists have previously described an immortal rat central-nervous-system progenitor cell line, AF5, which is able to exit the cell cycle and assume a differentiated state with neuronal properties. The phenotypic specification of differentiated AF5 cells, however, is not known. In the present study, when induced to differentiate by serum starvation in Neurobasal medium, AF5 cells down-regulate glial fibrillary acidic protein and up-regulate expression of beta-III-tubulin, medium-molecular-weight neurofilament protein, and neuronal growth-associated protein 43. Expression of the gamma-aminobutyric acid (GABA) lineage marker, glutamic acid decarboxylase 67 (GAD67), increases during differentiation, suggesting that AF5 cells adopt a GABAergic lineage. Time-course analysis of the GABAergic neuron specification transcription factor, Pitx2, by reverse transcription/polymerase chain reaction, has shown an increase in the Pitx2 transcript 48 h after initiation of differentiation. In differentiated AF5 cells, expression of the Pitx2 target gene products GAD65 and GABA transporter-1 increases. Cellular GABA levels in differentiated AF5 cells increase by about 26-fold, and GABA release into the medium is 150-fold higher compared with that of undifferentiated cells. Therefore, AF5 cells can be induced to differentiate to a neuronal phenotype with a GABAergic lineage. Sanchez, J.F., Crooks, D.R., Lee, C.T., Schoen, C.J., Amable, R., Zeng, X., Florival-Victor, T., Morales, N., Truckenmiller, M.E., Smith, D.R., and Freed, W.J. Cell Tissue Research, 324(1), pp. 1-8, 2006.

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Publications

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Grantee Honors

Cellular Pathobiology Unit, Development and Plasticity Section, Cellular Neurobiology Research Branch

Chronic Antidepressants Potentiate via Sigma-1 Receptors the Brain-Derived Neurotrophic Factor-Induced Signaling for Glutamate Release Up-regulation of BDNF (brain-derived neurotrophic factor) has been suggested to contribute to the action of antidepressants. However, it is unclear whether chronic treatment with antidepressants may influence acute BDNF signaling in central nervous system neurons. Because BDNF has been shown by us to reinforce excitatory glutamatergic transmission in cultured cortical neurons via the phospholipase-gamma (PLC-gamma)/inositol 1,4,5-trisphosphate (IP3)/Ca2+ pathway (Numakawa, T., Yamagishi, S., Adachi, N., Matsumoto, T., Yokomaku, D., Yamada, M., and Hatanaka, H. J. Biol. Chem. 277, pp. 6520-6529, 2002), IRP investigators examined in this study the possible effects of pretreatment with antidepressants on the BDNF signaling through the PLC-gamma)/IP3/Ca2+ pathway. Furthermore, because the PLC-gamma/IP3/Ca2+ pathway is regulated by sigma-1 receptors (Hayashi, T., and Su, T.P. Proc. Natl. Acad. Sci. U. S. A. 98, pp. 491-496, 2001), authors examined whether the BDNF signaling is modulated by sigma-1 receptors (Sig-1R). Authors found that the BDNF-stimulated PLC-gamma activation and the ensued increase in intracellular Ca2+ ([Ca2+]i) were potentiated by pretreatment with imipramine or fluvoxamine, so was the BDNF-induced glutamate release. Furthermore, enhancement of the interaction between PLC-gamma and TrkB (receptor for BDNF) after imipramine pretreatment was observed. Interestingly, BD1047, a potent Sig-1R antagonist, blocked the imipramine-dependent potentiation on the BDNF-induced PLC-gamma activation and glutamate release. In contrast, overexpression of Sig-1R per se, without antidepressant pretreatment, enhances BDNF-induced PLC-gamma activation and glutamate release. These results suggest that antidepressant pretreatment selectively enhance the BDNF signaling on the PLC-gamma/IP3/Ca2+ pathway via Sig-1R, and that Sig-1R plays an important role in BDNF signaling leading to glutamate release. Yagasaki, Y., Numakawa, T., Kumamaru, E., Hayashi, T., Su, T.P., and Kunugi, H. Journal of Biological Chemistry, 281(18), pp. 12941-12949, 2006.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Visualizing Cannabinoid Effects using Brain Slice Imaging and Electrophysiological Approaches The use of electrophysiological recordings in brain slices is now routinely used to assess the actions of cannabinoid ligands within various central nervous system nuclei. In this chapter IRP scientists describe common protocols involving both intracellular and extracellular recording techniques in the hippocampus, where the presynaptic modulatory effects of cannabinoid receptor activation have been studied in detail. In addition to describing the basic electrophysiological setup needed for these recordings, authors will address common technical problems and limitations involved in working with highly lipophilic compounds, such as the cannabinoid ligands, in brain slices. Hoffman, A.F. and Lupica, C.R. Methods in Molecular Medicine, 123, pp. 105-112, 2006.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Brain Tissue Lipidomics: Direct Probing Using Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Lipidomics is the new frontier in biomolecular structural studies. Not only are lipids the main components in membranes that define the contours of the cell and its organelles, but they are also used for storage. Lipids form stable noncovalent complexes with proteins

as well as with many drugs. Lipids are a storage depot for drugs and certain types of organic molecules. To study lipid composition and distribution, complex and time-consuming techniques are used. However, recent advances in mass spectrometry, mainly matrix-assisted laser desorption/ionization (MALDI) have made it possible to directly probe tissues to study structural components, as well as for the localization of drugs. Direct tissue imaging is a powerful tool as it gives a more complete and accurate structural picture and can trace and follow where drugs localize in tissue with minimal anatomical disruption and a minimum of manipulations. Hence, we believe that in addition to its accuracy and efficiency, this new approach will lead to a better understanding of physiological processes as well as the pathophysiology of disease. Woods, A.S. and Jackson, S.N. American Association of Pharmaceutical Scientists, 8(2), pp. E391-D395, 2006.

IR-MALDI-LDI Combined with Ion Mobility Orthogonal Time-of-Flight Mass Spectrometry Most MALDI instrumentation uses UV lasers. IRP scientists have designed a MALDI-IM-oTOF-MS which employs both a Nd:YAG laser pumped optical parametric oscillator (OPOTEK, lambda = 2.8-3.2 microm at 20 Hz) to perform IR-LDI or IR-MALDI and a Nd:YLF laser (Crystalaser, lambda = 249 nm at 200 Hz) for the UV. Ion mobility (IM) gives a fast separation and analysis of biomolecules from complex mixtures in which ions of similar chemical type fall along well-defined "trend lines". Data shows that ion mobility allows multiply charged monomers and multimers to be resolved; thus, yielding pure spectra of the singly charged protein ion which are virtually devoid of chemical noise. In addition, we have demonstrated that IR-LDI produced similar results as IR-MALDI for the direct tissue analysis of phospholipids from rat brain. Woods, A.S., Ugarov, M., Jackson, S.N., Egan, T., Wang, H.Y., Murray, K.K., and Schultz, J.A. Journal of Proteome Research, 5(6), pp. 1484-1487, 2006.

Decoy Peptides that Bind Dynorphin Noncovalently Prevent NMDA Receptor-Mediated Neurotoxicity Prodynorphin-derived peptides elicit various pathological effects including neurological dysfunction and cell death. These actions are reduced by N-methyl-d-aspartate receptor (NMDAR) but not opioid receptor antagonists suggesting NMDAR-mediation. Here, IRP researchers show that a conserved epitope (KVNSEEEEEDA) of the NR1 subunit of the NMDAR binds dynorphin peptides (DYNp) noncovalently. Synthetic peptides containing this epitope form stable complexes with DYNp and prevent the potentiation of NMDAR-gated currents produced by DYNp. They attenuate DYNp-evoked cell death in spinal cord and prevent, as well as reverse, DYNp-induced paralysis and allodynia. The data reveal a novel mechanism whereby prodynorphin-derived peptides facilitate NMDAR function and produce neurotoxicity. Furthermore, they suggest that synthetic peptides that bind DYNp, thus preventing their interaction with NMDAR, may be novel therapeutic agents for the treatment of spinal cord injury. Woods, A.S., Kaminski, R., Oz, M., Wang, Y., Hauser, K., Goody, R., Wang, H.Y., Jackson, S.N., Zeitz, P., Zeitz, K.P., Zolkowska, D., Schepers, R., Nold, M., Danielson, J., Graslund, A., Vukojevic, V., Bakalkin, G., Basbaum, A., and Shippenberg, T. Journal of Proteome Research, 5(4), pp. 1017-1023, 2006.

In Vivo Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Stability of Substantia Nigra Pars Reticulata Neuronal Discharge Rates during Dopamine Receptor Blockade and its Possible Mechanisms It is hypothesized that substantia nigra pars reticulata neurons become overactive during a deficit of dopamine transmission. In this study, IRP scientists examined how acute dopamine receptor blockade (SCH23390 and eticlopride) affects impulse activity of substantia nigra pars reticulata neurons and their response to iontophoretic gamma-amino-n-butyric acid in awake, unrestrained

rats. No changes in discharge rate were found during complete dopamine receptor blockade, but these neurons showed a diminished response to gamma-amino-n-butyric acid, suggesting gamma-amino-n-butyric acid receptor hyposensitivity. This may result from tonic increase in gamma-amino-n-butyric acid input from the striatum and globus pallidus, which are activated during dopamine receptor blockade. As substantia nigra pars reticulata neurons are autoactive and resistant to tonic increases in gamma-amino-n-butyric acid input, changes in their responsiveness to phasic gamma-amino-n-butyric acid inputs, not tonic increase discharge rate, may underlie movement disturbance following dopamine deficit. Windels, F. and Kiyatkin, E.A. NeuroReport, 17(10), pp. 1071-1075, 2006.

GABAergic Mechanisms in Regulating the Activity State of Substantia Nigra Pars Reticulata Neurons Substantia nigra reticulata is the major output structure of the basal ganglia involved in somatosensory integration and organization of movement. While previous work in vitro and in anesthetized animal preparations suggests that these neurons are autoactive and points to GABA as a primary input regulating their activity, single-unit recording coupled with iontophoresis was used in awake, unrestrained rats to further clarify the role of tonic and phasic GABA input in maintenance and fluctuations of substantia nigra reticulata neuronal activity under physiologically relevant conditions. In contrast to glutamate, which was virtually ineffective at stimulating substantia nigra reticulata neurons in awake rats, all substantia nigra reticulata neurons tested were inhibited by iontophoretic GABA and strongly excited by bicuculline, a GABA-A receptor blocker. The GABA-induced inhibition had short onset and offset latencies, a fading response pattern (a rapid decrease in rate followed by its relative restoration), and was independent of basal discharge rate. The bicuculline-induced excitation was inversely related to discharge rate and current (dose)-dependent in individual units. However, the average discharge rate during bicuculline applications at different currents increased to a similar plateau (approximately 60 impulses/s), which was about twice the mean basal rates. The excitatory effects of bicuculline were phasically inhibited or completely blocked by brief GABA applications and generally mimicked by gabazine, another selective GABA antagonist. These data as well as neuronal inhibitions induced by nipecotic acid, a selective GABA uptake inhibitor, suggest that substantia nigra reticulata neurons in awake, quietly resting conditions are under tonic, GABA-mediated inhibition. Therefore, because of inherent autoactivity and specifics of afferent inputs, substantia nigra reticulata neurons are very sensitive to phasic alterations in GABA input, which appears to be the primary factor determining fluctuations in their activity states under physiological conditions. While these cells are relatively insensitive to direct activation by glutamate, and resistant to a continuous increase in GABA input, they appear to be very sensitive to a diminished GABA input, which may release them from tonic inhibition and determine their functional hyperactivity. Windels, F. and Kiyatkin, E.A. Neuroscience, 140(4), pp. 1289-1299, 2006.

General Anesthesia as a Factor Affecting Impulse Activity and Neuronal Responses to Putative Neurotransmitters Although it is evident that general anesthesia should affect impulse activity and neurochemical responses of central neurons, there are limited studies in which these parameters were compared in both awake and anesthetized animal preparations. We used single-unit recording coupled with iontophoresis to examine impulse activity and responses of substantia nigra pars reticulata (SNr) neurons to GABA, glutamate (GLU), and dopamine (DA) in rats in awake, unrestrained conditions and during chloral hydrate anesthesia. SNr neurons in both conditions had similar organization of impulse flow, but during anesthesia, they have lower mean rates and discharge variability than in awake conditions. In individual units, discharge rate in awake, quietly resting rats was almost three-fold more variable than during anesthesia. These cells in both conditions were highly sensitive to iontophoretic GABA, but the response was stronger during

anesthesia. In contrast to virtually no responses to GLU in awake conditions, most SNr neurons during anesthesia were excited by GLU; the response occurred preferentially in slow-firing units, which were atypical of awake conditions. Consistent with no postsynaptic DA receptors on SNr neurons, iontophoretic DA was ineffective in altering discharge rates in awake conditions, but often induced weak excitations during anesthesia. Although SNr neurons are autoactive, generating discharges without any excitatory input (i.e., in vitro), their impulse activity and responses to natural neurochemical inputs are strongly affected by general anesthesia. Some alterations appear to be specific to the general anesthetic used, while others probably reflect changes in the activity of afferent inputs, brain metabolism and neurotransmitter uptake that are typical to any type of general anesthesia. Therefore, an awake, freely moving animal preparation appears to be advantageous for studying impulse activity and neurochemical interactions at single-neuron level during physiologically relevant conditions. Windels, F. and Kiyatkin, E.A. Brain Research, 1086(1), pp. 104-116, 2006.

Molecular Biology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Characterization of a Mouse Strain Expressing Cre Recombinase from the 3' Untranslated Region of the Dopamine Transporter Locus
Dopamine (DA) neurotransmission has been implicated in several neurological and psychiatric disorders. The dopamine transporter (DAT) is highly expressed in dopaminergic neurons of the ventral mesencephalon and regulates neurotransmission by transporting DA back into the presynaptic terminals. To mediate restricted DNA recombination events into DA neurons using the Cre/loxP technology, IRP investigators have generated a knockin mouse expressing Cre recombinase under the transcriptional control of the endogenous DAT promoter. To minimize interference with DAT function by preservation of both DAT alleles, Cre recombinase expression was driven from the 3' untranslated region (3'UTR) of the endogenous DAT gene by means of an internal ribosomal entry sequence. Crossing this murine line with a LacZ reporter showed colocalization of DAT immunocytochemistry and beta-galactosidase staining in all regions analyzed. This knockin mouse can be used for generating tissue specific knockouts in mice carrying genes flanked by loxP sites, and will facilitate the analysis of gene function in dopaminergic neurons. Backman, C.M., Malik, N., Zhang, Y., Shan, L., Grinberg, A., Hoffer, B.J., Westphal, H., and Tomac, A.C. Genesis, 44(8), pp. 383-390, 2006.

Gene Expression Patterns for GDNF and its Receptors in the Human Putamen Affected by Parkinson's Disease: A Real-Time PCR Study Glial cell line-derived neurotrophic factor (GDNF), a member of the transforming growth factor-beta superfamily, is a potent trophic factor for dopaminergic neurons of the ventral midbrain, which are known to degenerate during Parkinson's disease (PD). The neuroprotective, neurorestorative, and stimulatory properties of GDNF has prompted numerous suggestions that this trophic factor may be a potential therapeutic tool to treat PD, and it has also been widely speculated that altered GDNF expression levels may be involved in the pathophysiology of the disease. In this study, IRP scientists have investigated if mRNA expression levels for GDNF and/or its receptors are altered during PD in the human putamen, a target area for dopamine neurons of the substantia nigra compacta. Expression levels were analyzed with quantitative real-time reverse transcriptase polymerase reaction (RT qPCR) in post-mortem tissues from PD patients and aged matched controls. Primer pairs specific for GDNF (isoforms I and II), and its receptor molecules, GFRalpha1 and cRET were utilized. GDNF, cRET and GFRalpha1 mRNA expression was clearly detected in the putamen of control and Parkinson's disease patients. A modest but significant upregulation of GDNF mRNA levels (Isoform I) was observed in the putamen of Parkinson's disease patients with a marked loss of

nigral neurons. No significant changes were observed for the expression of cRet and GFRa1. These data suggest that the extensive loss of dopaminergic neurons in the substantia nigra, and concomitant loss of striatal dopamine, may induce compensatory changes in the expression of target derived GDNF, but not its receptor system. Backman, C.M., Shan, L., Zhang, Y.J., Hoffer, B.J., Leonard, S., Troncoso, J.C., Vonsatel, P., and Tomac A.C. Molecular and Cellular Endocrinology, 252(1-2), pp. 160-166, 2006.

Neural Protection and Regeneration Section, Molecular Neuropsychiatry Research Branch

Neuroprotective/Neuroregenerative Effects of Bone Morphogenetic Protein 7 and Adenosine A3 Receptor Agonists Authors found that bone morphogenetic protein -7 (BMP7) has neuroprotective and neuroregenerative effects in the CNS. Pretreatment with BMP-7 reduces methamphetamine-induced neuronal injury in primary dopaminergic neuronal culture. BMP-7, given after ischemic brain injury, improves locomotor activity. BMP7 treatment also enhanced immunoreactivity of BrdU in the subventricular zone, lesioned cortex, and corpus callosum. These BrdU positive cells co-labeled with nestin and NeuN. Behavioral and anatomical data suggest that BMP7 promotes neuroregeneration in stroke animals, possibly through the proliferation of new neuronal precursors after ischemia. Authors also found that selective adenosine A3 agonist reduces neurodegeneration induced by cerebral ischemia. The response was mediated through the inhibition of apoptosis. The possibility of endogeneous neuroprotection was further examined in A3R knock-out mice. After cerebral ischemia, an increase in cerebral infarction was found in the A3R knock-outs compared to the A3R wild-type controls, suggesting that A3Rs are tonically activated during ischemia. Inosine, an adenosine analog, also reduces cerebral injury and increases motor functions after brain injury through A3R receptor. Inosine did not alter basal glutamate release nor did it reduce ischemia -evoked glutamate overflow from cerebral cortex. However, inosine antagonized glutamate-induced electrophysiological excitation in cerebral cortical neurons. These data suggest that inosine inhibits glutamate post-synaptic responses and reduces cerebral infarction. Shen, H., Chen, G.J., Harvey, B.K., Bickford P.L., and Wang, Y. Stroke, 36, pp. 654-659, 2005.

Molecular Neurobiology Research Branch

Whole Genome Association for Alcohol Dependence Association genome scanning can identify markers for the allelic variants that contribute to vulnerability to complex disorders, including alcohol dependence. To improve the power and feasibility of this approach, IRP scientists validate "100k" microarray-based allelic frequency assessments in pooled DNA samples. Authors then use this approach with unrelated alcohol dependent vs control individuals sampled from pedigrees collected by the Collaborative Study on the Genetics of Alcoholism (COGA). Allele frequency differences between alcohol-dependent and control individuals are assessed in quadruplicate at 104,268 autosomal SNPs in pooled samples. One hundred thirty eight SNPs provide 1) the largest allele frequency differences between dependent vs control individuals, 2) t values > 3 for these differences and 3) clustering, so that 51 small chromosomal regions contain at least three SNPs that satisfy criteria 1 and 2 above (Monte Carlo p=0.00034). These positive SNP clusters identify interesting genes whose products are implicated in cellular signaling, gene regulation, development, "cell adhesion" and Mendelian disorders. The results converge with previous linkage and association results for alcohol and other addictive phenotypes. The data support polygenic contributions to vulnerability to alcohol dependence and support the idea that the brains of individuals who are vulnerable to alcohol dependence may differ from those who are less vulnerable. These SNPs provide new tools to aid the understanding, prevention and treatment of alcohol abuse and dependence. Johnson, C., Drgon, T., Liu,

Q.R., Walther, D., Edenberg, H., Rice, J., Foroud, T., and Uhl, GR. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 99, pp. 1-10, 2006.

Psychobiology Section, Medications Discovery Research Branch

Potential Medications for Treating Cocaine Abuse Several dopamine (DA) indirect agonists have been proposed as potential medications for treating cocaine abuse. The objective of the present study was to quantify the interactions among cocaine and DA uptake inhibitors or DA releasers in order to better understand how these drugs may be working when administered in combination. The DA uptake inhibitors GBR 12909, WIN 35,428, methylphenidate, indatraline, nomifensine and mazindol, and DA releasers methamphetamine, amphetamine, methcathinone, cathinone, fencamfamine and phentermine were examined alone and in combination with cocaine in rats trained to discriminate cocaine (10 mg/kg, i.p.) from saline injections. All of the DA indirect agonists dose-dependently substituted for cocaine, and shifted the cocaine dose-effect curve leftward. Isobolographic analysis indicated the interactions were generally additive, although both methamphetamine and d-amphetamine were quantitatively determined to be more potent than DA uptake inhibitors in shifting the cocaine dose-effect function to the left. The potential of d-amphetamine as an effective treatment for cocaine abuse, and negative clinical results with dopamine uptake inhibitors suggests that differences in shifts in dose-effect curves should be further examined with emerging clinical data as a predictive index of potential treatments for cocaine abuse. Li, S.M., Campbell, B.L., and Katz, J.L. Journal of Pharmacology and Experimental Therapeutics, 317, pp. 1088-1096, 2006.

Clinical Psychopharmacology Section, Medications Development Research Branch

Interaction of Amphetamines and Related Compounds at the Vesicular Monoamine Transporter Amphetamine-type agents interact with the vesicular monoamine transporter (VMAT2), promoting the release of intravesicular neurotransmitter and an increase in cytoplasmic neurotransmitter. Some compounds, like reserpine, "release" neurotransmitter by inhibiting the ability of VMAT2 to accumulate neurotransmitter in the vesicle, while other types of compounds can release neurotransmitter via a carrier-mediated exchange mechanism. The purpose of this study was to determine, for 42 mostly amphetamine-related compounds, their mode of interaction with the VMAT2. IRP researchers used a crude vesicular fraction prepared from rat caudate to assay VMAT2 activity. Test compounds were assessed in several assays including: a) inhibition of [(3)H]dihydrotetrabenazine binding, b) inhibition of vesicular [(3)H]dopamine uptake, and c) release of pre-loaded [(3)H]dopamine and [(3)H]tyramine. Several important findings derive from this comprehensive study. First, this work indicates that most agents are VMAT2 substrates. Two, these data strongly suggest that amphetamine-type agents deplete vesicular neurotransmitter via a carrier-mediated exchange mechanism rather than via a free-base effect, although this conclusion needs to be confirmed via direct measurement of vesicular pH. Three, these data fail to reveal differential VMAT2 interactions among agents which do and do not produce long-term 5-HT depletion. Four, the data reported revealed the presence of two pools of [(3)H]amine within the vesicle, that which is free, and that which is tightly associated with the ATP/protein complex that helps store amine. Finally, the VMAT2 assays the authors have developed should prove useful for guiding the synthesis and evaluation of novel VMAT2 agents as possible treatment agents for addictive disorders. Partilla, J.S., Dempsey, A.G., Nagpal, A.S., Blough, B.E., Baumann, M.H., and Rothman, R.B. Interaction of Amphetamines and Related Compounds at the Vesicular Monoamine Transporter. J Pharmacol Exp

Ther. 2006 [Epub ahead of print].

Medicinal Chemistry Section, Medications Discovery Research Branch

High Affinity Fluorescent Probes for the Dopamine Transporter A series of novel fluorescent ligands was synthesized to identify a high affinity probe that would enable visualization of the dopamine transporter (DAT) in living cells. In this series, fluorescent tags were extended from either the N- or 2-position of a cocaine analogue, 2b-carbomethoxy-3b-(3,4-dichlorophenyl)tropane, using an ethylamino-linker. The resulting 2-substituted- and N-substituted-rhodamine-labeled ligands provided the highest DAT binding affinities expressed in COS-7 cells (Ki= 27 and 18 nM, respectively) in the series. Visualization of the DAT with these fluorescent ligands was demonstrated by confocal fluorescence laser scanning microscopy in stably transfected HEK293 cells. The most effective fluorescent probe in this series, JHC 1-064 is currently being used to visualize dopamine neurons and is enabling the dynamic visualization of DAT trafficking. Cha, J. H., Zou, M.F., Adkins, E.M., Rasmussen, S.G.F., Loland, C.J., Schoenenberger, B., Gether, U., and Newman, A.H. Journal of Medicinal Chemistry, 48, pp. 7513-7516, 2005.

Cooperative Transcription Activation by Nurr1 and Pitx3 Induces Embryonic Stem Cell Maturation to the Midbrain Dopamine Neuron Phenotype Midbrain dopamine neurons (mDNs) play a central role in the regulation of voluntary movement and their degeneration is associated with Parkinson's disease (PD). Cell replacement therapies, and in particular the use of embryonic or adult stem cell-derived dopamine neurons, offer a potential treatment strategy for PD. However, such an approach relies on the efficient generation of mature dopamine neurons that are able to respond appropriately to environmental cues and establish functional connections in the CNS. It is therefore of particular interest to determine the regulatory pathways that underlie mDN maturation from precursors. Here IRP investigators describe factors that promote mDNs maturation and identify a combination of two transcription factors, Nurr1 and PitX3, which synergistically function in this process. Nurr1 and PitX3 coordinately induce mDN maturation in both mouse and human ES cultures, and transplantation of these cells improves motor function in a toxin-based murine model of PD. One experiment in this study used the fluorescent ligand JHC 1-064 to analyze midbrain dopaminergic neurons. Martinat, C., Bacci, J.-J., Leete, T., Kim, J., Vanti, W., Newman, A.H., Cha, J.H., Gether, U., Wang, H., and Abeliovich, A. Proceedings of the National Academy of Sciences U.S.A., 103, pp. 2874-2879, 2006.

TYR95 and ILE172 in Transmembrane Segments I and III of Human Serotonin Transporters Interact to Establish High-Affinity Recognition of Antidepressants In previous studies examining the structural determinants of antidepressant and substrate recognition by serotonin transporters (SERTs), IRP scientists identified Tyr-95 in transmembrane segment 1 (TM1) of human SERT as a major determinant of binding for several antagonists, including racemic citalopram ((±)-CIT). Here authors described a separate site in hSERT TM3 (Ile-172) that impacts (±)-CIT recognition when switched to the corresponding Drosophila SERT residue (I172M). The hSERT I172M mutant displays a marked loss of inhibitor potency for multiple inhibitors such as (±)-CIT, clomipramine, RTI-55, fluoxetine, cocaine, nisoxetine, mazindol, and nomifensine, whereas recognition of substrates, including serotonin and 3,4-methylene dioxymethamphetamine, is unaffected. Selectivity for antagonist interactions is evident with this substitution because the potencies of the antidepressants tianeptine and paroxetine are unchanged. Reduced cocaine analog recognition was verified in photoaffinity labeling studies using [125I]MFZ 2-24. In contrast to the I172M substitution, other substitutions at this position significantly affected substrate recognition and/or transport

activity. Additionally, the mouse mutation (mSERT I172M) exhibits similar selective changes in inhibitor potency. Unlike hSERT or mSERT, analogous substitutions in mouse dopamine transporter (V152M) or human norepinephrine transporter (V148M) result in transporters that bind substrate but are deficient in the subsequent translocation of the substrate. A double mutant hSERT Y95F/ I172M had a synergistic impact on (±)-CIT recognition (>10,000- fold decrease in (±)-CIT potency) in the context of normal serotonin recognition. The less active enantiomer (R)-CIT responded to the I172M substitution like (S)-CIT but was relatively insensitive to the Y95F substitution and did not display a synergistic loss at Y95F/ I172M.An hSERT mutant with single cysteine substitutions in TM1 and TM3 resulted in formation of a high affinity cadmium metal coordination site, suggesting proximity of these domains in the tertiary structure of SERT. These studies provided evidence for distinct binding sites coordinating SERT antagonists and revealed a close interaction between TM1 and TM3 differentially targeted by the stereoisomers of CIT. Henry, L.K., Field, J.R., Adkins, E. M., Parnas, M.L., Vaughan, R.A., Zou, M-F., and Newman, A.H., Blakely Journal of Biological Chemistry, 281, pp. 2012-2023, 2006.

Comparative Structure-Activity Relationships of Benztropine Analogues at the Dopamine Transporter and Histamine H1 Receptors Benztropine (BZT) and its analogues inhibit dopamine uptake and bind with moderate to high affinity to the dopamine transporter (DAT). However, many of these compounds, in contrast to other monoamine uptake inhibitors, lack cocaine-like behavioral effects and fail to potentiate the effects of cocaine. The BZT analogues also exhibit varied binding affinities for muscarinic M1 and histamine H1 receptors. In this study a comparative analysis was conducted of pharmacophoric features with respect to the activities of BZT analogues at the DAT and at the histamine H1 receptor. The BZT analogues showed a wide range of histamine H1 receptor (Ki =16-37600 nM) and DAT (Ki=8.5-6370 nM) binding affinities. A stereoselective histamine H1-antagonist pharmacophore, using a five-point superimposition of classical antagonists on the template, cyproheptadine, was developed. A series of superimpositions and comparisons were performed with various analogues of BZT. In general, smaller substituents were well tolerated on the aromatic rings of the diphenyl methoxy group for both the DAT and H1 receptor, however for the H1 receptor, substitution at only one of the aromatic rings was preferred. The substituents at the 2- and N-positions of the tropane ring were preferred for DAT however these groups seem to overlap receptor essential regions in the histamine H1 receptor. Molecular models at the DAT and the histamine H1 receptor provide further insight into the structural requirements for binding affinity and selectivity that can be implemented in future drug design. Kulkarni, S. S., Kopajtic, T., Katz, J. L., Newman, A. H. Bioorganic Medicinal Chemistry, 14, pp. 3625-3634, 2006.

Design and Synthesis of Noncompetitive Metabotropic Glutamate Receptor Subtype 5 Antagonists A series of diaryl amides was designed and synthesized as novel non-ethynyl mGluR5 antagonists. The systematic variation of the pharmacophoric groups led to the identification of a lead compound that demonstrated micromolar affinity for the mGluR5. Further optimization resulted in compounds with improved binding affinities and antagonist profiles, in vitro. The novel series of compounds described in this communication provide structurally distinct probes to investigate the role of mGluR5 in CNS disorders. The structure-activity relationships developed herein has led to the design of a new set of potential mGluR5 antagonists for in vivo investigation that will be reported in due course. Kulkarni, S.S., Nightingale, B., Dersch, C.M., Rothman, R.B., and Newman, A.H. Bioorganic Medicinal Chemistry Letters, 16, pp. 3371-3375, 2006.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Branch

Two Brain Sites for Cannabinoid Reward The recent findings that delta-9-tetrahydro- cannabional (THC), the active agent in marijuana and hashish, (1) is self-administered intravenously, (2) potentiates the rewarding effects of electrical brain stimulation, and (3) can establish conditioned place preferences in laboratory animals, suggest that these drugs activate biologically primitive brain reward mechanisms. Here, IRP scientists identify two chemical trigger zones for stimulant and rewarding actions of THC. Microinjections of THC into the posterior ventral tegmental area (VTA) or into the shell of the nucleus accumbens (NAS) increased locomotion, and rats learned to lever-press for injections of THC into each of these regions. Substitution of vehicle for drug or treatment with a cannabinoid CB1 receptor antagonist caused response cessation. Microinjections of THC into the posterior VTA and into the posterior shell of NAS established conditioned place preferences. Injections into the core of the NAS, the anterior VTA, or dorsal to the VTA were ineffective. These findings link the sites of rewarding action of THC to brain regions where such drugs as amphetamines, cocaine, heroin, and nicotine are also thought to have their sites of rewarding action. Zangen, A., Solinas, M., Ikemoto, S., Goldberg, S.R., and Wise, R.A. Journal of Neuroscience, 26, pp. 4901-4907, 2006.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Previous Exposure to THC Alters the Reinforcing Efficacy and Anxiety Related Effects of Cocaine in Rats The hypothesis that prior cannabis exposure increases the likelihood of becoming addicted to other drugs can be evaluated by giving rats a history of tetrahydrocannabinol (THC) exposure, then allowing them to self-administer other drugs. In Experiment 1, THC pre-exposure did not alter the acquisition of cocaine self-administration or the amount of cocaine taken under a fixed-ratio 1 (FR1) schedule, with one response required for each injection. Under a progressive-ratio schedule, with the response requirement increasing exponentially with each injection, cocaine-seeking was significantly reduced in THC-exposed rats, suggesting that the regimen of THC exposure used in the present study caused cocaine to be devalued as a reinforcer. In contrast, in an earlier study that used the same regimen, a history of THC exposure did not alter the value of heroin as a reinforcer under the progressive-ratio schedule, but it increased heroin self-administration under the FR1 schedule. Experiment 2 examined how this regimen of THC pre-exposure alters the locomotor effects of cocaine and heroin. THC pre-exposure produced cross-tolerance to the motor-depressant effects of heroin; this may explain the shortened post-injection pauses exhibited by THC-exposed rats under FR1 heroin self-administration. When given cocaine, THC-exposed rats exhibited normal increases in locomotion, but they avoided the center of the open field, suggesting that this THC pre-exposure regimen enhances the anxiogenic effects of cocaine. This enhanced anxiogenic effect-which was verified in Experiment 3 using another model of anxiety, the light-dark test-may explain the reduced reinforcing value of cocaine observed in THC-exposed rats in Experiment 1. Panlilio, L.V., Solinas, M., Matthews, S.A. and Goldberg, S.R. Neuropsychopharmacology, May 31, 2006, Epubmed ahead of print, PMID 16738542.

Heteromeric Nicotinic Acetylcholine-Dopamine Autoreceptor Complexes Modulate Striatal Dopamine Release In the striatum, dopamine and acetylcholine (ACh) modulate dopamine release by acting, respectively, on dopamine D(2) autoreceptors and nicotinic ACh (nACh) heteroreceptors localized on dopaminergic nerve terminals. The possibility that functional interactions exist between striatal D(2) autoreceptors and nACh receptors was studied with in vivo microdialysis in freely moving rats. Local perfusion of nicotine in the ventral striatum (shell of the nucleus accumbens) produced a marked increase in the extracellular levels of dopamine, which was

completely counteracted by co-perfusion with either the non-alpha(7) nACh receptor antagonist dihydro-beta-erythroidine or the D(2-3) receptor agonist quinpirole. Local perfusion of the D(2-3) receptor antagonist raclopride produced an increase in the extracellular levels of dopamine, which was partially, but significantly, counteracted by coperfusion with dihydro-beta-erythroidine. These findings demonstrate a potent crosstalk between G protein-coupled receptors and ligand-gated ion channels in dopaminergic nerve terminals, with the D(2) autoreceptor modulating the efficacy of non-alpha(7) nACh receptor-mediated modulation of dopamine release. Authors further demonstrate physical interactions between beta(2) subunits of non-alpha(7) nicotinic acetylcholine receptors and D(2) autoreceptors in co-immunoprecipitation experiments with membrane preparations from co-transfected mammalian cells and rat striatum. These results reveal that striatal non-alpha(7) nicotinic acetylcholine receptors form part of heteromeric dopamine autoreceptor complexes that modulate dopamine release. Quarta, D., Ciruela, F., Patkar, K., Borycz, J., Solinas, M., Lluis, C., Franco, R., Wise, R.A., Goldberg, S.R., Hope, B.T., Woods, A.S. and Ferre, S. Neuropsychopharmacology, May 17, 2006, Epubmed ahead of print, PMID 16710311.

Neuropsychopharmacology Section, Behavioral Neuroscience Research Branch

Dopamine D3 Receptor Antagonists as Potential Anti-Craving and Anti-Relapse Medications for the Treatment of Addiction IRP scientists have previously found that blockade of dopamine D3 receptors in the rat brain (which are neuroanatomically restricted to the mesolimbic dopamine system, implicated in drug-induced reward and drug-seeking behavior) by the high-potency high-selectivity dopamine D3 receptor antagonist SB277011A dose-dependently attenuates cocaine-enhanced brain-stimulation reward and cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their prior intravenous cocaine-taking behavior (see, e.g., Brain Research Reviews, 49, pp. 77-105, 2005). Now, these researchers have found that NGB2904, another high-potency high-selectivity dopamine D3 receptor antagonist, likewise dose-dependently attenuates cocaine-enhanced brain-stimulation reward and cocaine-triggered relapse to cocaine-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. These confirmatory findings with a new D3 receptor antagonist suggest that dopamine D3 receptor antagonists are worthy of further investigation as potential anti-addiction, anti-craving, and anti-relapse medications for the treatment of drug abuse. Xi, Z.-X., Newman, A.H., Gilbert, J.G., Pak, A.C., Peng, X.-Q., Ashby, C.R. Jr., Gitajn, L., and Gardner, E.L. Neuropsychopharmacology, 31, pp. 1393-1405, 2006.

Treatment Section, Clinical Pharmacology and Therapeutics Research Branch

Changes in HIV Risk Behaviors Among Patients Receiving Combined Pharmacological and Behavioral Interventions for Heroin and Cocaine Dependence Cocaine use is associated with injecting and sexual HIV risk behaviors. This study was a randomized controlled trial of behavioral interventions for cocaine dependence and HIV risk behaviors among dually (cocaine and heroin) dependent outpatients. Methadone maintenance was augmented with cognitive-behavioral therapy (CBT), contingency management (CM), both (CBT+CM), or neither. The study sample (n=81) was 52% female, 70% African American, and 37.9 ± 7.0 years old. Proportions reporting HIV risk behaviors at intake were: 96.3% (78/81) injection drug use, 56.8% (46/81) sharing needles, 30.9% (25/81) unprotected sex, 28.4% (23/81) trading sex for money or drugs. Proportions who no longer reported behaviors

at study exit were: 48.7% (38/78) injection drug use, 91.3% (42/46) sharing needles, 88% (22/25) unprotected sex, 91.3% (21/23) trading sex for money or drugs. Participants receiving CBT+CM were more likely to report cessation of unprotected sex relative to Control (OR=5.44, 95% CI 1.14-26.0, p=0.034) but this effect was reduced by adjusting for drug-negative urines. These results suggest broad beneficial effects of methadone maintenance augmented with behavioral interventions for reducing HIV risk behaviors. Schroeder, J.R., Epstein, D.H., Umbricht, A., and Preston, K.L. Addictive Behaviors, 31, pp. 868-879, 2006.

Adverse Events Among Patients in a Behavioral Treatment Trial for Heroin and Cocaine Dependence: Effects of Age, Race, and Gender
Safety monitoring is a critical element of clinical trials evaluating treatment for substance dependence, but is complicated by participants' high levels of medical and psychiatric comorbidity. This paper describes AEs reported in a large (N = 286), 29-week outpatient study of behavioral interventions for heroin and cocaine dependence in methadone-maintained outpatients. A total of 884 AEs were reported (3.1 per patient, 0.12 per patient-week), the most common being infections (26.8%), gastrointestinal (20.5%), musculoskeletal (12.3%), and general (10%) disorders. Serious AEs were uncommon (1.6% of total). Female participants reported significantly higher rates of AEs (incidence density ratio, IDR = 1.38, $p < 0.0001$); lower rates of AEs were reported by African Americans (IDR = 0.73, $p < 0.0001$) and participants over age 40 reported lower rates of AEs (IDR = 0.84, $p = 0.0095$). AE incidence was not associated with the study intervention or with psychiatric comorbidity. Further work is needed to adapt AE coding systems for behavioral trials for substance dependence; the standard Medical Dictionary for Regulatory Activities, International Federation of Pharmaceutical Manufacturers Associations (MedDRA) coding system used in this report did not contain a separate category for one of the most common types of AE, dental problems. Nonetheless, the data reported here should help provide a context in which investigators and IRBs can interpret the patterns of AEs they encounter. Schroeder, J.R., Schmittner, J.P., Epstein, D.H., and Preston, K.L. Drug and Alcohol Dependence, 80, pp. 45-51, 2005.

Menstrual Cycle Length During Methadone Maintenance While the menstrual disruption of heroin has been demonstrated, there are few published data concerning methadone maintenance and menstrual function. This study was conducted to evaluate whether cycle length was more regular during methadone maintenance. A total of 191 heroin and cocaine-using women who were maintained on methadone therapy (70-100 mg/day) in two clinical trials, lasting 25-29 weeks. Start/end dates of each menses were collected weekly. Menstrual patterns were classified as regular, irregular, transient amenorrhea, persistent amenorrhea or cycle restart. Repeated-measures regression modeling determined correlates of cycle length and predictors of long cycles (> 40 days) and short cycles (< 20 days). Bleeding episodes were defined as 1 or more bleeding days, bound by at least 2 non-bleeding days. Correlates/predictors examined were body mass index, drug use, methadone dose and race. In the 133 women for whom menstrual patterns could be determined, cycle-length irregularity was common: irregular, 62 (46.7%); regular, 37 (27.8%); cycle restart, 16 (12%); persistent amenorrhea, 11 (8.3%); transient amenorrhea, seven (5.3%). Each additional week on methadone maintenance was associated with decreased risk of long (OR = 0.96, $P < 0.01$ and short (OR = 0.92, $P < 0.01$) cycles. Of 27 women with secondary amenorrhea pre-study, 16 (59%) restarted menses. Positivity for opioids or cocaine was not significantly associated with short or long cycles. Cycle length begins to normalize during methadone maintenance. Menses resumption may occur. Methadone maintenance, despite interfering with menstrual function in an absolute sense, may interfere less than illicit heroin abuse. Schmittner, J., Schroeder, J.R., Epstein, D.H., and Preston, K.L. Addiction, 100, pp. 829-836, 2005.

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

Effect of Tobacco Craving Cues on Memory Encoding and Retrieval in Smokers Previous studies have shown that cue-elicited tobacco craving disrupted performance on cognitive tasks; however, no study has examined directly the effect of cue-elicited craving on memory encoding and retrieval. A distinction between encoding and retireval has been reported such that memory is more impaired when attention is divided at encoding than at retrieval. This study tested the hypothesis that active imagery of smoking situations would impair encoding processes, but have little effect on retrieval. Imagery scripts (cigarette craving and neutral content) were presented either before presentation of a word list (encoding trials) or before word recall (retrieval trials). A working memory task at encoding and free recall of words were assessed. Results indicated that active imagery disrupted working memory on encoding trials, but not on retrieval trials. There was a trend toward impaired working memory following craving scripts compared with neutral scripts. These data support the hypothesis that the cognitive underpinnings of encoding and retrieval processes are distinct. Heishman, S.J., Boas, Z.P., Hager, M.C., Taylor, R.C., Singleton, E.G., and Moolchan, E.T. Addictive Behaviors, 31, pp. 1116-1121, 2006.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

International Research

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Audiovestibular Dysfunction in Alcohol Dependence. Are We Worried?
Verma, R.K., Panda, N.K., Basu, D., and Raghunathan, M. Am J Otolaryngol. 27(4), pp. 225-228, July-August 2006. INVEST Fellow: Debasish Basu, India, 2001-2002. The purpose of this research was to study the audiovestibular function in patients of long-term alcohol dependence and compare these changes with social users of alcohol and complete abstainers. This was a prospective study of 20 randomly selected patients of long-term alcohol dependence fulfilling International Statistical Classification of Diseases, 10th Revision criteria of alcohol dependence. Audiovestibular function in this group was compared with social users of alcohol and complete abstainers. Statistically significant elevations of thresholds were found at higher frequencies (4000 and 8000 Hz) in the alcohol-dependent group ($P < .001$). Alcohol-dependent patients had elevated thresholds at 4 and 8 kHz. Brainstem-evoked response audiometry showed prolongation of latencies of waves I, III, and V alone with interpeak latencies of I-III and III-V. One third of alcohol-dependent patients had abnormal electronystagmographic (ENG) findings. Abnormal ENG findings were only seen in alcohol-dependent patients with vertigo. There was no significant correlation between duration of alcohol dependence and abnormal ENG. Authors concluded that elevated thresholds at higher frequencies can be the only abnormality in alcohol-dependent patients. Presence of vertigo in alcohol-dependent patient may be associated with abnormal ENG findings. There is no correlation of duration of dependence and ENG abnormalities.

Antidepressant-Like Effects of mGluR1 and mGluR5 Antagonists in the Rat Forced Swim and the Mouse Tail Suspension Tests
Belozertseva, I.V., Kos, T., Popik, P., Danysz, W., and Bespalov, A.Y. Eur Neuropsychopharmacol. April 19, 2006 [Epub ahead of print]. INVEST Fellow: Anton Bespalov, Russia, 1994-1995. Drugs that act to reduce glutamatergic neurotransmission such as NMDA receptor antagonists exert antidepressant-like effects in a variety of experimental paradigms, but their therapeutic application is limited by undesired side effects. In contrast, agents that reduce glutamatergic tone by blocking type I metabotropic glutamate receptors have been suggested to have more a favorable side-effect profile. The present study aimed to compare the effects of mGluR1 antagonist (EMQMCM; JNJ16567083, 3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate, 0.156-10 mg/kg) and mGluR5 antagonist (MTEP, [(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine, 1.25-10 mg/kg) in two behavioral screening assays commonly used to assess antidepressant-like activity. In the

modified forced swim test in rats, imipramine (used as a positive control) decreased immobility (MED 40 mg/kg) and increased the duration of escape-oriented (climbing and diving; MED 20 mg/kg) behaviors. Both EMQMCM and MTEP decreased the floating duration (MED 1.25 and 2.5 mg/kg) and increased the duration of mobile behaviors (paddling and swimming; MED 2.5 and 5 mg/kg). EMQMCM but not MTEP increased the duration of escape behaviors (climbing and diving; MED 1.25 mg/kg). In the mouse tail suspension test, EMQMCM (5 but not 2.5, 10 and 25 mg/kg), 2-methyl-6-(phenylethynyl)-pyridine (MPEP, 10 but not 1 mg/kg) and MTEP (MED 25 mg/kg) decreased immobility scores. For EMQMCM, the dose-effect relationship was biphasic. With the exception of EMQMCM (10 mg/kg), locomotor activity in mice was not affected by treatments. The present study therefore suggests that acute blockade of mGluR5 and also of mGluR1 exerts antidepressant-like effects in behavioral despair tests in rats and mice.

Prevalence and Correlates of Drug Use Disorders in Mexico
Medina-Mora, M.E., Borges, G., Fleiz, C., Benjet, C., Rojas, E., Zambrano, J., Villatoro, J., and Aguilar-Gaxiola, S. Rev Panam Salud Publica. 19(4), pp. 265-276, April 2006. INVEST Fellow: Guilherme Borges, Mexico, 1997-1998. The objective of this study was to describe the prevalence of drug use disorders, the correlates of drug use, and the utilization of specialized treatment services for drug users among the Mexican urban population 18-65 years old. The data were collected in 2001 and 2002 in the Mexican National Comorbidity Survey. The sample design was stratified probabilistically for six geographical areas of the country in a multistage process for census count areas, city blocks, groups of households, and individuals. The data were weighted, taking into account the probability of selection and the response rate. The information was collected using a computerized version of the World Mental Health Survey edition of the Composite International Diagnostic Interview. The weighted response rate for individuals was 76.6%. Overall, 2.3% of the population reported any illicit use of drugs in the preceding 12 months; marijuana and cocaine were the substances most often used. Low levels of education were significantly associated with use, abuse, and dependence. Use of any drug was significantly more common among those who were in the youngest age group (18-29 years), were male, or were living in the Northwest region of the country. Overall, 1.4% had a lifetime history of drug abuse or dependence, with this being much more common for men (2.9%) than for women (0.2%). The 12-month prevalence of drug abuse or dependence was 0.4% overall (0.9% for men, and 0.0% for women). The rate of treatment during the preceding 12 months for those with the 12-month criteria for abuse or dependence was 17.1%; 14.8% were seen in specialized treatment centers; 2.8% reported having attended self-help groups. A noticeable number of Mexicans have a drug use disorder, but demand for treatment is limited, in part due to stigma. These results indicate that there is an urgent need to organize the specialized services for persons with a substance abuse disorder according to the prevalence of dependence on different substances and the variation in prevalence in the different regions of the country.

Multicentre Study of Acute Alcohol Use and Non-Fatal Injuries: Data from the WHO Collaborative Study on Alcohol and Injuries
Borges, G., Cherpitel, C., Orozco, R., Bond, J., Ye, Y., Macdonald, S., Rehm, J., and Poznyak, V. Bull World Health Organ. 84(6), pp. 453-460, June 2006. INVEST Fellow: Guilherme Borges, Mexico, 1997-1998. The objectives of this study were to study the risk of non-fatal injury at low levels and moderate levels of alcohol consumption as well as the differences in risk across modes of injury and differences among alcoholics. Data are from patients aged 18 years and older collected in 2001-02 by the WHO collaborative study on alcohol and injuries from 10 emergency departments around the world (n = 4320). Authors used a case-crossover method to compare the use of alcohol during the 6 hours prior to the injury with the use of alcohol during same day of the week in the previous week. The risk of injury increased with consumption of a single

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drink (odds ratio (OR) = 3.3; 95% confidence interval = 1.9-5.7), and there was a 10-fold increase for participants who had consumed six or more drinks during the previous 6 hours. Participants who had sustained intentional injuries were at a higher risk than participants who had sustained unintentional injuries. Patients who had no symptoms of alcohol dependence had a higher OR. Since low levels of drinking were associated with an increased risk of sustaining a non-fatal injury, and patients who are not dependent on alcohol may be at higher risk of becoming injured, comprehensive strategies for reducing harm should be implemented for all drinkers seen in emergency departments.

Acute Alcohol Use and the Risk of Non-Fatal Injury in Sixteen Countries
Borges, G., Cherpitel, C.J., Orozco, R., Bond, J., Ye, Y., Macdonald, S., Giesbrecht, N., Stockwell, T., Cremonte, M., Moskalewicz, J., Swiatkiewicz, G., and Poznyak, V. Addiction. 101(7), pp. 993-1002, July 2006. INVEST Fellow: Guilherme Borges, Mexico, 1997-1998. The aims of this study were to determine the relative risk (RR) of non-fatal injury associated with alcohol consumption in a series of emergency departments (EDs), possible effect modifiers and the impact of contextual variables on differences across sites. The case-crossover method was used to obtain RR estimates of the effect of alcohol on non-fatal injuries. Meta-analysis was used to evaluate the consistency and magnitude of RR across sites, and the extent to which contextual variables explain differences in effect sizes. Study participants were probability samples of 11,536 injured patients attending 28 EDs studies in 16 countries (1984-2002). The majority of the sample was male (65%) and > 30 years old (53%). Exposed cases were those that consumed alcohol 6 hours prior to the injury. Usual alcohol consumption served as the control period. Drinking within 6 hours prior to the injury was reported by 21% of the sample. The estimated (random) pooled relative risk for patients who reported alcohol use within 6 hours prior to injury was 5.69 (95% confidence interval = 4.04-8.00), ranging from 1.05 in Canada to 35.00 in South Africa. Effect size was not homogeneous across studies, as societies with riskier consumption patterns had a higher relative risk for injury. Heavier drinkers also showed lower RR. Authors concluded that acute alcohol was a risk factor for non-fatal injuries in most sites. Policy measures addressed to the general population are recommended, especially in societies with riskier consumption patterns.

Effects of Topiramate on the Prepulse Inhibition of the Acoustic Startle in Rats
Frau, R., Orru, M., Fa, M., Casti, A., Manunta, M., Fais, N., Mereu, G., Gessa, G., and Bortolato, M. Neuropsychopharmacology. [Epub ahead of print] June 14, 2006. INVEST Fellow: Marco Bortolato, Italy, 2004-2005. The anticonvulsant topiramate (TPM) has been recently proposed as a novel adjuvant therapy for bipolar disorder and schizophrenia, yet its efficacy remains controversial. As both disorders are characterized by gating deficits, authors tested the effects of TPM on the behavioral paradigm of prepulse inhibition (PPI) of the acoustic startle response, a validated animal model of sensorimotor gating. TPM (10, 18, 32, 58, 100 mg/kg, intraperitoneal, i.p.) enhanced PPI in rats in a dose-dependent fashion, prevented the PPI reduction mediated by the dopaminergic agonist apomorphine (0.25 mg/kg, subcutaneous, s.c.) and potentiated the effects of the antipsychotic drugs haloperidol (0.05, 0.1 mg/kg, i.p.) and clozapine (2.5, 5 mg/kg, i.p.). Conversely, TPM elicited no significant effect on the PPI disruption mediated by the NMDA receptor antagonist dizocilpine (0.05, 0.1 mg/kg, s.c.) and surprisingly antagonized the attenuation of dizocilpine-induced PPI disruption mediated by clozapine (5 mg/kg, i.p.). Results suggest that TPM may exert diverse actions on the neural substrates of sensorimotor gating. While the pharmacological mechanisms of such effects are still elusive, these findings might contribute to shed light on some controversies on the therapeutic action of TPM, and point to this drug as a putative novel adjuvant therapy for some clusters of gating disturbances. Neuropsychopharmacology advance online

publication, 14 June 2006; doi:10.1038/sj.npp.1301115.

Toxicological Analysis in Rats Subjected to Heroin and Morphine Overdose
Strandberg, J.J., Kugelberg, F.C., Alkass, K., Gustavsson, A., Zahlsen, K., Spigset, O., and Druid, H. Toxicol Lett. [Epub ahead of print] May 16, 2006. INVEST Fellow: Henrik Druid, Sweden, 2000-2001. In heroin overdose deaths the blood morphine concentration varies substantially. To explore possible pharmacokinetic explanations for variable sensitivity to opiate toxicity authors studied mortality and drug concentrations in male Sprague-Dawley rats. Groups of rats were injected intravenously (i.v.) with heroin, 21.5mg/kg, or morphine, 223mg/kg, causing a 60-80% mortality among drug-naive rats. Additional groups of rats were pre-treated with morphine for 14 days, with or without 1 week of subsequent abstinence. Brain, lung and blood samples were analyzed for 6-acetylmorphine, morphine, morphine-3-glucuronide and morphine-6-glucuronide. i.v. morphine administration to drug-naive rats resulted in both rapid and delayed deaths. The brain morphine concentration conformed to an exponential elimination curve in all samples, ruling out accumulation of morphine as an explanation for delayed deaths. This study found no support for formation of toxic concentration of morphine-6-glucuronide. Spontaneous death among both heroin and morphine rats occurred at fairly uniform brain morphine concentrations. Morphine pre-treatment significantly reduced mortality upon i.v. morphine injection, but the protective effect was less evident upon i.v. heroin challenge. The morphine pre-treatment still afforded some protection after 1 week of abstinence among rats receiving i.v. morphine, whereas rats given i.v. heroin showed similar death rate as drug-naive rats.

Signal Transduction Induced by Opioids in Immune Cells: A Review
Martin-Kleiner, I., Balog, T., and Gabrilovac, J. Neuroimmunomodulation. 13(1), pp. 1-7 [Epub ahead of print] April 3, 2006. INVEST Fellow: Irena Martin-Kleiner, Croatia, 1995-1996. New data regarding signal transduction triggered by opioid ligands in immune cells are reviewed, and the signal transduction in neuronal cells is documented. Similar signaling pathways are induced by opioids in immune as well as neuronal cells. Opioids altered second messenger cAMP, intracellular calcium, and second messenger-induced kinases in immune cells. Met-enkephalin, preferentially delta-opioid, was bimodally regulated, while kappa-opioids inhibited these second messengers. delta-, kappa- and mu-opioids altered nitric oxide secretion, inducing cGMP as the second messenger in immune cells. Coupling of opioid agonists to opioid receptors activated mitogen-activated protein/extracellular signal-regulated protein kinases and various transcription factors in immune cells. Activator protein 1 (AP-1), c-fos, and nuclear factor-kappaB (NF-kappaB) are transcription factors shared by neuronal and immune cells. delta-Opioids activated AP-1, c-fos, activating transcription factor 2, Ikaros-1 and Ikaros-2 transcription factors in immune cells. Induction of kappa-opioid receptor gene by retinoic acid resulted in increased binding of Sp1 transcription factor to the promoter of the kappa-opioid receptor. mu-Opioids inhibited synthesis of common transcription factors AP-1, c-fos, NF-kappaB, and nuclear factor of activated T cells in activated or stimulated immune cells, whereas mu-opioids activated NF-kappaB, GATA-3, and Kruppel-like factor 7 transcription factors in non-stimulated immune cells.

Leber's Hereditary Optic Neuroretinopathy (LHON) Associated with Mitochondrial DNA Point Mutation G11778A in Two Croatian Families
Martin-Kleiner, I., Gabrilovac, J., Bradvica, M., Vidovic, T., Cerovski, B., Fumic, K., and Boranic, M. Coll Antropol. 30(1), pp. 171-174, March 2006. INVEST Fellow: Irena Martin-Kleiner, Croatia, 1995-1996). Leber's hereditary optic neuroretinopathy (LHON) is manifested as a bilateral acute or subacute loss of central vision due to optic atrophy. It is linked to point mutations of mitochondrial DNA, which is inherited maternally. The most common

mitochondrial DNA point mutations associated with LHON are G3460A, G11778A and T14484C. These mutations are linked with the defects of subunits of the complex I (NADH-dehydrogenase-ubiquinone reductase) in mitochondria. The G11778A mitochondrial DNA point mutation is manifested by a severe visual impairment. In this paper two Croatian families with the LHON G11778A mutation are presented. Three LHON patients from two families were younger males which had the visual acuity of 0.1 or below, the ophthalmoscopy revealed telangiectatic microangiopathy and papilloedema, while Goldmann kinetic perimetry showed a central scotoma. The mothers and female relatives were LHON mutants without symptoms, whereas their sons suffered from a severe visual impairment. Molecular diagnosis helps to explain the cause of LHON disease.

Personal, Interpersonal, and Cultural Predictors of Stages of Cigarette Smoking Among Adolescents in Johannesburg, South Africa
Brook, J.S., Morojele, N.K., Brook, D.W., Zhang, C., and Whiteman, M. Tob Control. 15 Suppl 1:i48-53, June 2006. INVEST Fellow: Neo Morojele, South Africa, 1998-1999. This study examined the personal, parental, peer, and cultural predictors of stage of smoking among South African urban adolescents. A cross-sectional design was employed. A stratified random approach based on census data was used to obtain the sample. Analyses were conducted using logistic regression. The study took place in communities in and around Johannesburg, South Africa. Participants consisted of 731 adolescents in the age range of 12-17 years old. The sample was 47% male and 53% female, and contained four ethnic classifications: white, black, Indian, and "coloured" (a South African term for mixed ancestry). A structured, in-person interview was administered to each participant in private by a trained interviewer, after obtaining consent. The dependent variables consisted of three stages of smoking: non-smoking, experimental smoking, and regular smoking. The independent measures were drawn from four domains: personal attributes, parental, peer, and cultural influences. Factors in all four domains significantly predicted three different stages of smoking. Personal attributes (internalizing and externalizing) distinguished among the three stages. Parental factors (for example, affection) reduced the odds of being a regular smoker compared with an experimental smoker or non-smoker, but did not differentiate experimental smokers from non-smokers. Findings from the peer domain (for example, peer substance use) predicted an increase in the risk of being a regular smoker compared with an experimental smoker or non-smoker. In the cultural domain, ethnic identification predicted a decrease in the risk of being a regular smoker compared with an experimental smoker, whereas discrimination and victimization predicted an increase in the risk of being an experimental smoker compared with a non-smoker. All the domains were important for all four ethnic groups. Four psychosocial domains are important in distinguishing among the three stages of smoking studied. Some predictors differentiated all stages of smoking, others between some of the stages of smoking. Therefore, intervention and prevention programs which are culturally and linguistically sensitive and appropriate should consider the individual's stage of smoking.

South African Adolescents: Pathways to Risky Sexual Behavior
Brook, D.W., Morojele, N.K., Zhang, C., and Brook, J.S. AIDS Educ Prev. 18(3), pp. 259-272, June 2006. INVEST Fellow: Neo Morojele, South Africa, 1998-1999. This study tested a developmental model of pathways to risky sexual behavior among South African adolescents. Participants comprised 633 adolescents, 12-17 years old, recruited from households in Durban, South Africa. Data were collected using in-person interviews. Topics included adolescents' sexual behaviors, household poverty levels, vulnerable personality and behavioral attributes, parent-child relations, and deviant peers. Structural equation modeling was used to assess the pathways to risky sexual behavior among the adolescents. The goodness-of-fit index (GFI) was .93. One major pathway indicated that family poverty was associated with difficulty in the parent-child relationship. This was related to vulnerable personality and

behavioral attributes and to association with deviant peers, which, in turn, were related to risky sexual behavior. Findings suggest that poverty, parent-child relations, personality and behavioral vulnerabilities, and peer influences should be among factors addressed by prevention and intervention programs to reduce sexual risk behaviors by South African adolescents.

Therapeutic Drug Monitoring (TDM) of Psychotropic Drugs: A Consensus Guideline of the AGNP-TDM Group

Baumann, P., Hiemke, C., Ulrich, S., Eckermann, G., Kuss, H.L., Laux, G., Muller-Oerlingenhausen, B., Rao, M.L., Riederer, P., Zernig, G. and AGNP-TDM. Rev Med Suisse. 2(67), pp. 1413-1418, 1420-1422, 1424-1426, May 24, 2006. INVEST Fellow: Gerald Zernig, Austria, 1993-1994. In psychiatry, therapeutic drug monitoring (TDM) is an established procedure for most psychotropic drugs. However, as its use in everyday clinical practice is far from optimal, the AGNP-TDM group has worked out consensus guidelines to assist psychiatrists and laboratories involved in drug analysis. Based on a thorough analysis of available literature, 5 levels of recommendation were defined with regard to TDM of psychoactive drugs, from 1) (strongly recommended) to 5) (not recommended). A list of indications for TDM, alone or in combination with pharmacogenetic tests is presented. Instructions are given with regard to preparation of TDM, analytical procedures, reporting and interpretation of results and the use of information for patient treatment. Using the consensus guideline will help to ensure optimal clinical benefit of TDM.

Activation of Muscarinic and Nicotinic Acetylcholine Receptors in the Nucleus Accumbens Core is Necessary for the Acquisition of Drug Reinforcement

Crespo, J.A., Sturm, K., Saria, A., and Zernig, G. J Neurosci. 26(22), pp. 6004-6010, May 31, 2006. INVEST Fellow: Gerald Zernig, 1993-1994. Neurotransmitter release in the nucleus accumbens core (NACore) during the acquisition of remifentanil or cocaine reinforcement was determined in an operant runway procedure by simultaneous tandem mass spectrometric analysis of dopamine, acetylcholine, and remifentanil or cocaine itself. Run times for remifentanil or cocaine continually decreased over the five consecutive runs of the experiment. Intra-NACore dopamine, acetylcholine, and drug peaked with each intravenous remifentanil or cocaine self-administration and decreased to pre-run baseline with half-lives of approximately 10 min. As expected, remifentanil or cocaine peaks did not vary between the five runs. Surprisingly, however, drug-contingent dopamine peaks also did not change over the five runs, whereas acetylcholine peaks did. Thus, the acquisition of drug reinforcement was paralleled by a continuous increase in acetylcholine overflow in the NACore, whereas the overflow of dopamine, the expected prime neurotransmitter candidate for conditioning in drug reinforcement, did not increase. Local intra-accumbens administration by reverse microdialysis of either atropine or mecamylamine completely and reversibly blocked the acquisition of remifentanil reinforcement. Findings suggest that activation of muscarinic and nicotinic acetylcholine receptors in the NACore by acetylcholine volume transmission is necessary during the acquisition phase of drug reinforcement conditioning.

Dopamine D4 Receptor Polymorphism Modulates Cue-elicited Heroin Craving in Chinese

Shao, C., Li, Y., Jiang, K., Zhang, D., Xu, Y., Lin, L., Wang, Q., Zhao, M., and Jin, L. Psychopharmacology (Berl). 186(2), pp. 185-190, June 2006. Epub 2006 Apr 27. [Epub ahead of print]. INVEST Fellow: Min Zhao, China, 2001-2002. Subjective craving, which contributes to the continuation of drug use in active abusers and the occurrence of relapse in detoxified abusers, is considered to be a central phenomenon in addiction. Dopamine pathway has been implicated in the mechanism underlying the cue-elicited craving for a variety of addictive substances. The objective of this study was to test the hypothesis that heroin addicts carrying D4 dopamine receptor gene (DRD4) variable number tandem

repeat (VNTR) long type allele would have higher craving after exposure to a heroin-related cue. Craving was induced by a series of exposure to neutral and heroin-related cue and were assessed in a cohort of Chinese heroin abusers (n=420) recruited from the Voluntary Drug Dependence Treatment Center at Shanghai. Significantly stronger cue-elicited heroin craving was found in individuals carrying DRD4 VNTR long type allele than the non-carriers ($F=31.040$, $p<0.001$). As for baseline craving and mean change in craving responding to neutral stimuli, no significance was found (1.06+/-0.34 vs 1.07+/-0.36, $F=0.067$, $p=0.797$ and 0.42+/-0.34 vs 0.45+/-0.37, $F=0.277$, $p=0.599$, respectively). The results of this study suggest that DRD4 VNTR polymorphism contributes to cue-elicited craving in heroin dependence, indicating DRD4 VNTR represents one of potential genetic risk factors for cue-induced craving.

HIV Sexual Risk Behaviors Among Injection Drug Users in Shanghai
Zhao, M., Du, J., Lu, G.H., Wang, Q.Y., Xu, H., Zhu, M., and McCoy, C.B. Drug Alcohol Depend. 82 Suppl 1, pp. S43-47, April 2006. INVEST Fellow: Min Zhao, China, 2001-2002. This study investigated the sexual risk behaviors among injection drug users (IDUs) in order to inform the development of sexual risk reduction interventions for IDUs. A cross-sectional survey of IDUs (n=141) was conducted in an in-patient detoxification treatment center in Shanghai, China, to collect information on demographics; drug use history; sexual risk behavior; HIV/AIDS knowledge, attitudes, and other psychosocial variables; and HIV, HBV, and HCV seroprevalence. Factors associated with HIV sexual risk behaviors and HBV and/or HCV infection were analyzed. Sexual risk behaviors among IDUs were common: the majority (77%) of the participants had not used a condom consistently in the previous 3 months, 25.5% had multiple partners, 48.2% had IDU partners, and 75.9% did not know their partner's HIV status. IDUs who were married (OR=4.83, $p<0.05$) or did not intend to use condoms in the future (OR=0.21, $p<0.05$) were more likely to have unprotected sex. The prevalence of HBV and HCV infection was 31.9% and 51.8%, respectively, but no one tested positive for HIV. IDUs with an injection history of 3 years or more (OR=5.86, $p<0.05$) and with an overdose history (OR=3.21, $p<0.05$) were more likely to be infected with HBV and/or HCV. Sexual risk behaviors among IDUs in Shanghai are common, and many IDUs are vulnerable for transmission of disease. Prevention efforts with IDUs should address sexual risk behaviors in addition to needle-sharing behaviors.

Antifungal Susceptibility Testing and Antifungal Traditional Chinese Medicines Screening of Oral Candida Isolated from Head and Neck Cancer Patients Treated with Radiotherapy or Chemotherapy [Article in Chinese]
Zhao, M., Zhou, Z.T., Zhang, W.D. Hua, Xi Kou Qiang Yi Xue Za Zhi. 24(2), pp. 131-134, April 2006. INVEST Fellow: Min Zhao, China, 2001-2002. The objective of this study was to evaluate the sensitivity and resistance of pathogenic oral Candida spp. isolated from head and neck cancer patients treated with radiotherapy or chemotherapy to antifungal agents. To screen antifungal agents from Chinese traditional and herbal drugs by NCCLS M27-A2 method. Using YBC Test Kit to identify 20 clinical oral Candida isolated from head and neck cancer patients treated with radiotherapy or chemotherapy. The in vitro susceptibilities of 20 oral Candida spp. to 5-flucytosine (5-FC), itraconazole (ITR), fluconazole (FLU), the extracts of 6 Chinese traditional and herbal drugs (caltrop, honeysuckle flower, dandelion, green tea, pine bark, red trefoil) and utility components of 7 Chinese traditional and herbal drugs (sophorcarpidine, aloperine, archin, glycyrrhizic acid, glycosides of white peony root, glycosides of baikal skullcap root, hydrochloric berberine) were determined by NCCLS M27-A2 method. The proportion of no-C. albicans in all Candida spp. were 25%. All strains were sensitive to 5-flucytosine, 25% stains were resistant to fluconazole and 40% strains were resistant to itraconazole. In all agents from Chinese traditional and herbal drugs, glycosides of white peony root and hydrochloric berberine ($C_{20}H_{18}CINO_4$) exhibited antifungal activity,

especially to C. glabrates. The proportion of no-C. albicans in all oral Candida spp. isolated from head and neck cancer patients treated with radiotherapy or chemotherapy was high. NCCLS M27-A2 micro-dilution method is a reliable and reproducible method and can be used to screen antifungal agents from Chinese traditional and herbal drugs.

Former Hubert H. Humphrey Drug Abuse Research Fellows

Factors Associated with Drug and Alcohol Use Among University Students [Article in Portuguese]
Silva, L.V., Malbergier, A., Stempliuk, Vde A., and Andrade, A.G. Rev Saude Publica. 40(2), pp. 280-288, April 2006. Epub 2006 March 29. HHH Fellows: Artur Guerra de Andrade, Brazil, 1991-1992; and Vladimir Stempliuk, Brazil, 2003-2004. Recent studies show an alarming rate of alcohol and drug use among university students. The objective of this study was to assess the level of association between lifestyle and socioeconomic status and the prevalence of alcohol, tobacco, medicine, and "illicit drug" use in the last 12 months among university students. The sample included 926 undergraduate students in the Biology Department of a university in Sao Paulo who completed an anonymous, self-applied questionnaire in 2000 and 2001. Anova and Chi-square tests were applied to verify the correlation between substance use and variables. Among students who reported having a religion, alcohol consumption was 83.1%, tobacco use 20.7%, and "illicit drugs" 24.6% during this period. Among students who reported not having a religion, reported alcohol use was higher in the last 12 months: alcohol (89.3%), tobacco (27.7%) and "illicit drugs" (37.7%). Monthly family income was related to alcohol and "illicit drug" use ($p<0.001$ for both). The students who used tobacco and "illicit drugs" reported more free time during the week than students who didn't smoke during the period of time analyzed ($p=0.033$ and $p=0.008$, respectively). Psychoactive drug use was common among students, indicating a need for policies to be implemented with the goal of reducing consumption. Students with higher family income and without religion should be considered to be at higher risk for alcohol and drug use among this group.

Human Vitamin B12 Absorption Measurement by Accelerator Mass Spectrometry Using Specifically Labeled (14)C-Cobalamin
Carkeet, C., Dueker, S.R., Lango, J., Buchholz, B.A., Miller, J.W., Green, R., Hammock, B.D., Roth, J.R., and Anderson, P.J. Proc Natl Acad Sci U S A. 103(15), pp. 5694-5699, April 11, 2006. Epub 2006 Apr 3. HHH Fellow: Józef Langó, Hungary, 1997-1998. There is a need for an improved test of human ability to assimilate dietary vitamin B(12). Assaying and understanding absorption and uptake of B(12) is important because defects can lead to hematological and neurological complications. Accelerator mass spectrometry is uniquely suited for assessing absorption and kinetics of carbon-14 ((14)C)-labeled substances after oral ingestion because it is more sensitive than decay counting and can measure levels of (14)C in microliter volumes of biological samples with negligible exposure of subjects to radioactivity. The test authors describe employs amounts of B(12) in the range of normal dietary intake. The B(12) used was quantitatively labeled with (14)C at one particular atom of the dimethylbenzimidazole (DMB) moiety by exploiting idiosyncrasies of Salmonella metabolism. To grow aerobically on ethanolamine, Salmonella enterica must be provided with either preformed B(12) or two of its precursors, cobinamide and DMB. When provided with (14)C-DMB specifically labeled in the C2 position, cells produced (14)C-B(12) of high specific activity (2.1 GBq/mmol, 58 mCi/mmol) (1 Ci = 37 GBq) and no detectable dilution of label from endogenous DMB synthesis. In a human kinetic study, a physiological dose (1.5 microg, 2.2 kBq/59 nCi) of purified (14)C-B(12) was administered and showed plasma appearance and clearance curves consistent with the predicted behavior of the pure vitamin. This method opens new avenues for study of B(12) assimilation.

Mirtazapine for Patients with Alcohol Dependence and Comorbid Depressive Disorders: A Multicentre, Open Label Study

Yoon, S.J., Pae, C.U., Kim, D.J., Namkoong, K., Lee, E., Oh, D.Y., Lee, Y.S., Shin, D.H., Jeong, Y.C., Kim, J.H., Choi, S.B., Hwang, I.B., Shin, Y.C., Cho, S.N., Lee, H.K., and Lee, C.T. Prog Neuropsychopharmacol Biol Psychiatry. April 17, 2006. [Epub ahead of print] HHH Fellow: Chung Tai Lee, South Korea, 1994-1995. Major depressive disorder and alcohol dependence are common and serious mental illnesses. There is a great interest in discovering useful treatments for both mood symptoms and alcohol abuse in those patients with depressive disorders and comorbid alcohol dependence. The primary purpose of this study was to evaluate the effectiveness and tolerability of mirtazapine for the treatment of patients with alcohol dependence comorbid with a depressive disorder in an open label, naturalistic multicentre treatment setting. The 17-item Hamilton Depression Rating Scale (HDRS), the Hamilton Anxiety Rating Scale (HARS) and the Clinical Global Impression-Severity (CGI-S) scale were measured at baseline and at weeks 4 and 8 for the assessment of treatment effectiveness. Alcohol craving was measured using the Obsessive Compulsive Drinking Scale (OCDS) and the Visual Analog Scale for Craving (VAS). This study showed a statistically significant reduction of the scores on the HDRS (13.9+/-7.3, $p<0.0001$), HARS (10.8+/-7.2, $p<0.0001$) and the CGI-S (1.7+/-1.0, $p<0.0001$) from baseline to the endpoint (week 8). The OCDS and VAS scores were also decreased significantly by 42.3% and 53.2% (9.0+/-10.0, $p<0.0001$; 2.5+/-2.4, $p<0.0001$, respectively). The number of patients with a 50% reduction or more in the HDRS and HARS scores was 103 (72.0%) and 106 (74.1%) at the endpoint, respectively. Adverse events related to mirtazapine were observed in 10% or more of the patients in this study. In conclusion, the results from this naturalistic study suggest that the use of mirtazapine for the patients with alcohol dependence comorbid with depressive disorder is accompanied by clinical improvement in their mood and alcohol craving.

Assessing Prescribing and Patient Care Indicators for Children Under Five Years Old With Malaria and Other Disease Conditions in Public Primary Health Care Facilities

Nsimba, S.E. Southeast Asian J Trop Med Public Health. 37(1):206-214, January 2006. HHH Fellow: Stephen Nsimba, Tanzania, 2005-2006. A prospective descriptive observational study using WHO indicator forms and questionnaire was carried out in Kibaha district public primary health care facilities. Authors assessed knowledge about drugs in mothers/guardians of sick children under age five years immediately after consulting clinicians and after receiving drugs from the dispenser. The questionnaires had closed- and open-ended questions. Interviews were administered by trained nurses and the authors. The prescribing, dispensing practices, including drug labeling and instructions given to mothers/guardians on how to use drugs at home, in these health facilities which are under the Essential Drugs Program (EDP), was assessed. A total of 652 prescriptions from mothers/ guardians with sick children under age five years were observed, recorded and analyzed. Prescribing indicators were used as stipulated by the WHO/DAP/93.1 how to investigate drug use in health facilities. The diagnosis for malaria cases made by the clinicians on average per facility were as follows: malaria alone 25, diarrhea alone 3, pneumonia alone 3, malaria and diarrhea 4 cases, malaria and pneumonia 2 cases and malaria and other conditions 14 cases. The average number of drugs per prescription in these facilities was 2.3 and the percentage generic prescribing was 87.0, antibiotics 30.5, and injections 26.2, with 93.5 % of all prescribed drugs being within the Essential Drugs List (EDL). The overall average dispensing time was 1.4 minutes per patient, of the drugs prescribed, 54.7 % were dispensed, whereas 21.4 % of drugs dispensed to mothers/guardians were adequately labeled, and 37.2 % of mothers knew how to administer drugs correctly to their sick children after receiving the drugs from the dispenser. These results suggest the need for educational intervention for prescribers (health care providers) on rational prescribing of drugs, such as

antimalarials, antibiotics, injections, proper dispensing, and adequate labeling drugs in packets, while the dispensing time for drugs was too short. It is necessary to correct these malpractices of irrational prescribing and dispensing drugs for treatment of malaria and other childhood illnesses in public primary health care facilities (PHC). Furthermore, inadequate physical examination and short consultation time needs to be improved. There is a need to advise the Ministry of Health to develop health education programs on a regular basis for all health care providers in the country and mothers/guardians of children in general public/rural communities on how to use/administer antimalarials and other drugs at home. All these can be achieved through well planned health education training programs.

HIV Seroprevalence Among Drug Users: An Analysis of Selected Variables Based on 10 Years of Data Collection in Porto Alegre, Brazil

Pechansky, F., Woody, G., Inciardi, J., Surratt, H., Kessler, F., Von Diemen, L., and Bumaguin, D.B. Drug Alcohol Depend. 82 Suppl 1, pp. S109-113, April 2006. HHH Fellow: Flavio Pechansky, Brazil, 1993-1994. Data from five studies were pooled to describe associations between drug use and HIV. The Risk Assessment. Battery in Porto Alegre, Brazil, was used to collect data from 1449 subjects in 5 separate studies conducted between 1995 and 2004. The subjects were divided into categories based on their pattern of drug use: (1) injection drug users (IDUs), (2) crack smokers, (3) frequent drug users, and (4) infrequent cocaine/alcohol/marijuana users. The sample consisted primarily of young males with low education and income levels. Half of the subjects reported frequent condom use, and exchanges involving drugs, sex, and money were infrequent (although more common in groups 1 and 2). The overall seroprevalence was 20.6%, and the prevalence was different across the four groups, showing a linear decrease from group 1 (57.1%) to group 4 (11.7%). The IDU and crack-smoking groups showed similarities in their risk levels when compared with the other two groups, and individuals in group 1, 2, and 3 were more likely to report having had four or more sex partners. After controlling for all other risk factors, IDU, males having sex with males, and crack use were highly associated with HIV (OR 7.30, 95% CI: 5.10.10.40; OR 3.04, 95%CI: 1.89,4.80; OR 2.03, 95%CI: 1.40, 2.92, respectively). The findings confirm that poverty, low education, and IDU remain risk factors for HIV in Porto Alegre, Brazil, and the study identities crack smoking as a new risk factor.

Poor Educational Attainment and Sexually Transmitted Infections Associated with Positive HIV Serostatus Among Female In-Patient Substance Abusers in Trinidad and Tobago

Reid, S.D. Drug Alcohol Depend. 82 Suppl 1, pp. S81-84, April 2006. HHH Fellow: Sandra Reid, Trinidad and Tobago, 1992-1993. Female crack cocaine users are at high risk for HIV infection. Data from 121 female substance abusers admitted to an all-female rehabilitation center in Trinidad and Tobago between 1996 and 2002 were reviewed retrospectively to determine human immunodeficiency virus (HIV) seroprevalence and associated risk factors. HIV seroprevalence was 19.8%, which is six times higher than in the general population. The univariate analysis identified the following factors associated with HIV infection: poor educational attainment, history of a sexually transmitted infection (STI), and use of crack cocaine. In the multivariate analysis, only poor educational attainment and history of an STI were independently associated with HIV seroprevalence. Female substance abusers, especially female crack cocaine users, are at high risk of acquiring and transmitting the HIV virus. To reduce risk of HIV infection, rehabilitation programs should address risky sexual behaviors and screen for STIs, and they also should improve educational attainment, develop skills, and provide vocational training.

Acute Hepatic Injury and Renal Failure After Ingestion of Snake Gallbladder

Chao, T.C., Wu, M.L., Tsai, W.J., Ger, J., and Deng, J.F. Clin Toxicol (Phila). 44(4), pp. 387-390, 2006. HHH Fellow: Wei-Jen Tsai, Taiwan, 1992-1993. Ingestion of snake gallbladder has been practiced in ancient Chinese civilizations to improve vision and relieve arthritic pain. Although little is known about the composition of snake gallbladder, ingestion is still practiced in some Chinese cultures. Adverse effects of ingesting snake gallbladder have not yet been reported. Here, authors present a case of acute hepatic injury and delayed-onset renal failure after ingestion of snake gallbladders. The patient subsequently recovered after supportive care, combined with plasma exchange and hemodialysis. He was the only survivor of the four victims suffering from intoxication of snake gallbladder in the last three years in our hospital.

U.S. - Netherlands Supplement-Supported Research Suggests Word Association Tasks and Working Memory Capacity Are Associated With Drug Use

Working with funding provided through the U.S. - Netherlands Binational Agreement, research teams led by Dr. Alan W. Stacy, University of Southern California, and Dr. Reinout Wiers, University of Maastricht, have reported that word association tasks appear to be more effective predictors of drug use than other major tests of implicit cognition, such as reaction time measures, and that adolescents with high levels of drug-related associations are at risk of using more drugs if they have lower versus higher levels of working memory capacity. The researchers also demonstrated the feasibility and utility of neuro-cognitive, laboratory-based batteries in small-group settings in the field. Their successful implementation of brief interventions for at-risk adolescents in a school setting could serve as a model for other high school intervention programs, especially for students who do not respond to group interventions. The group most recently published results in the Journal of Adolescent Medicine and Health (18, 53-67, 2006) and Evaluation and the Health Professions (29, 89-125, 2006), and presented their findings at a conference organized by the Dutch National Institute for Drug Abuse, Maastricht, the Netherlands, in March 2006. They have also completed a chapter, "Brief motivational interviewing and drug related problems," in Adolescence and Alcohol: An International Perspective (in press), edited by I. Kandel, J. Merrick, and L. Sher.

DISCA Researcher Examines Role of NMDA Receptors on Dopamine Efflux

2005 NIDA Distinguished International Scientist Dr. Luc Deneroy and colleagues at UniversitŽ Claude Bernard de Lyon, France, have published their research discussing how NMDA receptors inhibit the mild hypoxia-induced dopamine efflux in the rat striatum. The short communication appeared in Synapse, 59(7) 458 - 461.

Director's Report to the National Advisory Council on Drug Abuse - September, 2006

Program Activities

New NIDA PAs and RFAs

On July 10, 2006, NIDA issued a **Notice of Intent to Publish a Request for Applications for Mechanisms of Drug Abuse Interactions with HIV Neuropathogenesis (NOT-DA-06-016)**. The associated RFA is expected to be released in September 2006. This RFA will encourage a broad range of interdisciplinary research, using in vitro, animal and human approaches to address the basis of drug abuse and HIV interactions related to neuropathogenesis and neuropathology. This initiative was designed to broaden the AIDS research portfolio in both basic and clinical neuroscience.

On June 2, 2006, NIDA issued a Program Announcement (PA) entitled **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences (R36) PAR-06-446**. The purpose of this Funding Opportunity Announcement (FOA) is to invite applications for support of drug abuse doctoral dissertation research in epidemiology, prevention, treatment, services, and women and sex/gender differences.

On July 10, 2006, NIDA issued a Program Announcement (PA) entitled **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences (R36) PAR-06-476**. This is a reissuance of PAR-06-446, released June 2, 2006. The purpose of this Funding Opportunity Announcement (FOA) is to invite applications for support of drug abuse doctoral dissertation research in epidemiology, prevention, treatment, services, and women and sex/gender differences.

On July 26, 2006, NIDA issued a Program Announcement (PA) entitled **Health Services Research on Practice Improvement Utilizing Community Treatment Programs within the National Drug Abuse Clinical Trials Network (CTN) (R01) PA-06-495**. This Funding Opportunity Announcement (FOA) solicits health services research in conjunction with NIDA's Clinical Trials Network (CTN). The CTN is a research partnership between more than 150 community treatment programs (CTPs) and drug abuse researchers in multiple sites across the country. With its extensive network of providers serving diverse populations of drug users, the CTN provides an infrastructure for the investigation of (a) systems-level factors that facilitate practice improvement in community treatment programs, and (b) new research tools to facilitate higher quality health services research on practice improvement in drug abuse treatment.

On July 26, 2006, NIDA issued a Program Announcement (PA) entitled **Health Services Research on Practice Improvement Utilizing Community Treatment Programs within the National Drug Abuse Clinical Trials**

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Network (CTN) (R21) PA-06-496. This Funding Opportunity Announcement (FOA) solicits health services research in conjunction with NIDA's Clinical Trials Network (CTN). The CTN is a research partnership between more than 150 community treatment programs (CTPs) and drug abuse researchers in multiple sites across the country. With its extensive network of providers serving diverse populations of drug users, the CTN provides an infrastructure for the investigation of (a) systems-level factors that facilitate practice improvement in community treatment programs, and (b) new research tools to facilitate higher quality health services research on practice improvement in drug abuse treatment.

On July 26, 2006, NIDA issued a Program Announcement (PA) entitled **Health Services Research on Practice Improvement Utilizing Community Treatment Programs within the National Drug Abuse Clinical Trials Network (CTN) (R03) PA-06-497**. This Funding Opportunity Announcement (FOA) solicits health services research in conjunction with NIDA's Clinical Trials Network (CTN). The CTN is a research partnership between more than 150 community treatment programs (CTPs) and drug abuse researchers in multiple sites across the country. With its extensive network of providers serving diverse populations of drug users, the CTN provides an infrastructure for the investigation of (a) systems-level factors that facilitate practice improvement in community treatment programs, and (b) new research tools to facilitate higher quality health services research on practice improvement in drug abuse treatment.

On August 9, 2006, NIDA issued a Program Announcement (PA) entitled **Science Education Drug Abuse Partnership Award (R25) PAR-06-518**. This Funding Opportunity Announcement (FOA) solicits Research Education (R25) grant applications to fund the development and evaluation of innovative model programs and materials for enhancing knowledge and understanding of neuroscience and the biology of drug abuse and addiction among K-12 students, the general public, health care practitioners, and other groups. The award provides support for the formation of partnerships between scientists and educators, media experts, community leaders, and other interested organizations for the development and evaluation of programs and materials that will enhance knowledge and understanding of science related to drug abuse. The intended focus is on topics not well addressed in existing efforts by educational, community or media activities.

On August 14, 2006, NIDA issued a Program Announcement (PA) entitled **MDMA: Research Areas Needing More Emphasis (R03) PA-06-524**. This Funding Opportunity Announcement (FOA) is intended to increase the scope of NIDA's MDMA (3,4-methylenedioxymethamphetamine) research portfolio in order to provide an optimally comprehensive, strategic, and balanced MDMA research program. Clinical and preclinical research is needed.

On August 14, 2006, NIDA issued a Program Announcement (PA) entitled **MDMA: Research Areas Needing More Emphasis (R21) PA-06-525**. This Funding Opportunity Announcement (FOA) is intended to increase the scope of NIDA's MDMA (3,4-methylenedioxymethamphetamine) research portfolio in order to provide an optimally comprehensive, strategic, and balanced MDMA research program. Clinical and preclinical research is needed.

PAs and RFAs Issued With Other NIH Components/Agencies

On May 15, NIDA, in conjunction with numerous other NIH components, issued a Program Announcment (PA) entitled **Exploratory Innovations in Biomedical Computational Science and Technology (R21) PAR-06-411**. The NIH is interested in promoting research and developments in computational science and technology that will support rapid progress in areas of scientific opportunity in biomedical research. As defined here, biomedical

Publications

Staff Highlights

Grantee Honors

computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational and mathematical research including the development of structural, functional, integrative and analytical models and simulations.

On May 15, NIDA, in conjunction with numerous other NIH components, issued a Program Announcment (PA) entitled **Innovations in Biomedical Computational Science and Technology (R01) PAR-06-410**. The NIH is interested in promoting research and developments in computational science and technology that will support rapid progress in areas of scientific opportunity in biomedical research. As defined here, biomedical computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational and mathematical research including the development of structural, functional, integrative and analytical models and simulations.

On May 17, 2006, NIDA, in conjunction with numerous other NIH Institutes issued a Program Announcement (PA) entitled **Exploratory/Developmental Bioengineering Research Grants (EBRG) [R21] PA-06-418**. This Funding Opportunity Announcement (FOA) is intended to encourage innovation and high impact research. While minimal or no preliminary data are expected to be described in the application, applications should clearly indicate the significance of the proposed work and that the proposed research and/or development is scientifically sound, that the qualifications of the investigators are appropriate, and that resources available to the investigators are adequate.

On May 17, 2006, NIDA, in conjunction with numerous other NIH components issued a Program Announcement (PA) entitled **Bioengineering Research Grants (BRG) [R01] PA-06-419**. This funding opportunity will use the NIH R01 research grant award mechanism. The BRGs support multi-disciplinary research performed in a single laboratory or by a small number of investigators that applies an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose or treat disease or to understand health and behavior.

On May 17, NIDA in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Brain Disorders in the Developing World: Research Across the Lifespan (R21) PAR-06-420**. This Funding Opportunity Announcement (FOA) solicits applications for collaborative research projects, involving investigators in developed and developing countries, focusing on brain disorders throughout life relevant to developing nations. The collaborative research programs are expected to contribute to the long-term goal of building sustainable research capacity in developing countries to address neurological/ neurodevelopmental (including sensory, motor, cognitive and behavioral) function and impairment throughout life.

On May 19, 2006, NIDA and NIAAA jointly issued a Program Announcement (PA) entitled **Complementary and Alternative Medicine for Substance and Alcohol Related Disorders (R03) PA-06-424**. An important goal of this program is to identify, evaluate and develop safe and effective Complementary and Alternative Medicine therapies for the treatment of substance use disorders (SUD) and alcohol use disorders (AUD), including abuse or dependence on licit (alcohol and tobacco) and illicit drugs and for the treatment of neurological, psychiatric and medical consequences of drug and alcohol addiction.

On May 19, 2006, NIDA and NIAAA jointly issued a Program Announcement (PA) entitled **Complementary and Alternative Medicine for Substance and Alcohol Related Disorders (R21) PA-06-425**. An important goal of this

program is to identify, evaluate and develop safe and effective Complementary and Alternative Medicine therapies for the treatment of substance use disorders (SUD) and alcohol use disorders (AUD), including abuse or dependence on licit (alcohol and tobacco) and illicit drugs and for the treatment of neurological, psychiatric and medical consequences of drug and alcohol addiction.

On May 22, 2006, NIDA and NIMH jointly issued a Program Announcment (PA) entitled **Therapeutics Development for HIV/AIDS-Associated Neuropsychological Disorders (SBIR [R43/R44]) PA-06-432**. This funding opportunity announcement (FOA) solicits Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) for the development of therapeutics to treat HIV/AIDS-associated mental and neurological disorders. The NIMH Center for Mental Health Research on AIDS (CMHRA) and NIDA encourage the discovery and development of novel agents, methods, biomarkers and drug delivery technologies that can directly or indirectly eliminate/eradicate HIV reservoirs in the brain. Novel assays/models of neurotoxicity and treatment efficacy measures are invited as are novel in vitro/vivo models that can be used for screening potential therapeutic agents.

On May 22, 2006, NIDA and NIMH jointly issued a Program Announcment (PA) entitled **Therapeutics Development for HIV/AIDS-Associated Neuropsychological Disorders (STTR [R41/R42]) PA-06-433**. This funding opportunity announcement (FOA) solicits Small Business Technology Transfer (STTR) grant applications from small business concerns (SBCs) for the development of therapeutics to treat HIV/AIDS-associated mental and neurological disorders. The NIMH Center for Mental Health Research on AIDS (CMHRA) and NIDA encourage the discovery and development of novel agents, methods, biomarkers and drug delivery technologies that can directly or indirectly eliminate/eradicate HIV reservoirs in the brain. Novel assays/models of neurotoxicity and treatment efficacy measures are invited as are novel in vitro/vivo models that can be used for screening potential therapeutic agents.

On May 31, 2006, NIDA, in conjunction with a number of other NIH components, issued a Program Announcement (PA) entitled **International Research Collaboration-Basic Biomedical (FIRCA-BB) [R03] PAR-06-436**. This Funding Opportunity Announcement (FOA) facilitates collaborative basic biomedical research between scientists supported by the NIH and investigators in developing countries.

On May 31, 2006, NIDA, in conjunction with a number of other NIH components, issued a Program Announcement (PA) entitled **International Research Collaboration-Behavioral, Social Sciences (FIRCA-BSS) [R03] PAR-06-437**. This Funding Opportunity Announcement (FOA) facilitates collaborative behavioral and social science research between scientists supported by the NIH and investigators in developing countries.

On June 5, 2006, NIDA and NIMH jointly issued a Program Announcment (PA) entitled **The Development of Frontal Cortex and Limbic System and Their Roles in Drug Abuse or Mental Health (R01) PA-06-444**. This funding opportunity announcement (FOA) solicits research project (R01) grant applications to study the development of the frontal and prefrontal cortices, together with the subcortical areas of the limbic system, that play significant roles in mediating emotional and motivated behavior. This initiative is designed to support basic neuroscience research into the fundamental mechanisms of development of the frontal and prefrontal cortices, as well as the midbrain and basal forebrain structures that mediate a number of functions related to drug abuse and psychiatric disorders including the euphoric properties of drugs, actions of psychotherapeutic agents, and cognitive and emotional functions.

On June 5, 2006, NIDA and NIMH jointly issued a Program Announcment (PA) entitled **The Development of Frontal Cortex and Limbic System and Their Roles in Drug Abuse or Mental Health (R21) PA-06-445**. This

funding opportunity announcement (FOA) solicits exploratory/developmental (R21) grant applications to study the development of the frontal and prefrontal cortices, together with the subcortical areas of the limbic system, that play significant roles in mediating emotional and motivated behavior. This initiative is designed to support basic neuroscience research into the fundamental mechanisms of development of the frontal and prefrontal cortices, as well as the midbrain and basal forebrain structures that mediate a number of functions related to drug abuse and psychiatric disorders including the euphoric properties of drugs, actions of psychotherapeutic agents, and cognitive and emotional functions.

On June 12, 2006, NIDA, in conjunction with numerous other NIH Institutes issued a Program Announcement (PA) entitled **Bioengineering Research Partnerships (BRP) [R01] PAR-06-459**. Through this PA, participating Institutes and Centers of the NIH invite applications for R01 awards to support Bioengineering Research Partnerships (BRPs) for basic, applied, and translational multi-disciplinary research that addresses important biological or medical research problems.

On July 7, 2006, NIDA and NIMH jointly issed a Program Announcement (PA) entitled **Research on Rural Mental Health and Drug Abuse Dirorders (R01) PA-06-478**. The purpose of this Funding Opportunity Announcement (FOA) is to invite grant applications to stimulate research on mental health and/or drug abuse problems in rural and frontier communities that will: (1) enhance understanding of structural (including community risk and resilience factors) cultural, and individual factors that may enhance the provision and utilization of prevention and treatment services in these communities; and (2) generate knowledge to improve the organization, financing, efficiency, effectiveness, quality and outcomes of mental health and drug abuse services for diverse populations in rural and frontier populations.

On July 14, 2006, NIDA, in collaboration with NIAAA and the National Center for Complementary and Alternative Medicine (NCCAM) issued a Program Announcement (PA) entitled **Behavioral and Integrative Treatment Development Program (R01) PA-06-486**. This Funding Opportunity Announcement (FOA) invites applications for grant funding to support behavioral and integrative treatment research that will have a meaningful impact on improving treatment for drug and alcohol abuse and dependence.

On July 14, 2006, NIDA, in collaboration with NIAAA and the National Center for Complementary and Alternative Medicine (NCCAM) issued a Program Announcement (PA) entitled **Behavioral and Integrative Treatment Development Program (R21) PA-06-487**. This Funding Opportunity Announcement (FOA) invites applications for grant funding to support behavioral and integrative treatment research that will have a meaningful impact on improving treatment for drug and alcohol abuse and dependence.

On July 14, 2006, NIDA, in collaboration with NIAAA and the National Center for Complementary and Alternative Medicine (NCCAM) issued a Program Announcement (PA) entitled **Behavioral and Integrative Treatment Development Program (R03) PA-06-488**. This Funding Opportunity Announcement (FOA) invites applications for grant funding to support behavioral and integrative treatment research that will have a meaningful impact on improving treatment for drug and alcohol abuse and dependence.

On June 16, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grants (T32) PA-06-468**. The primary objective of this program is to prepare qualified individuals for careers that have a significant impact on the health-related research needs of the Nation.

On July 21, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Ruth L. Kirschstein National Research Service Award (NRSA) for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research PA-06-481**. The primary objective of this program is to help ensure that diverse pools of highly trained scientists will be available in appropriate research areas to carry out the Nation's biomedical, behavioral, health services or clinical research agenda.

On August 7, 2006, NIDA, in conjunction with a number of other NIH Institutes, issued a Program Announcement (PA) entitled **Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders (R21) PA-06-461**. This Funding Opportunity Announcement (FOA) invites NIH Exploratory/Developmental Grant (R21) applications from organizations/ institutions that propose the development of novel radioligands for positron emission tomography (PET) or single photon computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies.

On August 7, 2006, NIDA, in conjunction with a number of other NIH Institutes, issued a Program Announcement (PA) entitled **Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders (R33) PA-06-462**. This Funding Opportunity Announcement (FOA) invites Phase II Developmental (R33) grant applications from organizations/institutions that propose the development of novel radioligands for positron emission tomography (PET) or single photon computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies.

On August 7, 2006, NIDA, in conjunction with a number of other NIH Institutes, issued a Program Announcement (PA) entitled **Development and Application of PET and SPECT Imaging Ligands as Biomarkers for Drug Discovery and for Pathophysiological Studies of CNS Disorders (R21/R33) PA-06-463**. This Funding Opportunity Announcement (FOA) invites Phased Innovation (R21/R33) grant applications from organizations/institutions that propose the development of novel radioligands for positron emission tomography (PET) or single photon computed tomography (SPECT) imaging in human brain, and that incorporate pilot or clinical feasibility evaluation in pre-clinical studies, model development, or clinical studies.

On August 7, 2006, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Mentored Clinical Scientist Research Career Development Award (K08) PA-06-512**. This award represents the continuation of a long-standing NIH program that provides support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience in the fields of biomedical and behavioral research, including translational research.

On August 10, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Networks and Pathways Collaborative Research Projects (R01) PA-06-522**. This announcement solicits applications for research project grants that will leverage and complement ongoing technology development being pursued in the National Technology Centers for Networks and Pathways (TCNPs), a program of the NIH Roadmap for Medical Research. These collaborative projects should focus either on addressing a challenging biological problem using the technology developed in one or more of the TCNPs, or on the development of technology that will complement that which is being developed

in the centers.

On August 10, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Dissemination and Implementation Research in Health (R03) PAR-06-520**. This funding opportunity announcement (FOA) encourages investigators to submit research grant applications that will identify, develop and refine effective and efficient methods, structures and strategies that test models to disseminate and implement research-tested health behavior change interventions and evidence-based prevention, early detection, diagnostic, treatment and quality of life improvement services into public health and clinical practice settings.

On August 10, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement (PA) entitled **Dissemination and Implementation Research in Health (R21) PAR-06-521**. This funding opportunity announcement (FOA) encourages investigators to submit research grant applications that will identify, develop and refine effective and efficient methods, structures and strategies that test models to disseminate and implement research-tested health behavior change interventions and evidence-based prevention, early detection, diagnostic, treatment and quality of life improvement services into public health and clinical practice settings.

On August 15, 2006, NIDA, in collaboration with numerous other NIH components, issued a Program Announcment (PA) entitled **Independent Scientist Award (K02) PA-06-527**. In general, the Independent Scientist Award provides support for newly independent scientists who can demonstrate a need for a period of intensive research focus as a means of enhancing their research careers. The K02 is intended to foster the development of outstanding scientists and to enable them to expand their potential to make significant contributions to their field of research. The participating NIH components have distinctive guidelines, requirements, salary and research support levels provided under the auspices of this announcement.

On August 21, 2006, NIDA, in collaboration with NIMH and NINDS, issued a Program Announcement (PA) entitled **Preclinical Therapeutics Development for NeuroAIDS (R21) PA-06-528**. Through this PA, participating Institutes invite applications proposing novel models of HIV-related central or peripheral nervous system damage that can be used to screen for compounds showing promise as treatments in the patient population.

On August 21, 2006, NIDA, in collaboration with NIMH and NINDS, issued a Program Announcement (PA) entitled **Preclinical Therapeutics Development for NeuroAIDS (R03) PA-06-529**. Through this PA, participating Institutes invite applications proposing novel models of HIV-related central or peripheral nervous system damage that can be used to screen for compounds showing promise as treatments in the patient population.

On August 2, 2006, NIDA and a number of other NIH Institutes issued a Program Announcement (PA) entitled **Parenting Capacities and Health Outcomes in Youth and Adolescents (R21) PA-06-530**. This funding opportunity announcement solicits Exploratory/ Developmental (R21) grant applications from applicant organizations aimed at increasing the parenting skills and capacities of parents and caregivers to improve the health outcomes of their young and adolescent children.

On August 22, 2006, NIDA, in conjunction with numerous other NIH Institutes, issued a Program Announcement (PA) entitled **Functional Links Between the Immune System, Brain Function and Behavior (R21) PA-06-533**. This FOA requests research grant applications to study neuroimmune molecules and mechanisms involved in regulating normal and pathological central nervous

system (CNS) function.

On August 23, 2006, NIDA in conjunction with numerous other NIH components issued a Program Announcment (PA) entitled **Innovations in Biomedical Computational Science and Technology Initiative (STTR [R41/42]) PAR-06-534**. This funding opportunity announcement (FOA) solicits Small Business Technology Transfer (STTR) grant applications from small business concerns (SBCs) that propose innovative research in biomedical computational science and technology to promote the progress of biomedical research.

On August 23, 2006, NIDA in conjunction with numerous other NIH components issued a Program Announcment (PA) entitled **Innovations in Biomedical Computational Science and Technology Initiative (SBIR [R43/44]) PAR-06-535**. This funding opportunity announcement (FOA) solicits Small Business Innovation Research (SBIR) grant applications from small business concerns (SBCs) that propose innovative research in biomedical computational science and technology to promote the progress of biomedical research.

On June 2, 2006, NIDA, in conjunction with NIMH and NIAAA, issued a Program Announcement (PA) entitled **Research on the Reduction and Prevention of Suicidality (R01) PA-06-438**. The purpose of this Funding Opportunity Announcement (FOA) is to invite grant applications for research that will reduce the burden of suicidality (deaths, attempts, and ideation). The intent is to intensify investigator-initiated research on the topic, to attract new investigators to the field, and increase interdisciplinary approaches to developing effective strategies to reduce suicidality.

On June 2, 2006, NIDA, in conjunction with NIMH and NIAAA, issued a Program Announcment (PA) entitled **Risk Factors for Psychopathology Using Existing Data Sets (R01) PA-06-439**. The purpose of this Funding Opportunity Announcement (FOA) is to invite grant applications involving extensive and innovative use of existing data sets to study the development of psychopathology, including alcohol and drug abuse, in order to guide the development of preventive and treatment intervention strategies.

On June 12, 2006, NIDA, in collaboration with a number of other NIH components and the FDA, issued an RFA entitled **Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health (P50) RFA-OD-06-003**. Through this RFA, the Office of Research on Women's Health and other participating Institutes and the FDA seek to offer the Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health for the second time. These centers will provide opportunities for interdisciplinary approaches to advancing studies on how sex and gender factors affect women's health. Each SCOR should develop a research agenda bridging basic and clinical research on sex/gender factors underlying a health issue that affects women.

On June 13, 2006, NIDA, in conjunction with numerous other NIH components and the Agency for Healthcare Research and Quality (AHRQ) issued an RFA entitled **Building Interdisciplinary Research Careers in Women's Health (K12) RFA-OD-06-004**. Through this RFA the ORWH and its cosponsors invite institutional career development award applications for Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Programs. These programs will support mentored research career development of junior faculty members, known as BIRCWH Scholors, who have recently completed clinical training or postdoctoral fellowships, and who will be engaged in interdisciplinary basic, translational, behavioral, clinical, and/or health services research relevant to women's health or sex/gender factors. The goal of this initiative is to increase the number of skills of investigators through a mentored research and career development experience leading to an

independent scientific career that will benefit the health of women, including research on sex/gender similarities or differences in biology, health or disease.

On August 18, 2006, NIDA, in collaboration with numerous other NIH components, issued An RFA entitled **Clinical Research Education and Career Development (CRECD) in Minority Institutions (R25) RFA-RR-06-003**. This Funding Opportunity Announcement (FOA) is intended to encourage both current CRECD awardee institutions in the final year of funding and eligible institutions that have not received previous CRECD award to apply. These awards are intended to support development and implementation of curriculum-dependent programs in minority institutions to train selected doctoral or postdoctoral candidates in clinical research leading to a Masters of Science in Clinical Research or a Master of Public Health in a clinically relevant area. A successful program will result in an accredited master's degree program to produce trained clinical researchers who can become part of translational and/or patient-oriented research projects.

Other Program Activities

CTN Update

On August 3, 2006, NIDA/CCTN released RFA-DA-07-001, http://grants.nih.gov/grants/ guide/rfa-files/RFA-DA-07-001.html, Announcement of a Limited Competition of THE NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK (U10). This RFA announces a limited competition for competitive cooperative agreement renewal applications from established clinical investigators to participate in the National Drug Abuse Treatment Clinical Trials Network (CTN). The competition is restricted to only those institutions that currently house an existing, active Node in the CTN. As a nation-wide partnership among drug abuse treatment providers, researchers, and NIDA staff, the mission of the CTN is to improve the quality of drug abuse treatment throughout the country using science as the vehicle.

A total of 26 protocols and surveys have been initiated since 2001. A total of 11,778 participants were screened and 7,177 enrolled in studies as of July 27, 2006. Of these studies, 12 have completed enrollment and locked the data; eight completed enrollment and are in the follow-up phase; five are currently enrolling; and one is in the protocol development phase.

Twelve protocols have locked the data:
Protocol CTN 0001, Buprenorphine/Naloxone versus Clonidine for Inpatient Opiate Detoxification

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

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 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

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

Eight protocols have ended new enrollment and are in either follow-up or data-lock phase:
Protocol CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment in July 2003. Recruitment ended January 31, 2006.

Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers) began enrollment in November 2003 and reached its enrollment target of 200 randomized participants.

Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial) began in March 2004. The study reached its enrollment target in October 2005, and follow-up continues until fall 2006.

Protocol CTN 0017 (HIV and HCV Intervention in Drug Treatment Settings). The study began enrollment in November 2004 and enrolled at eight community treatment sites across five Nodes. Enrollment ended in February 2006; follow-up will be complete in summer 2006.

Protocol CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment) began enrolling in April 2004 and reached its target enrollment in September 2005. Follow-up will be complete in summer 2006.

Protocol CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment) began enrollment in May 2004 and reached its target in October 2005. Follow-up will continue until fall 2006.

Protocol CTN 0020 (Job Seekers Training for Substance Abusers). The protocol began enrollment in October 2004 and reached its enrollment target in February 2006. This study is also being conducted in a Navajo American Indian site, the Na'nizhoozhi Center, Inc. in Gallup, New Mexico, the first CTN study to be conducted there. Follow-up will continue through August 2006.

Protocol CTN 0021 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse) began enrollment in November 2003 and reached its target goal in October 2005. The follow-up phase was completed in March 2006. This is the first Spanish-only protocol in the CTN.

Five protocols are currently enrolling:
Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), has been implemented at eight sites. The study has reached 80% enrollment. There currently are a total of 385 randomized participants.

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 and includes nine sites. Seven of the sites are actively recruiting. There are a total of 28

randomized participants.

Protocol CTN 0028, Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD). Enrollment began March 17, 2006 in three sites; eight more sites should begin enrollment by September 2006.

Protocol CTN 0029, A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD). This study is being carried out at six community treatment sites across five Nodes. There are a total of 58 randomized participants. Thirty-one participants have completed the active treatment phase and are in follow-up; 24 have completed the full study.

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 will be carried out in 12 sites. Seven participants have been randomized so far.

One protocol is in the development phase:
Protocol CTN 0031, Twelve-Step Facilitation: Evaluation of an Intervention to Improve Substance Abuse Treatment Outcomes by Increasing 12-Step Involvement.

In addition to the primary CTN trials, there are currently 17 funded studies supported by independent grants that use CTN studies as a platform.

IECRN Best Practices Report
A key NIH Roadmap initiative, Inventory and Evaluation of Clinical Research networks (IECRN) under which Westat Corporation profiled all the active clinical research networks, amounting to more than 270, studied the Best Practices of a selected number of networks for transportable knowledge to the operations of other networks. NIDA's Clinical Trials Network (CTN) was one of the thirty-one networks studied for its Best Practices. The IECRN Best Practices Report recognized NIDA CTN's accomplishments in building trust and collegiality between provider and researcher, an essential ingredient that is necessary in building a truly effective and integrated network. Additionally, the Report noted that the CTN had a "robust IT" program and used sophisticated technology through its data coordinating center.

NIDA's New and Competing Continuation Grants Awarded Since May 2006

Abdala, Nadia -- Yale University
Identifying HIV-Bridge-Population In STI Clinics, Russia

Anand, Rene -- Louisiana State University Health Ssciences Center, New Orleans
Modulation of Nicotinic Receptors By Cytosolic Proteins

Baldwin, Gayle C. -- University of California, Los Angeles
In Vivo Modeling of Methamphetamine and HIV Interactions

Balster, Robert L. -- Virginia Commonwealth University
The Behavioral Pharmacology of Phencyclidine

Blackard, Jason T. -- University of Cincinnati
Extrahepatic Replication & Viral Evolution of HCV During HCV/HIV Co-Infection

Blanco, Carlos -- New York State Psychiatric Institute
Smart: Improving Detection & Outcome of Psychiatric Comorbidity In Drug Treatment

Bond, Kimberly R. -- Mental Health Systems, Inc.
Enhancing Substance Abuse Treatment Services for Women Offenders

Bruno, John P. -- Ohio State University
High-Speed Detection of Stimulant-Induced Cortical ACH Release

Calsyn, Donald A. -- University of Washington
Prescription Opioid Misuse In a Large HMO

Chun, Jerold -- Scripps Research Institute
Receptor-Mediated S1p Signaling In the Embryonic Brain

Clark, Pamela I. -- Battelle Centers/Public Health Research & Evaluation
Physiologic Impact of Variation In Smoke Ph

Clatts, Michael C. -- National Development & Research Institutes
Situational Adaptations to Katrina and HIV Risk

Colder, Craig R. -- State University of New York at Buffalo
Motivation In Context: Risk For Early Substance Use

Colfax, Grant N. -- Public Health Foundation Enterprises
Mirtazapine To Reduce Methamphetamine Use Among MSM With High-Risk HIV Behaviors

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

Coviello, Donna M. -- University of Pennsylvania
Employment Intervention For Offenders

Crits-Christoph, Paul -- University of Pennsylvania
Patient Feedback Effectiveness Study

Cunningham, Kathryn A. -- University of Texas Medical Branch, Galveston
Neurobehavioral Pharmacology of Stimulants

Dewey, William L. -- Virginia Commonwealth University
The Role of Protein Kinase C In Opioid Tolerance

Donohue, Bradley C. -- University of Nevada, Las Vegas
An Outcome Study Involving Drug Abusing Mothers In Child Protective Services

Duncan, Erica J. -- Emory University
Acoustic Startle Reduction In Cocaine Dependence

Edwards, Robert H. -- University of California, San Francisco
Presynaptic Mechanisms of Neural Plasticity

Eiden, Rina D. -- State University of New York at Buffalo
Prenatal & Ets Exposure: Effects On Child Regulation

Feske, Ulrike -- University of Pittsburgh at Pittsburgh
Drug Abuse and Risky Sex In Borderline Personality

Galli, Aurelio A. -- Vanderbilt University
Amphetamine Regulation of Dopamine Transport

Gehricke, Jean G. -- University of California, Irvine
The Reinforcing Mechanisms of Smoking In Adult ADHD

Gelernter, Joel E. -- Yale University
Genetics of Cocaine Dependence

Golden, Matthew R. -- University of Washington
Development of a Methamphetamine Early Intervention

Gudelsky, Gary A. -- University of Cincinnati
Determinants and Consequences of MDMA Neurotoxicity

Heflinger, Craig A. -- Vanderbilt University
Substance Use Disorders & Service Use Among Rural Youth

Higgins, Stephen T. -- University of Vermont & State Agricultural College
Voucher-Based Incentives To Treat Pregnant Smokers

Hohmann, Andrea G. -- University of Georgia
An Endocannabinoid Mechanism for Stress-Induced Analgesia

Hooks, Shelly B. -- University of Georgia
Regulation of Dopamine Signaling By Striatal Rgs9-2; Mechanisms and Specificity

Iacono, William G. -- University of Minnesota, Twin Cities
Twin Study of ADHD, CD and Substance Abuse

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

Kerns, John G. -- University of Missouri, Columbia
Anterior Cingulate, Prefrontal Cortex, and Conflict-Control Loop Theory

Killeen, Therese K. -- Medical University of South Carolina
Contingency Management/Adolescents With Marijuana Use Disorders

Kral, Alexander H. -- Research Triangle Institute
Correlates of Sexual Risk For HIV/STI Among Women Who Use Methamphetamine

Kranzler, Henry R. -- University of Connecticut School of Medicine and Dentistry
Genetics of Cocaine Dependence

Ling, Walter -- University of California, Los Angeles
Optimizing Outcomes Using Suboxone for Opiate Dependence

Loh, Horace H. -- University of Minnesota, Twin Cities
Neurochemical Basis of Opiate Addiction

Maier, Steven F. -- University of Colorado at Boulder
Stressor Controllability, Drugs of Abuse, and Serotonin

Malison, Robert T. -- Yale University
Drug Abuse, Sleep, and Cognition

Marlatt, G. Alan -- University of Washington
Efficacy of Mindfulness-Based Relapse Prevention

Martin, Eileen M. -- University of Illinois at Chicago
Cognitive Neuropsychology of HIV and Drug Abuse

Molina, Patricia E. -- Louisiana State University Health Sciences Center, New Orleans
Cannabinoid Effects on HIV/AIDS

Muehlbach, Britta -- Daytop Village
Technology Transfer: Promoting Change In The Therapeutic Community

Nestler, Eric J. -- University of Texas Southwest Medical Center, Dallas

Molecular Studies of Cocaine Action In Brain

O'Farrell, Timothy J. -- Harvard University Medical School
Opioid Patients: Behavioral Family Counseling and Naltrexone

Oliveto Beaudoin, Alison -- University of Arkansas Medical Sciences, Little Rock
Disulfiram for Cocaine Abuse In Methadone - Patients

Ondersma, Steven J. -- Wayne State University
Computer-Based Brief Intervention for Perinatal Drug, Alcohol, and Tobacco Abuse

Operario, Don -- University of Oxford
Gender, Relationship Dynamics, and HIV Risk

Pacula, Rosalie L. -- Rand Corporation
Economic Cost of Drug Use and Abuse

Parsons, Jeffrey T. -- Hunter College
Risk Reduction Intervention for Highly Vulnerable Emerging Adult Males

Pasternak, Gavril W. -- Sloan-Kettering Institute for Cancer Research
Biochemical Characterization of Opioid Receptors

Payne, Brian K. -- University of North Carolina, Chapel Hill
Neural Bases of Automatic and Controlled Affective Responses To Smoking Cues

Pearlson, Godfrey D. -- Yale University
Reward, Impulsivity and Cocaine Addiction: fMRI Studies

Porrino, Linda J. -- Wake Forest University Health Sciences
Early Exposure To Stimulants As A Risk Factor For Substance Abuse

Powell, Elizabeth M. -- University of Maryland Baltimore Professional School
Mechanisms of Forebrain Development

Ressler, Kerry J. -- Emory University
Molecular Regulation of GABA(A) Receptor Function In Amygdala

Reynolds, Brady -- Children's Research Institute
Impulsivity at Different Stages of Adolescent Smoking

Rigotti, Nancy A. -- Massachusetts General Hospital
Bupropion for Smoking Cessation In Postpartum Women

Roth, Michael D. -- University of California, Los Angeles
Vector-Based Generation of Monoclonal Antibodies Against The CB2 Receptor

Rush, Craig R. -- University of Kentucky
Agonist Replacement Therapy for Cocaine Dependence: Identifying Novel Medications

Sarafian, Theodore A. -- University of California, Los Angeles
Pulmonary Mitochondrial Injury Caused By Tetrahydrocannabinol

Sigmon, Stacey C. -- University of Vermont & State Agricultural College
Effective Treatment for Prescription Opioid Abuse

Slesinger, Paul A. -- Salk Institute for Biological Studies
Kir 3 Channel Subunits In Drug Abuse With GABAB Agonists

Small, Dana M. -- John B. Pierce Laboratory, Inc.
Interactions Between Nicotine Addiction and Food Reward

Smith, Sheryl S. -- SUNY Downstate Medical Center
Steroids and GABA: Physiology of Receptor Subunit Change

Sprague, Jeff R. -- University of Oregon
Positive Behavior Support and the Prevention of Adolescent Problems

Srivatsan, Malathi -- Arkansas State University
Nicotine and Development of Autonomic Neurons

Staley, Julie K. -- Yale University
Cognition, Tobacco Smoke and Nicotinic Receptor Occupancy

Stone, Laura S. -- University of Minnesota, Twin Cities
Proteomic Studies of Human Chronic Pain

Sweedler, Jonathan V. -- University of Illinois, Urbana-Champaign
Neuropeptides In the CNS With New Mass Spectrometric Sampling Protocols

Tangney, June P. -- George Mason University
Jail-Based Treatment To Reduce Substance Abuse, Recidivism and Risky Behavior

Tapert, Susan F. -- Veterans Medical Research Foundation, San Diego
fMRI and Cognition In Adolescent Cannabis Users

Tidey, Jennifer W. -- Brown University
Biological and Behavioral Mechanisms of Smoking In Schizophrenia

Todorov, Alexandre A. -- Washington University
Genetic Epidemiology of Opioid Dependence In Bulgaria

Toll, Lawrence R. -- SRI International
Subtype-Selective Nicotinic Receptor Ligands As Smoking Cessation Pharmacotherapy

Valdez, Avelardo -- University of Houston
Substance Use and Other Health Consequences Among Katrina Evacuees In Houston

Vulchanova, Lyudmila H. -- University of Minnesota, Twin Cities
Combined Proteomic and Functional Analysis of Sensory Neuron Plasticity

Walsh, Sharon L. -- University of Kentucky
Evaluation of Novel Treatments for Stimulant Dependence

Wang, Shaomeng -- University of Michigan at Ann Arbor
Design, Synthesis and Characterization of Dopamine Receptor 3 Ligands

Ward, Kenneth D. -- University of Memphis
Population-Based Assessment of Post-Katrina Smoking Relapse

Weissman, Daniel -- University of Michigan at Ann Arbor
Neural Substrates of Executive Control Revealed By fMRI

Westling, Erika H. -- University of California, Los Angeles
Pubertal Timing and Substance Use In Children and Adolescents: Gender Differences

Winters, Ken C. -- Treatment Research Institute, Inc.
Brief Intervention for Drug-Abusing Delinquents/Parents

Woody, George E. -- University of Pennsylvania
Methadone Maintenance and HIV Risk In Ukraine

Woolley, Catherine S. -- Northwestern University

Gender Differences In the Neural Circuitry of Addiction

Wu, Ping -- Columbia University Health Sciences
Ecstasy "Epidemic" and Youth: Trends, Comorbidity, Risk and Protective Factors

Xu, Jiansong -- University of California, Los Angeles
Cigarette Smoking and the Efficiency of the Frontoparietal Attentional Network

Yu, Lei -- Rutgers The State University of New Jersey, Newark
Human Genetic Polymorphism Impact In A Mouse Model

Zhang, Xiuwu -- Duke University
Conditional Interference-Mediated Reversal Cocaine Reinforcement

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1485 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 1226 applications.

OEA arranged and managed 26 grant review meetings in which 706 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 14 contract proposal reviews and 2 concept reviews and 144 applications to the Loan Repayment Program.

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 22 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
Center Grant Applications
The Minority Institutions' Drug Abuse Research Development Program (MIDARP)
Program Project Grant applications
Mechanism For Time-Sensitive Research Opportunities
Behavioral Science Track Award for Rapid Transition (B/START)
Cutting Edge Basic Research Awards (CEBRA)
Imaging Science Track Awards for Research Transition (I/START)
Conference Grants (R13)
Loan Repayment Programs
NIH Pathway To Independence (PI) Awards (K99/R00)
8 Special Emphasis Panels that reviewed RFA submissions

OEA managed the following RFA reviews:

Contract Reviews (R&D and non-R&D)

- DA06-002: Pilot Clinical Trials Of Pharmacotherapies For Substance Related Disorders
- DA06-004: Social Neuroscience
- DA06-005: Prescription Opioid Use And Abuse In The Treatment Of Pain
- DA06-006: Developmental Centers For Translational Research On The Clinical Neurobiology Of Drug Addiction (P20)

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- DA06-007: Epigenetics Of Neurobiology And Addiction
- DA06-008: Training In Translational Research In Neurobiology Of Disease (T32)
- DA06-010: Training In Computational Neuroscience: From Biology To Model And Back Again (T90)
- DA06-011: Training In Neuroimaging: Integrating First Principles And Applications (T90)

Completed Contract Reviews from the Contracts Review Branch since the last Council are as follows:

Contract Reviews (R&D and non-R&D)

- N01DA-6-1129: NIDA's Science Meetings Logistical Support
- N01DA-6-8866: Development and Manufacture of Pharmaceutical Products
- N01DA-6-8867: Pharmacokinetic and Pharmacodynamic Studies for Medication Development

Phase I SBIR Reviews

- N43DA-7-7757 (Topic 083): Establishment of High Quality C57BL/6 ES Cell Lines

Phase II SBIR Reviews

- N44DA-6-5530 (Topic 073): Online Buprenorphine Practice Manager for Physicians

R&D Concept Reviews

- N01DA-7-8870: Pharmacokinetic Analysis Resource Center
- N43DA-7-4408: Develop a Real-time fMRI Feedback System that Allows Drug Abusers to Control Cravings and Urges and/or Increase their Self-Control of their Drug Taking
- N43DA-7-2209: Automation of the Development of Electronic Data Capture (EDC) System for Clinical Trials Data Collection and Management
- N43DA-7-5536: Development of State-of-the-Art Mechanisms for Epidemiological Research
- N43DA-7-2210: Development of Practical Training Materials for Evidence-Based Treatment
- N43DA-7-8868: Design and Synthesis of Treatment Agents for Drug Abuse
- N43DA-7-7760: Metabolomics in Drug Abuse Research
- N43DA-7-1131: Mechanisms and Methods to Maximize Data Utilization
- N43DA-7-5535: Marketing Evidence-Based Prevention Interventions for Substance Abuse and Related HIV Prevention

CTN-Related Review Activities

The Data and Safety Monitoring Board (DSMB) conducted a review on May 26, 2006 via Web conference. The board discussed the Final Study Reports of three studies: CTN 0009 Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs, CTN 0011 A Feasibility Study of a Telephone Enhancement Procedure (TELE) to Improve Participation in Continuing Care Activities, and CTN 0003 Bup/Nx: Comparison of Two Taper Schedules.

The DSMB met on July 27, 2006 in Bethesda, MD to review and discuss the study protocol: CTN 0014 Brief Strategic Family Therapy for Adolescent Drug

Publications

Staff Highlights

Grantee Honors

Abusers (BSFT); and to discuss the Final Study Reports of studies CTN 0004 MET (Motivational Enhancement Treatment) To Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse and CTN 0021 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse).

Certificates of Confidentiality

Between April 28, 2006 and August 14, 2006, OEA prepared 83 new Certificates, 37 Certificate extensions, and 4 Certificate amendments.

Extramural Outreach

Dr. Rita Liu, OEA, participated in a NIH Grantsmanship Workshop On July 12, 2006 for the 2006 International Narcotics Research Conference (INRC) in St. Paul, MN. This Workshop was co-sponsored by the University of Minnesota Postdoc Association. Other participants from NIH were Dr. Christine Colvis of the Division of Basic Neuroscience and Behavioral Research, NIDA, and Dr. Sayed Hussain of the Center for Scientific Review, NIH.

Dr. Rita Liu co-chaired a NIH Grants Writing Workshop on July 19, 2006, at the 11th SCBA (Society for Chinese Bioscientists in America) International Symposium in San Francisco, covering the topic of Peer Review aspects of the grant application process. Other participants from NIH were Dr. Yen Li of NIAID and Dr. Roy Wu of NCI.

Dr. Teresa Levitin, Director, OEA, gave a presentation in San Francisco on electronic grant submission of applications in July 2006 at the 11th International Symposium of the Society of Chinese Bioscientists in America.

Dr. Levitin served as faculty for a workshop in May 2006 on grant writing for graduate students and new faculty at the 18th Annual Convention of the Association for Psychological Science in New York.

Dr. Eliane Lazar-Wesley, OEA, gave a presentation entitled "Training and Career Opportunities at NIDA" at the INRC meeting in Minneapolis in July 2006.

Dr. Gerald McLaughlin, OEA, is the NIDA Liaison to the NIH-wide committee dealing with all aspects of the transition to electronic grant submission. He presented a 90-minute educational talk on this topic to the 2006 HMO Research Network Conference, and has provided brochures and other presentation materials to NIDA staff to disseminate at additional professional meetings including the 2006 American Society of Addiction Medicine, the Prevention Sciences meeting, and others.

Dr. Gerald McLaughlin has co-arranged sessions for review staff of NINDS/NIMH/NIDA to learn inter-Institute operating and training procedures in these Institutes' review units.

Dr. Gerald McLaughlin is a member of the trans-NIH workgroup that addresses issues related to public or community members in peer review meetings, and attended a COPR meeting in which related issues were discussed with the NIH OD. He is also updating NIDA guidelines for public and community reviewers.

Dr. Gerald McLaughlin is a member of the trans-NIH workgroup tasked with implementing the electronic transition of the R01 and U01 grant mechanisms.

Dr. Gerald McLaughlin is a member of the trans-NIH workgroup to improve technologies and SOP's associated with contract-provided reviewer lodging and review meeting room arrangements. He is also the NIDA representative to this group's parent trans-NIH PSA Review User Group transition team. He is also

preparing related NIDA OEA's guidelines.

Dr. Mark Green, OEA, continues to participate on the NIH-wide Electronic Submission/424 Contingency Workgroup that deals with emerging issues related to the transition to electronic submission of grant applications.

Dr. Mark Green ran a mock review at the June 2006 NIDA International Forum to introduce international researchers to the peer review process.

Dr. Mark Green made a presentation "Update on Electronic Grant Submission and Process for Foreign Investigators" at the June 2006 NIDA International Forum.

Dr. Teri Levitin co-chaired with Dr. Mark Green a workshop at the June 2006 CPDD meeting entitled "Job Interviews: Tips, Tricks, and Traps". The panelists were Dr. Linda Cottler, Dr. Barry Hoffer, Dr. Mary Jeanne Kreek, and Dr. James Smith.

Dr. Mark Green co-chaired with Dr. Teri Levitin a workshop at the June 2006 CPDD meeting entitled "What's New at NIDA and NIH: Electronic Submission of Applications and More."

Dr. Mark Green presented a talk about the NIH peer review process as part of the workshop on Grant Writing at the June meeting of CPDD.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the spring and summer. Topics included a number of policy updates including changes to the PHS 398, SF424 and PHS 2590 instructions; required disclaimer/acknowledgement of NIH support on R13/U13 mechanisms; pilot study to shorten the review cycle for new investigator R01s; publication by OER of the new NIH Extramural NEXUS bimonthly update for grantees and applicants; Katrina supplements/extensions; DEAS re-engineering; changes to summary statement format; initiatives to examine the need for appendix materials and the possibility of shortening the length of the research plan in grant applications; K99/R00 review update.

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Congressional Affairs (Prepared September 12, 2006)

Labor-HHS Appropriation FY 2007

The Senate Appropriations Committee approved its FY 2007 Labor-HHS-Education appropriations bill (S. 3708; S. Rept. 109-287) on July 20, 2006 after the Labor-HHS-Education Subcommittee passed the bill on July 18, 2006. The bill provides $142.8 billion in discretionary funding for FY 2007, an increase of nearly $1.27 billion (0.9 percent) over the current year's funding level. The House Appropriations Committee approved its version of the bill (H.R. 5647; H. Rept. 109-515) on June 13 after the Labor-HHS-Education Subcommittee marked up the bill June 7. The bill provides $141.9 billion in discretionary funding, an increase of $712 million (0.5 percent) over the comparable FY 2006 funding level.

National Institutes of Health: The Senate bill includes a program level of $28.459 billion for NIH, an increase of $220 million (0.8 percent) over the FY 2006 comparable amount. The program level includes an appropriation of $28.551 billion, minus $100 million transferred from NIH to the Global AIDS/HIV Fund, plus the transfer of $8.2 million in evaluation funds to the National Library of Medicine. The Senate bill is $201 million over the program level of $28.258 billion in the House bill.

NIDA: The Senate bill includes $1,000,342,000 for NIDA, an increase of $1,000,000 (.1%) over the FY 2006 level (including the 1% government-wide recission). The House bill includes $994,829,000, which is equal to the President's request - a decrease of $4.5 million (.5%)

Outlook: At this point the outlook for appropriations is unclear. Most sources of information seem to indicate that the Labor-HHS appropriations bill will remain contentious, with final action occurring some time after the November elections.

Hearings, Briefings, and Events of Interest

Prevention Congressional Briefing Sponsored by the Friends of NIDA

On June 12, 2006, the Friends of NIDA sponsored a Congressional Briefing titled "Preventing Drug Abuse: Putting Science to Practice for Real World Solutions." NIDA Director Dr. Nora Volkow provided overview comments on NIDA's prevention research portfolio. In addition to Dr. Volkow, Dr. Richard Spoth (Director, Partnerships in Prevention Science Institute, Iowa State University) presented empirical findings from his 15 years of NIDA-funded experimental research on partnership-based implementation of a range of interventions for youth and families, including long-term positive outcomes, economic benefits, success of the evidence-based PROSPER partnership model,

and future directions in partnership network development.

For a community perspective on the issue, Ms. Diane Eckert, a leader in a Fairfax, Virginia community-based prevention coalition, discussed how evidence based practices have been effective within her community. Anna Freund, a Fairfax high school student, provided a youth perspective on the problem of adolescent drug abuse, and shared her experiences as a young advocate educating her peers on the risks and costs of drug abuse.

The briefing drew an audience of approximately 100 people, comprised largely of congressional staff and representatives of NIDA's various constituent organizations. Presentations from this briefing and a fact sheet on prevention research can be found at http://www.thefriendsofnida.org/briefing-2006-06.php.

House Hearing on Methamphetamine Addiction Treatment

On June 28, 2006, the House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources conducted a hearing entitled, "Availability and Effectiveness of Programs to Treat Victims of the Methamphetamine Epidemic." The hearing was led by Subcommittee Chairman Mark Souder (R-IN) and Ranking Member Elijah Cummings (D-MD).

Witnesses providing testimony to the Subcommittee included Mr. Charles Currie, Administrator of the Substance Abuse and Mental Health Services Administration (SAMHSA); Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA); Dr. Bertha Madras, Deputy Director for Demand Reduction at the White House Office of National Control Drug Policy (ONDCP); Ms. Leah Heaston, Director for Noble County (Indiana) of the Otis R. Bowen Center for Human Services; Dr. Richard Rawson, Associate Director of Integrated Substance Abuse Programs at the UCLA; Mr. Russell Cronkhite, an individual in recovery from addiction to methamphetamine; Mr. Darren and Ms. Aaronette Noble, individuals in recovery from addiction to methamphetamine, and their son, Joey Binckley; Mr. Michael Harle, President and CEO of Gaudenzia, Inc.; and Mr. Pat Fleming, Director of Salt Lake County Substance Abuse Services.

In his opening statement to the Subcommittee, Chairman Souder countered the misconception that drug treatment services are not effective for people addicted to methamphetamine, stating that methamphetamine addiction can be treated effectively. Chairman Souder did express his concern that effective treatment for people addicted to methamphetamine is not available where people need it the most and that a treatment vacuum exists. Chairman Souder also noted that while there currently are no approved medications for methamphetamine treatment, intense behavioral interventions have proven effective. Ranking Member Cummings, in his comments to the Subcommittee, also spoke about the effectiveness of treatment for addiction to methamphetamine and other drugs. Congressman Cummings, emphasizing the importance of getting people with alcohol and other drug problems into treatment, noted the connection between drug use, crime, and risky behaviors including those that can cause transmission of HIV and other diseases.

Dr. Volkow, in her testimony to the Subcommittee, explained how methamphetamine is extremely addictive and that addiction to methamphetamine (indeed addiction generally) is a disease of the brain. Dr. Volkow also spoke about how treatment for addiction to methamphetamine is effective and that NIDA continues to research emerging types of behavioral interventions and medications to assist in the treatment process. Dr. Volkow cited the intersection between addiction and crime, and spoke about NIDA's Criminal Justice Drug Abuse Treatment Research Studies (CJ-DATS), a major research initiative that has brought together researchers, criminal justice professionals, and addiction treatment providers to develop new strategies to

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help individuals in the criminal justice system with histories of drug use and addiction.

House Hearing on Prescription Drug Abuse

On July 26, 2006, the House Committee on Government Reform Subcommittee on Criminal Justice, Drug Policy, and Human Services held a hearing entitled "Prescription Drug Abuse: What is Being Done to Address this New Drug Epidemic?" The hearing was co-chaired by Congressman Mark Souder (R-IN), Chairman of the Subcommittee and Congressman Elijah Cummings (D-MD), Ranking Member of the Subcommittee. The first panel included: Dr. Bertha Madras, Deputy Director, Demand Reduction, Office of National Drug Control Policy; Dr. Nora Volkow, Director, National Institute on Drug Abuse; Dr. Sandra Kweder, Deputy Director, Office of New Drugs, Food and Drug Administration; and Joseph Rannazzisi, Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Agency. Included in the second panel were three mothers who each lost a son to prescription drug misuse, Misty Fetco, Linda Surks, and Barbara van Rooyan; Mathea Falco, J.D., President, Drug Strategies; Stephen Johnson, Executive Director, Commercial Planning, Pain Therapeutics, Inc; Dr. Laxmaiah Manchikanti, CEO, American Society for Interventional Pain Physicians; and Steve Pasierb, President and CEO, the Partnership for a Drug-Free America.

In his opening statement, Representative Souder remarked that the non-medical use of prescription drugs is not receiving enough attention and expressed his concern that this form of drug use is increasingly common and serving as a pathway to misuse of other drugs. Rep. Souder stated that the abuse of prescription drugs is a problem of epidemic proportions that demands focused attention and aggressive action by both the government and the private sectors. Representative Cummings began by expressing that the non-medical use of prescription and over the counter medications is not a new problem, and that there is a dangerous misperception that pharmaceuticals are not harmful. Rep. Cummings outlined his ideas for action steps, which include requiring that purchases for prescriptions from online pharmacies involve a valid prescription and identification of the purchaser, prescription drug monitoring programs, education of the public, creation of drug formulations that are resistant to abuse, and preventing illegal diversion.

In her testimony, Dr. Volkow acknowledged the extreme importance, and beneficial uses of prescription drugs, in particular psychotherapeutics, as well as their substantial abuse potential. She agreed with Rep. Souder that the problem of non-medical use of prescription drugs is urgent and is not receiving the attention it needs. She noted NIDA's particular concern with the increase in prescription drug abuse over the past five years among adolescents, the potential misuse or unintentional use by older Americans as well as potential misuse by women. Dr. Volkow spoke about NIDA's efforts to address this issue including the work of the Community Epidemiology Work Group (CEWG) sites that provide ongoing community-level surveillance of drug abuse profiles through analysis of quantitative and qualitative research data. Dr. Volkow spoke to the Subcommittee about NIDA's multi-pronged strategy aimed at better understanding the prescription drug phenomena, including an initiative on "Prescription Opioid Use and Abuse in the Treatment of Pain" and conducting a multi-center study through their Clinical Trials Network (CTN) to evaluate treatment regimens using oral buprenorphine/naloxone. In closing, Dr. Volkow assured the Subcommittee that NIDA's close collaborations with physician's organizations, the Office of National Drug Control Policy (ONDCP), SAMHSA and other Federal agencies, as well as professional associations would continue.

Congressional Symposium on Use of Buprenorphine for Treatment of Opioid Addiction

On August 3, 2006, Senators Carl Levin (D-MI) and Orrin Hatch (R-UT) sponsored a bipartisan press conference and symposium on the use of buprenorphine for the treatment of opioid addiction. The event provided an opportunity for federal officials, individuals in recovery, and addiction treatment and medical professionals to discuss both the positive and negative experiences associated with use of the medication. In addition the briefing's sponsors sought to increase public awareness about buprenorphine since less than two percent of primary care physicians have applied for certification to dispense the drug. Presenters spoke about how buprenorphine has proven successful in treating people with addictions to heroin as well as other opioids such as Vicodin and OxyContin. Speakers at the press conference and symposium included: Senators Hatch and Levin; Dr. Nora Volkow, Director of the National Institute on Drug Abuse; Dr. Westley Clark, Director of the Center for Substance Abuse Treatment at the Substance Abuse and Mental Health Services Administration (SAMHSA); Dr. Herbert Kleber, Director of the Division on Substance Abuse in the College of Physicians and Surgeons at Columbia University; Dr. Charles Schuster, Professor of Psychiatry and Behavioral Neuroscience at the Wayne State University School of Medicine; Dr. David Fiellin, Associate Professor of Medicine at Yale University School of Medicine; Dr. Jim Finch, Family Practice Physician from Durham, North Carolina; and Terry Horton, M.D., Medical Director, Phoenix House.

Senator Carl Levin provided comments at the symposium, discussing legislation he cosponsored and helped to pass into law, "the Drug Abuse Treatment Act of 2000." This legislation modified the Controlled Substances Act to allow the dissemination of opioids for the use of drug treatment in doctor's offices. However, Senator Levin and a number of the other presenters expressed concern that the current law requires that doctors maintain a limit of 30 patients who are under their care and for whom they are prescribing buprenorphine, and argued that this policy is a significant barrier to dissemination of the medication. A number of the physicians presenting at the symposium reported having to turn people away because they were either at or over their 30 patient limit and that they felt this conflicted with a doctor's professional and moral obligation to provide treatment to those in need.

Dr. Volkow provided comments on the value of using buprenorphine to treat opioid addiction; in particular its effectiveness in relieving drug cravings without potential for dependence or dangerous side effects. Dr. Volkow stated that although new and effective medications are available, individuals with opioid addiction cannot readily obtain them because of an insufficient infrastructure for their distribution. In addition, Dr. Volkow noted the stigma still associated with medication-assisted treatment but expressed that buprenorphine presents an opportunity for people to seek help and live healthy, productive lives. Dr. Westley Clark of the Center for Substance Abuse Treatment (CSAT) stated that the availability of buprenorphine in office-based settings will open more doors to treatment. He emphasized that buprenorphine represents an important breakthrough because it has proven to be effective in treating addiction to both non-prescription and prescription opioids.

Additional speakers, including a number of physicians and researchers, expressed that buprenorphine is a significant medical breakthrough and that the medication positively impacts the way that heroin addiction can be treated. Because doctors are now able to prescribe the drug in their offices a number of the speakers emphasized there is potential that more people will seek treatment because of the lack of stigma attached to visiting a private doctor and receiving a prescription. Also discussed was the adoption by Phoenix House, a primarily abstinence-based model of long-term drug treatment, of the short term use of buprenorphine-naloxone as an initial bridge to continued care and to improve access to their program. In addition, two individuals who have taken buprenorphine to assist with their opioid addiction spoke about their positive experiences with the medication and how it has helped their recovery

process.

Additional information about the symposium can be found on Senator Levin's website.

PASSED BILLS OF INTEREST — 109th Congress

H.R. 3 - This law was originally introduced by Representative Young (R-AK) as the "Transportation Equity Act: A Legacy for Users," a bill to authorize funds for federal aid for highways, highway safety programs, and transit programs. The original House version of this bill included language (Section 2013 "Drug Impaired Driving Research and Prevention Act") that would require the development of a model statute for States relating to drug impaired driving. The model would include threshold levels of impairment for a controlled substance; methods for detecting the presence of controlled substances; and penalties for drug impaired driving. It would be based on recommendations contained in a report to be developed by NIH and submitted to Congress not later than 18 months after the date of enactment. The final version of the law maintains the requirements for model statute development, and for a report to be developed on the problem of drug-impaired driving. The Secretary of Transportation will develop the report, "in cooperation with the National Institutes of Health." The President signed the bill into law (109-59) on August 10.

H.R. 2520/S. 1317 - On December 20, 2005 the President signed into law, as Public Law 109-129, the Stem Cell Therapeutic and Research Act of 2005. H.R. 2520 passed the House on May 24, 2005. An amended version passed the Senate on December 16, and the House on December 17. The bill does not have a direct impact on NIH. It would require the Secretary of HHS, acting through the Director of the Health Resources and Services Administration, to establish the C.W. Bill Young Cell Transplantation Program, a network of cord blood banks to facilitate the use of cord blood for transplantation purposes. Cord blood units that are collected, but not appropriate for clinical use, would be required to be made available for peer-reviewed research.

H.R. 3199 - On March 2nd, the full Senate approved the conference report for H.R. 3199, the USA PATRIOT and Terrorism Prevention Reauthorization Act of 2005. The House of Representatives approved the final legislative package on March 8th. Provisions from the "Combat Meth Act," the "Drug Courts Improvement Act," and "The Meth Epidemic Elimination Act" were included in the legislation, which was signed into law (P.L. 109-177) by the President on March 9.

This law imposes federal regulations on the sale of products containing pseudoephedrine by requiring stores to keep medications with pseudoephedrine behind the counter and by requiring purchasers of the medication to show photo identification and sign a log. In addition, individuals are restricted from buying more than 3.6 grams per day and 9 grams per month of pseudoephedrine. The law does not preclude states from adopting or enforcing regulations or penalties more strict than those in the federal law.

The law also creates a sentencing enhancement for individuals convicted of manufacturing, distributing, or possessing with the intent to manufacture or distribute, methamphetamine on a premises where children reside. Under this provision, in addition to any other sentence imposed, another sentence of imprisonment for a period up 20 years, a fine or both would be applied. The Attorney General is authorized under the bill to award grants to States, territories, and American Indian tribes to address use of methamphetamine among pregnant and parenting women in the criminal justice system by facilitating or enhancing collaboration between the criminal justice, child welfare and State substance abuse systems.

S. 45/H.R. 869 - Senator Carl Levin (D-MI) in the Senate and Representative Mark Souder (R-IN) in the House introduced identical bills to amend the Controlled Substances Act to lift the patient limitation on prescribing drug addiction treatments by medical practitioners in group practices, and for other purposes. Both the House and Senate passed their bills and the President signed it into law (P.L. 109-56) on August 2. This law will impact practices that prescribe buprenorphine products for treatment of opiate addiction, making the medication available to more patients across the country.

S. 518/H.R. 1132 - Senator Sessions (R-AL) in the Senate and Representative Whitfield (R-KY) in the House introduced identical bills, the "National All Schedules Prescription Electronic Reporting Act of 2005." This law (P.L. 109-60) will provide for the establishment of a controlled substance monitoring program in each State; it was signed by the President on August 11.

H.R. 2829 - On March 9th, the House passed this bill, legislation to reauthorize the Office of National Drug Control Policy (ONDCP). The bill enhances certain current ONDCP functions, and does not address the banning and testing for anabolic steroids in professional sports. A number of amendments to the legislation were offered during consideration on the House floor. Successful amendments to the original bill text will:

- Require the ONDCP Director to complete an assessment of report materials, studies, and statistics to determine the extent to which children who are 12 to 17 years of age (a) experiment with and regularly use marijuana, alcohol, cigarettes, prescription drugs without a prescription, designer drugs such as ecstasy, other illicit drugs such as cocaine, and (b) have access to intervention services or programs, including drug testing, counseling, rehabilitation, legal representation and other services or programs associated with prevention, treatment and punishment of substance abuse.
- Require the ONDCP Director to submit to Congress a comprehensive strategy that addresses the increased threat from methamphetamine.
- Require the ONDCP Director to provide for a corporation to (a) advise States on establishing laws and policies to address alcohol and other drug issues, based on the model State drug laws developed by the President's Commission on Model State Drug Laws in 1993, and (b) revise such model State drug laws and draft supplementary model State laws to take into consideration changes in the alcohol and drug abuse problems in the State involved.
- Require the ONDCP Director to request the Institute of Medicine to conduct a study to examine certain aspects of addiction to prescription drugs such as OxyContin.
- Require the ONDCP Director to conduct a study on drug court programs that conduct hearings in nontraditional public places such as schools.
- Direct the ONDCP Director, in consultation with the Secretary of State, the Attorney General, the Secretary of Homeland Security, the Secretary of Health and Human Services, and the United States Trade Representative, to seek to convene an international summit on the threat of methamphetamine and synthetic drug precursors.

S. 3504 - On July 18, the Senate passed S. 3504, the Fetus Farming Prohibition Act of 2006, by a vote of 100-0. The House also passed S. 3504 on July 18 by a vote of 425-0. The bill was signed by the President on July 19 and became Public-Law 109-242. The bill was introduced on June 13 by Senator Rick Santorum (R-PA), and would prohibit soliciting or knowingly receiving or accepting a donation of human fetal tissue knowing that "a human pregnancy was deliberately initiated to provide such tissue." The bill would also prohibit receiving or accepting tissues or cells "obtained from a human embryo or fetus that was gestated in the uterus of a nonhuman animal."

S. 3525 - On July 13th, the full Senate approved S. 3525, the "Improving Outcomes for Children Affected by Meth Act of 2006." The Senate-approved bill would reauthorize the Safe and Stable Families program within the Department of Health and Human Services and would authorize additional funding for treatment programs that serve parents who are addicted to methamphetamine and their families. On July 25th the full House approved a different version of S. 3525 named the "Child and Family Services Improvement Act of 2006." The House-approved version of the legislation also reauthorizes the Safe and Stable Families program, but does not include the provisions on improving access to methamphetamine addiction treatment found in the Senate bill.

H. Res. 556/S. Res. 313 - On April 6, the House passed a resolution stating that (1) a National Methamphetamine Prevention Week should be established to increase awareness of methamphetamine and educate the public on effective ways to help prevent methamphetamine use at the international, Federal, State, and local levels; and (2) the people of the United States and interested groups should be encouraged to observe National Methamphetamine Prevention Week with appropriate ceremonies and activities. The Senate passed the resolution on May 15.

BILLS OF INTEREST - SENATE

[For the full text and additional information about any bill, go to the Library of Congress website at http://thomas.loc.gov]

S. 103 - Senator Talent (R-MO) introduced on January 24, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and use of methamphetamine in the United States, and for other purposes. See above, H.R. 3199, for final disposition.

S. 259 - Senator Johnson (D-SD) introduced on February 2, 2005 a bill to require that federal forfeiture funds be used, in part, to clean up methamphetamine laboratories. Committee: Judiciary.

S. 399 - Senators Coleman (R-MN) and Feinstein (D-CA) introduced on February 16, 2005 the Internet Pharmacy Consumer Protection Act, to amend the Federal Food, Drug, and Cosmetic Act with respect to the sale of prescription drugs through the Internet, and for other purposes. Committee: Health, Education, Labor, and Pensions. Related bill: H.R. 840.

S. 408 - Senator DeWine (R-OH) introduced on February 16, 2005 the "STOP Underage Drinking Act." In part, the bill would authorize the Director of ONDCP to award "enhancement grants" to eligible entities to design, test, evaluate and disseminate strategies to maximize the effectiveness of community-wide approaches to preventing and reducing underage drinking. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 864.

S. 521 - Senator Hutchison (R-TX) introduced on March 3, 2005 the "Hepatitis C Epidemic Control and Prevention Act," a bill to amend the Public Health Service Act to direct the Secretary HHS to establish, promote, and support a comprehensive prevention, research, and medical management referral program for hepatitis C virus infection. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 1290.

S. 537 - Senator Bingaman (D-NM) introduced on March 7, 2005 the "Child Healthcare Crisis Relief Act" a bill to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to children and adolescents, and for other purposes. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 1106.

S. 538 - Senator Biden (D-DE) introduced on March 7, 2005 the "Health

Professionals Substance Abuse Education Act." In introductory remarks, he explained that the bill would do three things for each of the fiscal years 2006 thru 2010: (1) authorize $9 million in grants to train medical generalists to recognize substance abuse and know properly how to refer patients and their families for treatment; (2) authorize $6 million to fund a faculty fellowship program at educational institutions to teach courses on substance abuse, incorporate substance abuse issues into required courses, and educate health professionals about matters involving non-therapeutic uses of prescription medications; and (3) authorize $6 million to establish centers of excellence at medical centers or universities to initiate and implement training, research and clinical activities related to special focal areas of substance abuse, and provide opportunities for interdisciplinary collaboration in curriculum development, clinical practice, research and policy analysis. Committee: Health, Education, Labor and Pensions. Related bill: H.R. 1789.

S. 550 - On September 21, former Senator John Corzine (D-NJ) introduced S. 550, the Microbicide Development Act, to facilitate the development of microbicides for preventing transmission of HIV and other diseases, and for other purposes. Research provisions would require the Director of the NIH Office of AIDS Research to: 1) expedite implementation of a Federal microbicide research and development strategic plan, 2) expand, intensify and coordinate the relevant activities of appropriate NIH research components, and 3) prepare and submit, within six months of enactment and annually thereafter, a report to Congress on Federal microbicide research implementation strategies. The bill would also require the Director of NIAID to establish a microbicide development unit within its Division of AIDS. The measure also contains provisions for relevant activities at the CDC and the U.S. Agency for International Development. Committee: Health, Education, Labor and Pensions. Related bill: H.R. 3854.

S. 666 - Senator DeWine (R-OH) introduced on March 17, 2005 the "Family Smoking Prevention and Tobacco Control Act," a bill to protect the public health by providing the FDA with certain authority to regulate tobacco products. Committee: Health, Education, Labor and Pensions. Related bill: H.R. 1376.

S. 803 - Senators Norm Coleman (R-MN) and Hillary Rodham Clinton (D-NY) introduced on April 14, 2005 the "Help Expand Access to Recovery and Treatment Act of 2005," to provide parity with respect to substance abuse treatment benefits under group health plans and health insurance coverage. Committee: Health, Education, Labor and Pensions. Related Bills, see H.R. 1258.

S. 884 - Senator Cantwell (D-WA) introduced on April 25, 2005 the "Methamphetamine and Identity Theft Study Act of 2005," instructing the Attorney General to conduct a study evaluating whether there is a connection between the commission of crimes involving methamphetamine and the commission of identity theft crimes. Committee: Judiciary. Related Bill: H.R. 3325.

S. 927 - Former Senator Corzine (D-NJ) introduced on April 27, 2005 the "Medicare Mental Health Modernization Act of 2005," which would amend Title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare program. Committee: Finance. Related Bills: See H.R. 1946.

S. 930 - On April 27, Senator Charles Grassley (R-IA) introduced the FDA Safety Act of 2005, to amend the Federal Food, Drug, and Cosmetic Act with respect to drug safety, and for other purposes. Committee: Health, Education, Labor, and Pensions. Related bill: H.R. 4429.

S. 1051 - Senator Dodd (D-CT) introduced on May 17, 2005 the "Children and Family HIV/AIDS Research and Care Act of 2005," to amend the Public Health

Service Act to reauthorize and extend certain programs to provide coordinated services and research with respect to children and families with HIV/AIDS. Committee: Health, Education, Labor, and Pensions.

S. 1332 - On June 29, Senator Arlen Specter (R-PA) introduced S. 1332, the Personal Data Privacy and Security Act of 2005. Of specific interest to NIH, the measure would prohibit the display, sale or purchase of Social Security numbers (SSNs) to third parties without an individual's informed consent. Exemptions are included for public health and research conducted for the purpose of advancing public knowledge. Researchers would be required to provide adequate assurances that the SSNs will not be used inappropriately, and that there are safeguards to protect the privacy and confidentiality of any information about individuals. S. 1332, which has two cosponsors, was placed on the Senate Legislative Calendar under General Orders.

S. 1334 - On June 29, Senator Bunning (R-KY) introduced the "Professional Sports Integrity and Accountability Act," to provide for integrity and accountability in professional sports. In late September, the Commerce, Science and Transportation Committee held a hearing to discuss the bill. Committees: Finance; Commerce, Science and Transportation.

S. 1436 - On July 20, Senator Mike DeWine (R-OH) introduced S. 1436, the Campus-Based Underage Alcohol Use Reduction Act. The bill would require the Secretary of Education to award grants to reduce the rate of underage alcohol use and binge drinking among students at institutions of higher education. Committee: Health, Education, Labor, and Pensions.

S. 1722 - On September 19th, Senator Lisa Murkowski (R-AK) introduced S. 1722, the "Advancing FASD Research, Prevention, and Services Act." This legislation would amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program. S. 1722 would require the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health and in coordination with the Interagency Coordinating Committee on Fetal Alcohol Syndrome to establish a research agenda for Fetal Alcohol Spectrum Disorders (FASD) and award grants, contracts, or cooperative agreements to public or private nonprofit entities to pay all or part of carrying out research under such agenda. Committee: Health, Education, Labor, and Pensions. Related bill HR 4212.

S. 1934 - On October 27th, several cosponsoring Senators introduced the "Second Chance Act of 2005: Community Safety Through Recidivism Prevention." of 2005," which would reauthorize the grant program of the Department of Justice for reentry of offenders into the community, to establish a task force on Federal programs and activities relating to the reentry of offenders into the community, and for other purposes. Committee: Judiciary. Related bill: see H.R.1704.

S. 1960 - On November 3, Senator Jim Bunning (R-KY) introduced S. 1960, the Integrity in Professional Sports Act, to protect the health and safety of all athletes, to promote the integrity of professional sports by establishing minimum standards for the testing of steroids and other performance-enhancing substances and methods by professional sports leagues, and for other purposes. Status: Placed on Senate legislative calendar under general orders.

S. 1974 - On November 8, Senator Bill Nelson (D-FL) introduced S. 1974, the Drug Free Varsity Sports Act of 2005. The bill would provide states with the resources needed to rid our schools of performance enhancing drug use. Committee: Health, Education, Labor, and Pensions.

S. 2046 - On November 17, Senator Mike DeWine (R-OH) introduced S. 2046, the National Methamphetamine Information Clearinghouse Act of 2005, to

establish a National Methamphetamine Information Clearinghouse to promote sharing information regarding successful law enforcement, treatment, environmental, social services, and other programs related to the production, use, or effects of methamphetamine and grants available for such programs, and for other purposes. Committee: Judiciary.

S. 2104 - On December 14, Senator Joseph Lieberman (D-CT) introduced the "American Center for Cures Act of 2005," to amend the Public Health Service Act to establish the American Center for Cures to accelerate the development of public and private research efforts towards tools and therapies for human diseases with the goal of early disease detection, prevention, and cures. Specific aims of this proposed legislation are to: 1) expedite translational research and 2) implement some recommendations from the 2003 NAS study entitled "Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges." Committee: Health, Education, Labor, and Pensions.

S. 2315 - On February 16, Senator Burns (R-MT) introduced the "Methamphetamine Awareness and Prevention Act of 2006," to amend the Public Health Service Act to establish a federally-supported education and awareness campaign for the prevention of methamphetamine use. Committee: Health, Education, Labor, and Pensions.

S. 2560 - On April 6, Senator Specter (R-PA) introduced the "Office of National Drug Control Policy Reauthorization Act of 2006" to authorize and enhance the operations of the Office of National Drug Control Policy. The bill as introduced differs significantly from its related House bill (H.R. 2829). Committee: Judiciary. Reported favorably by the Judiciary Committee on May 25, 2006. Floor action pending.

S. 2643 - On April 25, Senator Bingaman (D-NM) introduced the "Native American Methamphetamine Enforcement and Treatment Act of 2006," To amend the Omnibus Crime Control and Safe Streets Act of 1968 to clarify that Indian tribes are eligible to receive grants for confronting the use of methamphetamine. Committee: Judiciary.

S. 2695 - On May 2, Senators Cornyn (R-TX) and Lieberman (D-CT) introduced the "Federal Research Public Access Act of 2006," which would require every Federal agency with an annual extramural research budget of $100 million or more to implement a public access policy that is consistent with and advances purposes of the Federal agency. The bill requires that articles resulting from Federally funded research be deposited in a public archive and made available no later than six months after publication in a peer-reviewed journal. Committee: Homeland Security and Governmental Affairs.

S. 2754 - On July 18, the Senate passed S. 2754, the Alternative Pluripotent Stem Cells Therapies Enhancement Act, by a vote of 100-0. The bill was introduced on May 5 by Senator Rick Santorum (R-PA), and would require NIH to fund peer-reviewed research to develop techniques for the isolation and production of pluripotent stem cells, without deriving such cells from human embryos. The bill would also require the Secretary, in consultation with the Director of NIH, to issue guidelines within 90 days of the bill's enactment that would outline and prioritize such research. The House considered the measure on July 18 under "suspension of the rules," but it failed by a vote of 273-154 (2/3 required for passage). The bill may be considered by the House again under general House rules which would require a simple majority for passage.

S. 3055 - On May 25, Senator James Talent (R-MO) introduced the Family Based Meth Treatment Act of 2006, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other purposes. Committee: Health, Education, Labor and Pensions. Related Bill: H.R.

5493.

S.3557 - On June 22, Senator Richard Durbin introduced the Drug Overdose Reduction Act, authorizing funding to train first responders, law enforcement officials and corrections officials on how to recognize and respond to an overdose. Funding also would be available for drug overdose prevention programs that provide direct services to people most at risk of an overdose death. Committee: Health, Education, Labor and Pensions.

S. 3834 - On August 3, Senators Jeff Sessions (R-AL) and Diane Feinstein (D-CA) introduced the Online Pharmacy Consumer Protection Act, to prohibit online sale of medications and controlled substances without valid prescriptions. Committee: Judiciary.

S. Res. 462 - On May 3, Senator Grassley (R-IA) introduced a resolution "designating June 6, 2006 as the day of a National Vigil for Lost Promise, to call public attention to the tremendous promise which has been lost with the deaths of those affected by drugs.

BILLS OF INTEREST - HOUSE

H.R. 240 - Representative Pryce (R-OH) introduced on January 4, 2005 the "Personal Responsibility, Work, and Family Promotion Act of 2005." The bill, which would extend welfare legislation, was approved by the Ways and Means Committee's Human Resources Subcommittee on March 15, 2005. The subcommittee amended the bill to cut federal welfare funding to any state that does not drug test those applying for or receiving welfare benefits. No state currently drug tests welfare recipients. In fact, a 2003 ruling by a federal appeals court that covers the states of Kentucky, Michigan, Ohio, and Tennessee ruled that states cannot drug test welfare recipients because it is unconstitutional. Those states, and many others, could lose federal funding if the drug testing provision makes it into law. Status: pending at House Financial Services.

H.R. 314 - Representative Blunt (R-MO) introduced on January 25, 2005 the "Combat Meth Act of 2005," a bill to respond to the illegal production, distribution, and use of methamphetamine in the United States, and for other purposes. See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 370 - Representative Bilirakis (R-FL) introduced on January 26, 2005 the "Biomedical Research Assistance Voluntary Option Act," a bill to amend the Internal Revenue Service Code to allow taxpayers to designate part or all of any income tax refund be paid for use in biomedical research conducted through the NIH. Committees: Energy and Commerce, Subcommittee on Health; Ways and Means.

H.R. 798 - Representative Gordon (D-TN) introduced on February 16, 2005 the "Methamphetamine Remediation Research Act of 2005," a bill to provide for a research program for remediation of closed methamphetamine production laboratories, and for other purposes. Committee: Science, Subcommittee on Environment, Technology, and Standards. Status: passed by the House. Pending in the Senate (Environment and Public Works).

H.R. 810 - On July 17, the Senate passed H.R. 810, the Stem Cell Research Enhancement Act of 2005," by a vote of 63-37. The bill had previously passed the House on May 24 by a vote of 238-194. The bill, which would have effectively overturned the President's 2001 stem cell policy, would have required NIH to fund research on human embryonic stem cells notwithstanding the date on which such cells were derived. The measure was vetoed by the President on July 19. The House failed to override the veto by a vote of 235-193 (2/3 required for a successful override motion).

H.R. 812 - Representative Cummings (D-MD) introduced on February 16, 2005 the "Dawson Family Community Protection Act," a bill to amend the Office of National Drug Control Policy Reauthorization Act of 1998 to ensure that adequate funding is provided for certain high intensity drug trafficking areas. Committees: Government Reform; Energy and Commerce. The text of this bill was included in the Office of National Drug Control Policy Reauthorization Act of 2005 (H.R. 2829) which passed the House on March 9).

H.R. 840 - Representative Tom Davis (R-VA) introduced on February 16, 2005 a bill to amend the federal Food, Drug and Cosmetic Act with respect to the sale of prescription drugs through the internet, and for other purposes. Committee: Energy and Commerce, Subcommittee on Health. Related Bill: S. 399.

H.R. 864 - Representative Roybal-Allard (D-CA) introduced on February 16, 2005 a bill to provide for programs and activities with respect to the prevention of underage drinking. Committee: Energy and Commerce, Subcommittee on Health. Related Bills: See S. 408.

H.R. 1020 - Representative Rogers (R-MI) introduced on March 1, 2005 a bill to declare adequate pain care research, education, and treatment as national public health priorities, and for other purposes. In part the bill would establish within NIH a center to be known as the National Center for Pain and Palliative Care Research. Committees: Energy and Commerce, Subcommittee on Health; Veterans Affairs, Subcommittee on Health; Ways and Means; Armed Services.

H.R. 1054 - Representative Green (R-WI) introduced on March 2, 2005 the "Tools for Community Initiatives Act," which would establish an Office of Faith Based and Community Initiatives in the Executive Office of the President. Committee: Government Reform.

H.R. 1055 - Representative Hooley (D-OR) introduced on March 2, 2005 the "Comprehensive Methamphetamine Response Act," a bill to provide for the designation and funding of high intensity methamphetamine abuse and trafficking areas. Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related bill: see H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1056 - Representative Hooley (D-OR) introduced on March 2, 2005 the "Methamphetamine Precursor Control Act of 2005," a bill to amend the Controlled Substances Act with respect to the distribution of pseudoephedrine. Section 7 of the bill would authorize funding for NIH to conduct research on medical alternatives to pseudoephedrine. Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related bill: See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1106 - Representative Kennedy (D-RI) introduced on March 3, 2005 the "Veterans Medical Research Assistance Voluntary Option Act of 2005," a bill to increase the number of well-trained mental health service professionals (including those based in schools) providing clinical mental health care to children and adolescents, and for other purposes. Committees: Energy and Commerce, Subcommittee on Health; Ways and Means. Related Bills: See S.537.

H.R. 1258 - Representative Ramstad (R-MN) introduced on March 10, 2005 the "Time for Recovery and Equal Access to Treatment in America (TREAT America) Act, a bill to amend the Employee Retirement Income Security Act of 1974, PHSA and the IRS Code of 1986 to provide parity with respect to substance abuse treatment benefits under group health plans and health insurance coverage. Committees: Energy and Commerce, Subcommittee on Health; Education and Workforce, Subcommittee on Employer-Employee Relations; Ways and Means. Related Bills: See S. 803.

H.R. 1290 - Representative Wilson (R-NM) introduced on March 14, 2005 the "Hepatitis C Epidemic Control Prevention Act," to require the Secretary of Health and Human Services to establish, promote, and support a comprehensive prevention, research, and medical management referral program for hepatitis C virus infection. The bill also would require the Director of NIH to establish a Liver Disease Research Advisory Board, which would be charged with developing a Liver Disease Research Plan. Committee: Energy and Commerce, Subcommittee on Health. Related Bills: See S. 521.

H.R. 1350 - Representative Peterson (D-MN) introduced on March 16, 2005 the "Methamphetamine Blister Pack Loophole Elimination Act of 2005," a bill to eliminate the safe-harbor exception for certain packaged pseudoephedrine products used in the manufacture of methamphetamine. Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related Bills: See H.R. 1446. Related bill: See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1357 - Representative Weldon (R-FL) introduced on March 17, 2005, the Human Cloning Prohibition Act of 2005, a bill to prohibit human cloning. Committee: House Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security.

H.R. 1376 - Representative Davis (R-VA) introduced on March 17, 2005 the "Family Smoking Prevention and Tobacco Control Act," a bill to protect the public health by providing the FDA with certain authority to regulate tobacco products. The bill text states that the use of tobacco products by the Nation's children is a pediatric disease of considerable proportions that results in new generations of tobacco-dependent children and adults and that nicotine is an addictive drug. Committee: Energy and Commerce, Subcommittee on Health. Related bill: S. 666.

H.R. 1378 - Representative Emerson (R-MO) introduced on March 17, 2005 the "Ephedrine Alkaloids Regulation Act of 2005," a bill to amend the Controlled Substances Act with respect to regulation of ephedrine alkaloids, including ephedrine and pseudoephedrine. The bill states that methamphetamine is a highly addictive drug that can be readily made from products and precursors purchased from retail stores. Committee: Energy and Commerce, Subcommittee on Health. Related bill: See H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1402 - Representative Kennedy (D-RI) introduced on March 17, 2005 the "Paul Wellstone Mental Health Equitable Treatment Act of 2005," a bill to provide for equal coverage of mental health benefits with respect to health insurance coverage unless comparable limitations are imposed on medical and surgical benefits. Committees: Education and the Workforce, Subcommittee on Employer-Employee Relations; Energy and Commerce, Subcommittee on Health.

H.R. 1446 - Representative Souder (R-IN) introduced on March 17, 2005 the "Methamphetamine Abuse Prevention Act of 2005," a bill to eliminate the safe-harbor exception for certain packaged pseudoephedrine products used in the manufacture of methamphetamine, Committees: Energy and Commerce, Subcommittee on Health; Judiciary. Related Bills: See H.R.1350; see H.R. 3199 above, under "Passed Bills of Interest."

H.R. 1528 - Representative James Sensenbrenner (R-WI) introduced on April 6, 2005 the "Defending America's Most Vulnerable: Safe Access to Drug Treatment and Child Protection Act of 2005," which would amend the Controlled Substances Act to protect vulnerable persons from drug trafficking, and for other purposes. Committees: Energy and Commerce, Subcommittee on Health; Judiciary, Subcommittee on Crime, Terrorism and Homeland Security.

H.R. 1639 - Representative DeLauro (D-CT) introduced on April 14, 2005 the

"Military Health Services Improvement Act of 2005," which would require pre- and post-deployment mental health screenings for members of the Armed Forces, and for other purposes. Committee: Armed Services.

H.R. 1704 - Representative Portman (R-OH [now resigned from the House]) introduced on April 19, 2005 the "Second Chance Act: Community Safety Through Recidivism Prevention Act of 2005," which would reauthorize the grant program of the Department of Justice for reentry of offenders into the community, to establish a task force on Federal programs and activities relating to the reentry of offenders into the community, and for other purposes. Committees: Judiciary; Education and the Workforce. Related bill: see S. 1934. The bill was marked up and reported favorably by the Judiciary Committee on July 26, 2006. House floor action is pending.

H.R. 1758 - Representative Andrews (D-NJ) introduced on April 21, 2005 the "Open Air Drug Market Penalty Act of 2005," which would amend the Controlled Substances Act to provide penalties for open air drug markets, and for other purposes. Committees: Judiciary; Energy and Commerce.

H.R. 1789 - Representative Kennedy (D-RI) introduced on April 21, 2005 the "Health Professionals Substance Abuse Education Act," designed to educate health professionals concerning substance use disorders and addiction. Committee: Energy and Commerce. Related Bill: See S. 538.

H.R. 1808 - On April 21, Representative Greg Walden (R-WA) introduced the Safe Online Drug Act of 2005, to amend the Federal Food, Drug, and Cosmetic Act to create a uniform certification standard for Internet pharmacies and to prohibit Internet pharmacies from engaging in certain advertising activities, to prohibit the use of certain bank instruments for purchases associated with illegal Internet pharmacies, and for other purposes. Committees: Energy and Commerce; Financial Services.

H.R. 1862 - Representative Stearns (R-FL) introduced on April 26, 2005 the "Drug Free Sports Act," which would direct the Secretary of Commerce to issue regulations requiring testing for steroids and other performance-enhancing substances for certain sports associations engaged in interstate commerce. Committee: Education and Commerce; Education and the Workforce.

H.R. 1946 - Representative Stark (D-CA) introduced on April 27, 2005 the "Medicare Mental Health Modernization Act of 2005," which would amend Title XVIII of the Social Security Act to expand and improve coverage of mental health services under the Medicare program. Committees: Ways and Means; Energy and Commerce. Related Bills: See S. 927.

H.R. 2087 - Representative Frank (D-MA) introduced on May 4, 2005 the "States' Rights to Medical Marijuana Act," which would provide for the medical use of marijuana in accordance with the laws of the various States. Committee: Energy and Commerce.

H.R. 2124 - Representative Weldon (R-FL) introduced on May 5, 2005 the "Clinical Research Act of 2005," which would amend the Public Health Service Act to provide for clinical research support grants, clinical research infrastructure grants, and a demonstration program on partnerships in clinical research, and for other purposes. Committee: Energy and Commerce.

H.R. 2195 - Representative Lynch (D-MA) introduced on May 5, 2005 the "Act to Ban Oxycontin," which would provide for the withdrawal of the drug OxyContin from the commercial market. Committee: Energy and Commerce.

H.R. 2565 - Representative Davis (R-VA) on May 24 introduced the "Office of National Drug Control Policy Reauthorization Act," to reauthorize the Office of National Drug Control Policy Act and to establish minimum drug testing standards for major professional sports leagues. Committees: Government

Reform, Energy and Commerce, Education and the Workforce. Related bill: see H.R. 2829 - House leadership chose to move forward with this bill regarding ONDCP reauthorization.

H.R. 3084 - On June 28, Representative Cliff Stearns (R-FL) introduced H.R. 3084, the Drug Free Sports Act of 2005. The bill would direct the Secretary of Commerce to issue regulations requiring testing for steroids and other performance enhancing substances for certain sports associations engaged in interstate commerce. The bill would also require the Secretary of Health and Human Services, in consultation with the NIDA Director, to prescribe the substances for which professional athletes are tested, establish criteria by which professional sports associations may provide substances to athletes prior to or after any drug test, and establish criteria for test administration. The measure also calls for penalties for a positive test, and criteria under which the names of athletes testing positive may be disclosed. Committees: Energy and Commerce, Education and the Workforce. Status: Reported by all committees, awaiting further action.

H.R. 3196 - On June 30, Representative Henry Waxman (D-CA) introduced H.R. 3196, the Fair Access to Clinical Trials Act (FACT). The measure would require sponsors of privately and publicly funded studies of drugs, biologics, or medical devices to register using a database that builds on the National Library of Medicine's www.clinicaltrials.gov. It would provide public access to basic information on studies before they begin, such as the disease or condition with which the trial is concerned, the hypothesis being tested, the sponsor and principal investigator, and the sources of funding. Public access to the results of clinical studies, including primary and secondary outcomes and significant adverse events, would also be permitted under the legislation. H.R. 3196 also would authorize the Secretary of HHS to impose penalties for noncompliance, including revoking a sponsor's eligibility for further Federal funding and imposing civil money penalties. Committee: Committee on Energy and Commerce.

H.R. 3325 - On July 18, Representative David Reichert introduced the Methamphetamine and Identity Theft Study Act of 2005, to conduct a study evaluating whether there are correlations between the commission of methamphetamine crimes and identity theft crimes. Committee: Judiciary. Related Bill: S.884.

H.R. 3739 - On September 13th, Representative John Boozman (R-AR) introduced the "Drug Courts Improvement Act of 2005." This Act would amend existing law by requiring the Attorney General to set uniform standards for mandatory drug testing that drug courts receiving funds from the Department of Justice's (DOJ) Drug Court grant program would be required to follow. In addition, the legislation would require drug courts receiving grant money from this federal program to impose mandatory sanctions whenever a participant fails a drug test. Committee: Judiciary. Text from this bill was included in H.R. 3199 - see above under "Passed bills of Interest."

H.R. 3854 - On September 21, Representative Christopher Shays (R-CT) introduced H.R. 3854, the Microbicide Development Act, to facilitate the development of microbicides for preventing transmission of HIV and other diseases, and for other purposes. Research provisions would require the Director of the NIH Office of AIDS Research to: 1) expedite implementation of a Federal microbicide research and development strategic plan, 2) expand, intensify and coordinate the relevant activities of appropriate NIH research components, and 3) prepare and submit, within six months of enactment and annually thereafter, a report to Congress on Federal microbicide research implementation strategies. The bill would also require the Director of NIAID to establish a microbicide development unit within its Division of AIDS. The measure also contains provisions for relevant activities at the CDC and the U.S. Agency for International Development. Committees: Energy and Commerce,

International Relations. Related bill: see S.550.

H.R. 3889 - On September 22, Representative Mark Souder introduced H.R. 3889, the "Methamphetamine Epidemic Elimination Act," to further regulate and punish illicit conduct relating to methamphetamine, and for other purposes. Status: passed by the House. Related bill and legislative action: see S. 103, H.R. 314. See above H.R. 3199, under "Passed Bills of Interest."

H.R. 3942 - On September 29, Representative James Sensenbrenner (R-WI) introduced the Professional Sports Responsibility Act of 2005, to establish a Federal Office of Steroids Testing Enforcement and Prevention to establish and enforce standards for the testing for the illegal use in professional sports of performance enhancing substances and other controlled substances. Committees: Judiciary; Energy and Commerce; Education and the Workforce.

H.R. 3955 - On September 29, Representative Steve King (R-IA) introduced the "Meth Lab Eradication Act," to amend the Controlled Substances Act to provide for the transfer of ephedrine, pseudoephedrine, and phenylpropanolamine to schedule V of the schedules of controlled substances, and for other purposes. Committees: Energy and Commerce; Judiciary.

H.R. 4212 - On November 2, Representative Frank Pallone (D-NJ) introduced the Advancing FASD Research, Prevention, and Services Act, to amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program, and for other purposes. Committees: Energy and Commerce; Education and the Workforce. Related bill: see S. 1722.

H.R. 4272 - On November 9, Representative Sam Farr (D-CA) introduced H.R. 4272, the "Steve McWilliams Truth in Trials Act," to amend the Controlled Substances Act to provide an affirmative defense for the medical use of marijuana in accordance with the laws of the various states, and for other purposes. Committees: Judiciary; Energy and Commerce.

H.R. 4429 - On April 27, Representative John Tierney (D-MA) introduced the FDA Safety Act of 2005, to amend the Federal Food, Drug, and Cosmetic Act with respect to drug safety, and for other purposes. Committee: Energy and Commerce. Related bill: S.930.

H.R. 4763 - On February 15th, Representative Oberstar (D-MN) introduced the "Methamphetamine Eradication Act," provide a comprehensive Federal response to the problems relating to methamphetamine use and addiction. Committees: Judiciary; Energy and Commerce; Science, Education and the Workforce; Transportation and Infrastructure Committees.

H.R. 4769 - On February 16th, Representative Charles Norwood (R-GA) introduced the "Prescription Drug Abuse Elimination Act of 2006," to amend the Federal Food, Drug, and Cosmetic Act, the Controlled Substances Import and Export Act, and the Public Health Service Act to impose requirements respecting Internet pharmacies, to require manufacturers to implement chain-of-custody procedures, to restrict an exemption respecting the importation of controlled substances for personal use, and for other purposes. Committee: Energy and Commerce.

H.R. 4910 - On March 8, Representative Ed Whitfield (R-KY) introduced the "National Drug Testing Integrity Act," to prohibit the manufacture, sale, marketing, or distribution of products or substances designed or intended to defraud a drug test. Committee: Energy and Commerce.

H.R. 5493 - On May 25, Representative Barbary Cubin (R-WY) introduced the Family Based Meth Treatment Access Act of 2006, to amend the Public Health Service Act regarding residential treatment programs for pregnant and parenting women, a program to reduce substance abuse among nonviolent offenders, and for other purposes. Committee: Commerce and Energy,

Subcommittee on Health. Related bill: S. 3055.

H.R. 5526 - On June 6, Representative Roscoe Bartlett (R-MD), with cosponsor Representative Phil Gingrey (R-GA) introduced H.R. 5526, the Alternative Pluripotent Stem Cell Therapies Enhancement Act. The bill would require NIH to fund peer-reviewed research to develop techniques for the isolation and production of pluripotent stem cells, without deriving such cells from human embryos. The bill would also require the Secretary, in consultation with the Director of NIH, to issue guidelines within 90 days of the bill's enactment that would outline and prioritize such research. In the bill, the term "human embryo" has the meaning given in the applicable appropriations act. The applicable appropriations act is defined as the appropriations act providing funding for HHS in the fiscal year the research is conducted or supported. If there were no definition in that year's appropriation act, then the applicable appropriations act would be the act of the previous fiscal year. H.R. 5526 is a companion, or identical version, of S. 2754, legislation introduced by Senators Rick Santorum (R-PA) and Arlen Specter (R-PA) on May 5. Committee: Energy and Commerce, Subcommittee on Health.

H.R. 5975 - On July 28, Representative Tom Allen (D-MD) introduced H.R. 5975, the Prescription Drug Comparativeness Effectiveness Act of 2006. The bill would require Agency for Healthcare Research and Quality, in consultation with NIH, to conduct research to develop valid scientific evidence regarding comparative clinical effectiveness, outcomes, and appropriateness of prescription drugs, medical devices, and procedures. Representative Allen's bill from the 108th Congress tasked NIH as the lead for conducting such research. Committee: Energy and Commerce.

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International Activities

NIDA International Forum

Global Drug Abuse Research Community and NIDA Staff Focus on Drug Control, Regional Networks, and Priorities
More than 289 registrants from 53 countries participated in the NIDA International Forum, which was held June 16-19, 2006, in Scottsdale, Arizona. Drug abuse research being conducted around the world, international drug control debates, regional and treatment-based drug abuse research networks, Web-based tools for drug abuse scientists, and updates on NIDA research interests and funding priorities were the highlights of the 2006 NIDA International Forum: International Trends and Needs in Drug Abuse Research. The meeting, which was held immediately before the Annual Scientific Meeting of the College on Problems of Drug Dependence, was organized by the NIDA International Program and featured plenary, workshop, or poster presentations by the following NIDA staff members: Steven W. Gust and Dale Weiss, IP; David Shurtleff, DBNBR: Kevin P. Conway and Joseph Frascella, DCNBR; Wilson M. Compton and Jack Stein, DESPR; Jag H. Khalsa, Ivan Montoya, and Frank Vocci, DPMCDA; Jacques Normand, AIDS Research Program; Betty Tai, CCTN; Mark Green, OEA; and Steven R. Goldberg and Barry J. Hoffer, IRP.

The keynote address was delivered by Dr. Willem Scholten, World Health Organization, who summarized international drug control policies and described how efforts to prevent abuse and trafficking can interfere with legitimate medical access to controlled substances. He discussed the public health benefits of treating opioid dependence with methadone and buprenorphine, and argued that all countries should permit access to these medically necessary controlled substances as an essential human right. NIDA International Program Director Dr. Steven W. Gust reviewed the Institute's research portfolio and described how NIDA is strengthening and stimulating research networks, collaborating with other international funding organizations, and creating Web-based research and training tools. CPDD International Committee Chair Dr. Gabrielle Fischer, Austria, introduced the 2006 WHO/NIDA/CPDD International Travelling Fellows, Dr. Konstantyn Dumchev, Ukraine, and Dr. Min Zhao, China. Representatives from NIDA, the Inter-American Drug Abuse Control Commission, United Nations Office on Drugs and Crime (UNODC), the Pan-American Health Organization, the U.S. Department of State, and the National Hispanic Science Network reviewed efforts to address drug addiction and its consequences in Latin America, discussing projects designed to promote regional cooperation on drug abuse research, surveillance, clinical trials, and training programs.

During the poster session, more than 160 drug abuse scientists from around the world presented their research to NIDA Forum and CPDD participants while NIDA representatives presented posters summarizing the goals, research

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interests, international focus, and international funding priorities of 9 Institute components. Forum participants also received copies of the NIDA International Program supplement to Drug and Alcohol Dependence. The peer-reviewed supplement, *Drug Abuse and HIV/AIDS: International Research Lessons and Imperatives*, provides an international perspective on research exploring the intersections between drug abuse and HIV/AIDS.

Workshops focused on submitting competitive grant applications, including a mock grant review and updates on electronic submission requirements; Web-based tools for researchers, including NIDA's forthcoming online *Manual on Opioid Substitution Pharmacotherapies* and the International Society of Addiction Journal Editors online resource for addiction publishing (www.PARINT.org); building a Latin American research network, which was conducted in Spanish; and the UNODC international capacity-building and training network on drug abuse treatment.

NIDA Components Outline International Focus
During the June 2006 NIDA International Forum poster session, representatives from nine NIDA components presented posters summarizing the units' goals, research interests, international focus, and international funding priorities. The posters were prepared for the Division of Basic Neuroscience and Behavioral Research; Division of Clinical Neuroscience and Behavioral Research; Division of Epidemiology, Services and Prevention Research; Division of Pharmacotherapies and Medical Consequences of Drug Abuse; International Program; Intramural Research Program; AIDS Research Program; Center for the Clinical Trials Network; and Special Populations Office.

International Program Summarizes FY 2005 Activities
NIDA International Program activities both foster international cooperation on biomedical and behavioral research into drug abuse and addiction and promote the research priorities of other NIDA components. Current initiatives focus on high impact priority areas, and resources are leveraged through partnerships with other NIH Institutes, international governments, and affiliated research organizations. The International Program now leads a network of scientists who function as full partners with their NIDA-supported U.S. peers to collaborate on drug abuse research nationally, regionally, and globally. A summary of FY 2005 activities supported by the NIDA International Program demonstrates the ways in which international efforts successfully contribute to the NIDA research mission.

First NIDA International Awards of Excellence Presented
The NIDA International Program has inaugurated an award program to recognize mentors, researchers, binational collaborative teams, and individuals who have demonstrated sustained support of the NIDA International Program mission through outstanding contributions to international cooperation in drug abuse research and training. The awards will be presented each June at the NIDA International Forum; two-page written nominations may be submitted to the International Program by March 1. The 2006 NIDA International Program Awards of Excellence were presented to Robert L. Balster, Virginia Commonwealth University, for excellence in mentoring; Flávio Pechansky, Federal University of Rio Grande do Sul, Brazil, for excellence in international leadership; George Woody, University of Pennsylvania, and Edwin Zvartau, Pavlov State Medical University, Russia, for excellence in collaborative research; and to Judy McCormally, IQ Solutions, Inc., for special recognition.

NIDA-Sponsored Meetings

NIDA Supports Latin American Participants at CEWG
As part of its Latin America Initiative, NIDA supported the participation of Latin American scientists at the June 2006 NIDA Community Epidemiology Work Group (CEWG) meeting in Minneapolis, Minnesota. A panel on drug abuse in

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Latin American countries featured reports on drug abuse patterns, trends, and emerging problems in the region. NIDA-supported speakers included Dr. Fernando Salazar, Universidad Peruana Cayetano Heredia, Peru; Dr. Leonel Valdivia, University of Chile; and former NIDA Hubert H. Humphrey Drug Abuse Research Fellow Dr. Vladimir de Andrade Stempliuk, Brazilian Observatory on Drug Information. In addition to their presentations, the Latin American representatives observed the CEWG meeting, including reports by 21 regional representatives, discussions with Federal officials about data sources, and local initiatives such as sobriety high schools and treatment programs. Ms. Marya Hynes Dowell, Inter-American Drug Abuse Control Commission (CICAD) at the Organization of American States, also participated in the meeting.

NHSN Summer Research Training Institute
NIDA supported two Latin American participants at the National Hispanic Science Network Summer Research Training Institute, which was held June 13-20, 2006, at the University of Houston, Texas. Juan Enrique Huerta-Wong, Universidad Autónoma de Nuevo León, Mexico, and Pablo Dragotto, Programa Cambio, Argentina, participated in the week-long graduate student-training institute in drug research methods. Students learn about drug research issues, receive guidance in producing a publishable manuscript on Hispanic-focused drug research, and are introduced to leading Hispanic drug abuse researchers who could serve as mentors.

Research Training and Exchange Programs

NIDA HHH Fellow Earns Doctorate
Former NIDA Hubert H. Humphrey Drug Abuse Research Fellow Evodia Mabuza-Mokoko (South Africa, 1999-2000) has earned her doctoral degree. Dr. Mokoko is now the Social Work Manager for South Africa's Central Drug Authority.

International Visitors

Visitors from Turkmenistan came to NIDA on May 17, 2006. Their visit was part of a U.S. Department of State sponsored program entitled, "Substance Abuse Education, Treatment and Prevention". The visitors are NGO managers working mainly with youth in Turkmenistan. Ms. Kim Zink, International Program contractor staff hosted the visit. Meeting with the visitors from NIDA were Dr. Liz Ginexi, DESPR and Mr. Brian Marquis, OSPC.

On June 5-9, 2006, NIDA staff met with Dr. Shu-Fen Liu, Epidemiology and Education Division Chief, National Bureau of Controlled Drugs, Taiwan Department of Health, and Dr. Liu's assistant, Ms. Chun-Jung Liao. Dr. Liu and Ms. Liao, who were in the United States to attend the June NIDA Community Epidemiology Work Group (CEWG) meeting, met with Dr. Wilson Compton and Ms. Moira O'Brien, DESPR; Dr. Steve Gust and Ms. Dale Weiss, IP; and Dr. Betty Tai, CTN. NIDA also arranged for Dr. Liu and Ms. Liao to visit officials at the Drug Enforcement Administration and the Substance Abuse and Mental Health Services Administration, NIDA grantees at the University of Maryland and Research Triangle Institute, and with CEWG contractor staff.

Dr Leonel Valdivia from the University of Chile visited NIDA on June 8, 2006. Dr. Valdivia discussed his current projects and planned work and heard about NIDA international work in particular its Latin American initiative. Dr. Valdivia met with Dr. Steve Gust and Ms. Dale Weiss, IP.

Two visitors from Romania, Ms. Ramun_ Visockyt_, Member of Parliament and Mr. Saulius Vitk_nas, Director General of the Prison Department, visited NIDA on June 26, 2006. Staff from NIDA met with the visitors to learn about NIDA's prevention and treatment programs.

Mr. Robert George Kroeker, Executive Director, B.C. Crystal Meth Secretariat, Canada visited on July 14, 2006. Mr. Kroeker was in the United States under the auspices of the U.S. Department of State International Visitor Leadership Program to learn more about the U.S. response to treating crystal meth users among other topics. Meeting with Mr. Kroeker from NIDA were Ms. Jan Lipkin, OSPC, Dr. Jim Colliver, DESPR and Dr. Roberta Kahn, DPMCDA.

Dr. Hulya Yuksel from the University of Dumlupinar in Turkey visited NIDA on July 17, 2006. Dr. Yuksel is interested in smoking/tobacco prevention and treatment programs for her country of Turkey. She met with Ms. Debra Grossman, DCNBR, and Ms. Dale Weiss, IP from NIDA.

Other International Activities

Dr. Frank Vocci, Director, DPMCDA, presented on medications development for cocaine dependence at the European Association for Addiction Treatment in London on July 8, 2006.

Dr. Dionne Jones, DESPR, presented on "Research Opportunities at the National Institute on Drug Abuse" at the Caribbean Health Research Council Annual Meeting, St. Kitts, West Indies, April 28, 2006.

Dr. Thomas Hilton, DESPR, participated in a three-day conference April 12 through 14, 2006 in Sofia Bulgaria entitled: "Bridging the Gap Between Science and Practice," during which he presented several papers. He also met with Dr. Valeri Tzekov, Deputy Minister of Health; Dr. Dorita Krasteva, Director of the Sofia Municiple Centre for Addictions and her staff; and Dr. Tsveta Raycheva, Director of the National Centre on Addictions and her staff during which plans were discussed for moving to a case-based patient management system, development of a medical residency program in addictions, and developing a Bulgarian language version of the Addiction Severity Index.

The Prevention Research Branch hosted Dr. Gregor Burkhart of the European Monitoring Centre for Drug and Drug Addiction, Lisbon, Portugal on June 7, 2006 at the Neuroscience Center . Discussion related to the translation of interventions proven to be effective in the United States for use in Europe.

Dr. Rao Rapaka, DBNBR, co-chaired a session titled "Bioactive Lipids and Analytical Lipidology," at the International Cannabinoid Research Society's Annual Meeting in Budapest, Hungary, June 18-24, 2006. He also was a discussant on a panel on European/American Funding Initiatives.

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Meetings/Conferences

The National Institute on Drug Abuse (NIDA), in collaboration with the Center for Substance Abuse Treatment (CSAT), and the National Association of State Alcohol and Drug Abuse Directors (NASADAD) held a meeting **"Blending Research and Practice: Enhancing State Capacity to Implement Evidence-Based Practices,"** on June 4, 2006, in Albuquerque, New Mexico in conjunction with the 2006 Annual NASADAD Conference. This meeting built on a series of meetings held over the past two years to enhance state-based blending of research, practice, and policy to improve the quality of drug abuse services nationwide. The participants discussed and identified strategies for implementing science-based practices in drug abuse treatment and prevention based on State-specific needs.

The National Institute on Drug Abuse (NIDA) convened the first **"Blending Initiative Task Force"** meeting on June 8 and 9, 2006, in Washington DC. The Task Force was chaired by NIDA's Deputy Director, Dr. Timothy Condon and was coordinated by Dr. Denise Pintello, Special Assistant to the Deputy Director. Task Force members reviewed the drug abuse treatment community's needs for evidence-based practices, discussed NIDA's research portfolio and identified criteria to assess the applicability of NIDA-sponsored research for potential NIDA/SAMHSA Blending Teams.

On June 21-23, 2006, NIDA participated in the **10th Anniversary Celebration of the Office of Behavioral and Social Sciences Research, NIH**. For this event, NIDA staff and grantees were involved in a scientific conference and congressional event highlighting behavioral and social science research across the NIH. At these events, NIDA showcased its comprehensive behavioral research portfolio and featured the work of two NIDA grantees in the areas of vulnerability and relapse to drug abuse.

NIDA, in collaboration with **American Psychological Association** (APA) Divisions 28 (Psychopharmacology and Substance Abuse) and 50 (Addictions) organized a large program of research symposia and other events conducted as part of the APA annual meeting held in New Orleans, LA, August 9-13, 2006. In addition to these presentations of NIDA supported research made by NIDA staff and researchers in the field, NIDA, NIAAA and Divisions 28 and 50 sponsored an Early Career Investigators Poster Session and Social Hour. This event provided the opportunity for 70 early career researchers, including several researchers from NIDA's IRP, to travel to the conference and present their work to the members of the Divisions and to interact with senior researchers in the field. The program was organized at NIDA by Meyer Glantz, Ph.D., Minda Lynch, Ph.D., Cora Lee Wetherington, Ph.D., Jane Smither, David Shurtleff, Ph.D., Lula Beatty Ph.D., Melissa Racioppo Ph.D., Teresa Levitin Ph.D., Steven Oversby Ph.D., Janet Levy, Ph.D., Carol Myers, Ph.D., Harold Perl, Ph.D. and Cecelia McNamara Spitznas, Ph.D.

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NIDA awarded 29 **Women & Gender Junior Investigator Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 17-22, 2006, Scottsdale, AZ. These $750 awards, which have been made annually beginning in 2000, are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. To further promote research in this field, NIDA published a mini-program book, *Focus on Women & Sex/Gender Differences*, for the CPDD meeting. Excerpted from the CPPD program book, it contains only those program listings related to women and sex/gender differences. It also contains the CPDD abstracts on women and sex/gender differences, information about the Women & Gender Junior Investigator Travel Awardees, announcement of the travel award program for CPDD 2007, and information on current NIDA program announcements in this area.

NIDA's Special Populations Office developed a three-part **Summer Seminar Series** for NIDA's summer interns and students. Juan Carlos Couto, a HACU intern, coordinated the series. Sessions focused on 1) Understanding Drug Addiction and Its Consequences, 2) Career Opportunities in Drug Abuse Research, and 3) Making A Difference: NIDA's Programs. Participating NIDA staff were Joe Frascella, Yonette Thomas, Lynda Erinoff, Suman Rao King, Paul Schnur, Frank Vocci, Betty Tai, Jack Stein, Kevin Conway and Lula Beatty.

NIDA's Special Populations Office collaborated with the American Psychological Association's Office on AIDS in the development of a web-based resource for racial/ethnic minority students and new investigators interested in HIV research. An APA summer intern, DaRel Barksdale, worked in the SPO office to develop the resource focusing on NIDA and NIH research.

Dr. Timothy P. Condon, Deputy Director, NIDA, provided technical assistance to the Wisconsin legislature and presented "Neurobiology of Addiction" at the Wisconsin Association on Alcohol and Other Drug Abuse conference on May 9, 2006, in Madison, Wisconsin.

Dr. Timothy P. Condon presented an "Update on the Blending Initiative: The Partnership Between the National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA)" at the National Association of State Alcohol/Drug Abuse Directors (NASADAD) conference on Blending Research and Practice: Enhancing State Capacity to Implement Evidence-Based Practices on June 4, 2006, in Albuquerque, New Mexico.

Dr. Timothy P. Condon presented "The National Institute on Drug Abuse (NIDA): Institute and Blending Initiative Update" at the Blending Initiative Task Force Evidence-Based Practices meeting on June 8, 2006, in North Bethesda, Maryland.

Dr. Timothy P. Condon presented "Neurobiology of Addiction: Implications for Relapse" at the Center for Substance Abuse Treatment (CSAT) College on Problems of Drug Dependence (CPDD) Satellite Session on the Science of Relapse Prevention and Recovery Services on June 17, 2006, in Scottsdale, Arizona.

Dr. Timothy P. Condon presented "The NIH Roadmap: Progress and Impact on NIDA" at the 68th College on Problems of Drug Dependence on June 20, 2006, in Scottsdale, Arizona.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt - The Neuroscience of Addiction & Judicial Decision Making" at the Federal Judicial Center's National Workshop for District Judges II on June 22, 2006, in San Diego, California.

Dr. Timothy P. Condon provided an overview of NIDA's Networks at Exploring Opportunities for Information-Sharing and Collaboration across NIDA's

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Networks on July 20, 2006, in North Bethesda, Maryland.

Dr. Timothy P. Condon provided an overview of "NIDA's Principles for Criminal Justice Involved Addicts," to the American Probation and Parole Association Board of Directors, on July 23, 2006, in Chicago, Illinois.

Dr. Timothy P. Condon presented "It's a Brain Disease: Beyond a Reasonable Doubt - The Neuroscience of Addiction & Judicial Decision Making" at the Federal Judicial Center's National Workshop for District Judges III on August 8, 2006, in Denver, Colorado.

Dr. Cindy Miner, Deputy Director, OSPC delivered the Keynote Address at the 2006 Chief Resident Immersion Training Program (CRIT) on May 11, 2006 in Chatham, MA.

Dr. Cindy Miner, Deputy Director, OSPC presented "Reading and Interpreting the Request for Proposals" at the Society for Academic Emergency Medicine 2006 Annual Meeting on May 17, 2007 in San Francisco, CA.

Dr. Cindy Miner, Deputy Director, OSPC co-chaired a Grantwriting Workshop at the CPDD 68th Annual Scientific Meeting Program on June 20, 2006 in Scottsdale, AZ.

Dr. Cindy Miner, Deputy Director, OSPC moderated a session entitled "Who Are NIDA's Networks? What Do They Do?" at the Exploring Opportunities for Information-Sharing and Collaboration across NIDA's Networks Conference on July 20, 2006 in Bethesda, Maryland.

Dr. Cindy Miner, Deputy Director, OSPC chaired a workshop on the "Neurobiology of Addiction" at CADCA's Mid Year Training Institute on August 14-15, 2006 in Las Vegas, Nevada.

Dr. Gayathri Dowling, OSPC, gave a presentation entitled "Methamphetamine: The Science of Addiction and Recovery" as part of a panel, "Addressing Meth and Substance Abuse Comprehensively," at the South/Southeast Methamphetamine Legislative and Policy Planning Conference, convened by the Office of National Drug Control Policy, the Office of Justice Programs/Bureau of Justice Assistance, the Substance Abuse and Mental Health Services Administration and the National Alliance for Model State Drug Laws, in Birmingham, AL on July 13th, 2006.

Dr. Cathrine Sasek, OSPC, participated in a workshop entitled "Beyond Science: Getting SBIR/STTR Social-Behavioral-Education Health Products to the Commercial Marketplace" at the 8th annual NIH SBIR/STTR Conference in Cleveland, Ohio on July 13, 2006.

Dr. Suman Rao King, OSPC, chaired/coordinated the following activities at CPDD, June 17-22, 2006, in Scottsdale, AZ: [1] NIDA Tutorials Workshop at CPDD this year where four NIDA Training Directors presented their research and its future directions to the 30 NIDA Director's Travel Awardees; [2] NIDA Training Mixer, which provided a forum for training directors, trainees, and NIDA staff to learn about the different training programs that NIDA supports; [3] NIDA Grant Writing Workshop where Drs. Cindy Miner, David Shurtleff, Mark Green, and Scott Lukas provided an overview, respectively, on NIDA Research Training opportunities, Program interests, review procedures, and grant writing tips to prospective candidates.

Dr. Suman Rao King participated in writing and presenting on the NIH Research Training and Career Development programs for the Program Assessment Rating Tool (PART) process conducted by the Office of Management and Budget (OMB).

Dr. Suman Rao King presented on August 1, 2006 at the NIDA Summer

Seminar series on "Career Opportunities in Drug Abuse and Addiction Research."

Dr. Lula Beatty, Chief, Special Populations Office, participated as the discussant in the symposium titled "Ethnic Disparities in Drug Abuse Treatment" at the CPDD annual meeting in Scottsdale, AZ in June 2006.

Dr. Lula Beatty presented a talk titled "Minority Health Disparities at NIDA" during the plenary session "New Ideas in Minority Health Disparities: Beyond Descriptive Epidemiology" at the Society for Prevention Research conference in San Antonio, Texas in June 2006.

Dr. Lula Beatty participated as a panelist at the Society for Prevention Research conference in San Antonio, Texas in June 2006. She discussed "Health Disparities at NIDA: Drug Abuse, Criminal Justice, and HIV."

Dr. Lula Beatty participated in a CSAT meeting titled "Healing Historical Trauma in African-Americans" in Gaithersburg in June 2006.

Dr. Lula Beatty chaired a session titled "Preparing Women for Professional Success: Mentoring across Gender and Ethnicity," at the annual convention of the American Psychological Association in New Orleans in August 2006. Panelists included NIDA grantees Lynn Singer and Crystal Fuller.

Dr. Lula Beatty moderated a session titled "Research and Training Funding" at the annual convention of the American Psychological Association in New Orleans in August 2006.

Ana Anders convened and led a meeting of NIDA's Asian American and Pacific Islander Researchers and Scholars Workgroup in Los Angeles, California on July 25-27, 2006.

Flair Lindsey, SPO, coordinated the 10th Summer Research with NIDA program. Through the program, 77 high school and undergraduate students engaged in valuable drug abuse research with over 30 of NIDA's grantees.

In August 2006, Dr. Wilson Compton, Director, DESPR: 1) presented a keynote presentation to the CALDAR Summer Institute, Los Angeles, California, and 2) presented to the Therapeutic Communities of America/NIDA Research Symposium in New York City, New York.

On July 11, 2006, Dr. Compton presented a keynote address to the State Associations of Addiction Services National Conference in Chicago.

During June, 2006 Dr. Compton: 1) presented at the CPDD conference in Scottsdale, Arizona on preparing for revisions to the DSM; 2) co-chaired a meeting to review communication campaign research strategies with the Montana Meth Project in Bethesda, Maryland, and 3) presented to the SMI Pain Therapeutics Conference, London, England on the problem of opioid abuse and addiction.

In May 2006 Dr. Compton made several drug abuse presentations at the American Psychiatric Association annual meeting, Toronto, Canada.

Drs. Meyer Glantz, DESPR, and Steven Grant, DCNBR, cochaired a symposium at the 2006 annual meeting of American Psychological Association held in New Orleans, LA, August 9-13. The symposium was titled, "Inhibitory Dysregulation and Drug Abuse" and addressed the neuronal processes and brain regions revealed by neuroimaging that contribute to inhibitory control deficits in substance abusers. Presenters included Harriet de Wit, Ph.D., Hallam Hurt, M.D., Martin Paulus, Ph.D. and Ralph Tarter, Ph.D. Roy F. Baumeister, Ph.D. served as the Discussant.

Dr. Wilson Compton, Director of DESPR, delivered opening remarks at an NIMH

workshop on Gene x Environment Interactions and Developmental Psychopathology: Research Challenges and Opportunities, in Washington DC in June, 2006. Dr. Naimah Weinberg and Dr. Yonette Thomas of ERB served on the planning committee for this meeting.

Drs. Elizabeth Robertson, Wilson Compton, David Reiss, and Phyllis Panzano gave the Presidential Address titled "Developments in Translational Research" at the 14th annual meeting of the Society for Prevention Research on June 1, 2006 in San Antonio, TX.

Dr. Elizabeth Robertson chaired a session which was organized by Dr. Shakeh Kaftarian at the Society for Prevention Research annual meeting titled "Exploring Intervention Fidelity and Adaptation: Replications that Didn't Work." Session participants included Drs. Gilbert Botvin, Phyllis Ellickson, Richard Spoth, Tena St. Pierre and Ms. Bridget Ryan. This meeting took place in San Antonio, TX on May 31, 2006.

Dr. Elizabeth Robertson gave a presentation at the PRIDE annual conference titled "HIV Prevention: What Youth Should Know" on April 13, 2006 in Washington, DC.

Dr. Yonette Thomas served as faculty for the Hispanic Science Network in June 2006 and presented on the Epidemiology of Drug Abuse.

Dr. Yonette Thomas participated in the 2006 Add Health Users Conference in July 2006 as moderating for the Paper Session on Smoking, Drugs, and Criminal Behavior and as panel member with Drs. David Abrams, Christine Bachrach, and Kathleen Mullan Harris on how Add Health helps OBSSR respond to the "New Horizons in Health" report produced by the Institute of Medicine.

Redonna K. Chandler, Ph.D., presented "Practical Approaches to Substance Abuse Issues: The Role of Judges" as part of a continuing education training for judges at the National Judicial College, March 2006 Reno, NV.

Peter Hartsock, Dr. PH, participated in a meeting of the UNAIDS Uniformed Services Task Force June 6, 2006 in Washington, D.C., at which he described NIDA-supported research on AIDS modeling, particularly on routine HIV testing to reduce new infections and provide treatment to persons who are HIV infected.

Dr. James Colliver of DESPR presented survey and data system findings on methamphetamine use, abuse, dependence and treatment in the NIDA-sponsored symposium on the Methamphetamine Epidemic in the U.S. at the annual meeting of the American Psychiatric Association in Toronto in May 2006.

Dr. Naimah Weinberg organized and chaired a symposium on "Environmental Risk and Substance Use," at the annual meeting of the Behavior Genetics Association in Storrs, CT, in June, 2006. This symposium, sponsored in part by the NIDA Genetics Workgroup, presented four papers and discussant using genetically informative approaches to understanding the contributions of peer and family environment and of gene-environment correlation in the onset of drug use.

Drs. Naimah Weinberg and Kay Wanke of DESPR/ERB, and Dr. Kevin Conway of DCNBR, chaired a session on Gene-Environment Interaction at the June meeting of the NIDA Genetics Consortium in Rockville, MD.

Peter Hartsock, Dr. PH, participated in a meeting at the Center for Strategic and International Studies (CSIS) on "Combating Avian Influenza and HIV/AIDS: Vietnam's National Policy," Washington, D.C., June 19, 2006, where he described NIDA's AIDS modeling research, particularly the work showing that routine HIV testing is a major prevention measure.

Elizabeth Lambert, M.Sc., DESPR, attended the New York HIV Research Centers Consortium 2006 Scientific Conference, "Acute HIV Infection: A Multidisciplinary Symposium," June 12, 2006 in New York City. NIDA and NIMH HIV/AIDS Research Center Grantees jointly sponsored the Conference.

Dr. Shakeh Kaftarian organized a meeting between NIDA and Agency for Healthcare Research and Quality (AHRQ) senior staff to discuss AHRQ's experience using delivery-based research networks in their attempt to reduce the gap between research and practice in multiple disciplines. This meeting took place on Feb 28, 2006, at NIDA.

Dr. Belinda Sims, DESPR, participated in organizing and presenting a pre-conference on the NIH transition to electronic grant submission at the annual meeting of the Society for Prevention Research, held May 30, 2006, in San Antonio, TX.

Drs. Elizabeth Ginexi, PRB, DESPR and Karen Sirocco, BDB, DCNBR organized a Scientific Dialogue at the annual meeting for the Society for Prevention Research in San Antonio, TX on June 1, 2006 titled "Imaging Brain Function: Principles, Methods, and Future Directions." This 90 minute educational session was designed to introduce prevention scientists to the basic methods of neuroimaging. The dialogue was chaired by Dr. Karen Sirocco and the main lecture was delivered by Dr. Scott Huettel of the Brain Imaging and Analysis Center at Duke University.

Drs. Aria Crump and Belinda Sims, DESPR, co-chaired a research roundtable entitled "Evaluating the Inter-Ethnic and Cross-Cultural Relevance of Measures Utilized in Research on Youth Drug Abuse, Violence and Delinquency" at the annual meeting of the Society for Prevention Research, held May 31-June 2, 2006, in San Antonio, TX.

Drs. Belinda Sims and Aria Crump, DESPR, co-chaired a symposium entitled "Adapting Evidence-Based Interventions for Minority and Rural Populations: The Incredible Years Series" at the annual meeting of the Society for Prevention Research, held May 31-June 2, 2006, in San Antonio, TX.

Drs. Augie Diana and Elizabeth Robertson chaired a round table session organized by Dr. Shakeh Kaftarian on "Accelerated Approaches for Development, Implementation, Dissemination and Practice of Prevention Technology" at the Society for Prevention Research annual meeting in San Antonio, TX on June 1, 2006. Roundtable discussants were Drs. Linda Collins, Tony Biglan, and Dennis Embry.

Dr. Elizabeth Ginexi, PRB, DESPR served as the Chair and the Discussant for a Paper Symposium at the annual meeting for the Society for Prevention Research in San Antonio, TX on May 31, 2006 titled "Neurobiological Methods, Measures and Models for Prevention Science." Drs. Philip A. Fisher of the Oregon Social Learning Center, Laurie Miller Brotman of New York University, and Diana H. Fishbein of RTI International presented papers.

Dr. Elizabeth Ginexi, PRB, DESPR served as the Chair for a Paper Symposium at the annual meeting for the Society for Prevention Research in San Antonio, TX on June 1, 2006 titled "Integrating Neurobiological Measures Into Prevention Research." Drs. Marsha Bates of Rutgers University, Jacqueline Bruce of the Oregon Social Learning Center and Jane Joseph of the University of Kentucky presented papers. Michael Bardo, Ph.D. of University of Kentucky led discussion.

Dr. Elizabeth Ginexi, PRB, DESPR served as the Chair and the Discussant for a Paper Symposium at the annual meeting for the Society for Prevention Research in San Antonio, TX on June 2, 2006 titled "A Call For Cross-Disciplinary Research Collaborations: Social-Emotional Neuroscience Meets Prevention Science." Drs. Antoine Bechara of the University of Southern

California, Joan Kaufman of Yale University, and Mark Greenberg of Pennsylvania State University presented papers.

Dr. Aria Crump chaired a joint NIDA-NIMH preconference on the NIH transition to the SF 424 and electronic submission at the Society for Prevention Research Meeting in San Antonio, Texas on May 30, 2006.

Dr. Belinda Sims is a member of the NIH Staff Training in Extramural Programs (STEP) Committee, serving a 3-year term. This trans-NIH committee coordinates training relevant to all of the NIH extramural staff that deal with work place strategies, science for all, and administrative strategies, based on suggestions from staff. On June 5-6, 2006, Dr. Sims attended the annual planning meeting, where topics for the 2006-2007 STEP program were selected. Two topics submitted by NIDA staff were selected and will be developed into forums for the coming year. Also, Dr. Sims was selected to be Chair of the STEP Nominations Committee. This committee will choose the STEP Class of 2010.

Dr. Gina Hijjawi chaired a Scientific Dialogue/Roundtable Discussion at the Society for Prevention Research Conference in San Antonio, Texas on June 2, 2006. The title of the Roundtable Discussion was "The Complexities, Challenges, and Rewards of Conducting International Research in Drug Abuse-Related HIV Prevention." The panel of discussants included: Anne Brisson (Columbia University), Betsy Davis (Oregon Research Institute), Marguerita Lightfoot (University of California, Los Angeles), Melanie M. Domenech Rodriguez (Utah State University), Liz Weiling (University of Minnesota), Steven Gust (NIDA), Richard Jenkins (NIDA) and Eve Reider (NIDA).

Dr. Gina Hijjawi chaired a Scientific Dialogue/Roundtable Discussion at the Society for Prevention Research Conference in San Antonio, Texas on June 2, 2006. The title of the Roundtable Discussion was: "Drug Abuse, Criminal Justice, and HIV Prevention: How Best to Understand and Address Health Disparities." The panel of discussants included: Murelle Harrison (Southern University), Barbara Lopez (University of Miami), Mary Jane Rotheram-Borus (University of California , Los Angeles), Lula Beatty (NIDA), and Eve Reider (NIDA).

Dr. Thomas F. Hilton, DESPR co-presented a two-day grantsmanship workshop March 13 and 14, 2006 with program officials David Chambers at NIMH and Michael Harrison at AHRQ. Over 60 potential grant applicants attended from across the country.

Richard Denisco, M.D., M.P.H. presented "Co-Morbidity of Pain and Substance Abuse Disorders in the United States" at the Annual Meeting of the College of Problems of Drug Dependence in Scottsdale, Arizona, on June 11, 2006. This was part of a presentation regarding the continuing issue of prescription drug-abuse.

Dr. Dionne Jones, DESPR, organized and was Discussant for a panel entitled "Effective Interventions for Drug-Abusing Women At-Risk for HIV/AIDS" at the Annual Meeting of the American Psychological Association, New Orleans, LA, August 10-13, 2006.

Dr. Dionne Jones, DESPR, presented a 2-hour session entitled "Effective Techniques for Proposal Writing." at the United Negro College Fund Special Programs/National Library of Medicine eHealth Conference in Bethesda, MD, June 21, 2006.

An oral abstract presentation,"Epidemiology of Chronic Pain Substance Use Disorders " by Dr. Richard Denisco, et al. was accepted by the American Psychiatric Association, for presentation at their Annual Meeting in Toronto, Canada May, 2006.

On June 15, 2006 the Prevention Research Branch hosted a scientific advisory meeting for the principle of the Montana Meth Project. Ten NIDA funded scientists participated in the meeting which took place at the Embassy Suites Hotel in Washington, DC.

Douglas Rugh, Ph.D., facilitated a panel in Minneapolis, MN, on Monitoring Drug Abuse in New Orleans after Hurricane Katrina. This panel discussion was part of the bi-annual Community Epidemiology Work Group.

Drs. Diane Lawrence, David Shurtleff, and Charles Sharp, all of DBNBR, participated in "Meet the Mentors" session at the annual meeting of the Society for Neuroimmune Pharmacology, Santa Fe, NM, April 2006.

Dr. David Shurtleff, Director, DBNBR, gave a presentation entitled "Research Funding Opportunities: Navigating the NIH System" at the annual meeting of the Society for Neuroimmune Pharmacology, Santa Fe, NM, April 2006.

Drs. Joni Rutter and David Shurtleff, DBNBR, were co-chairs and Dr. Joni Rutter was a discussant in the Symposium entitled, "Pharmacogenetics and Drug Abuse Research" at the American Psychiatric Association Meeting in Toronto, CA in May 2006.

Dr. Christine Colvis, DBNBR, organized and chaired a NIDA/CPDD workshop Entitled "HTS And Pubchem: Nuts And Bolts," at the annual meeting of the College on Problems of Drug Dependence, Scottsdale, AZ, June 2006.

Dr. David Shurtleff chaired a NIDA sponsored symposium entitled "Using Microarrays in Research" at the annual meeting of the College on Problems of Drug Dependence, Scottsdale, AZ, June 2006.

Dr. David Shurtleff gave a presentation entitled "Research Funding Opportunities: The Role of NIDA Program" as part of NIDA's sponsored Grant Writing Workshop at the at the annual meeting of the College on Problems of Drug Dependence, Scottsdale, AZ, June 2006.

Dr. Timothy P. Condon, Deputy Director, NIDA, Dr. Lisa Onken, DCNBR, and Dr. Allison Chausmer, DBNBR, presented Roadmap related information during the "The NIH Roadmap: Opportunities For Inter-Disciplinary Training And Behavioral Research" session at the annual meeting of the College on Problems of Drug Dependence, Scottsdale, AZ, June 2006.

Dr. Joni Rutter, DBNBR, was an invited speaker at the International Narcotics Research Conference in July 2006. Her talk was entitled, "Overview of Pharmacogenetics and Drug Addiction."

Drs. Shurtleff, Schnur and Rapaka, all of DBNBR, organized a NIDA workshop titled, "Obesity and Addiction: Common Neurological Mechanisms and Drug Development," held on May 31-June 2, 2006, in Bethesda, MD. The workshop had six sessions and 25 speakers made presentations. The proceedings will likely be published as a special volume of "Physiology and Behavior."

Dr. David Thomas, DBNBR, co-chaired a workshop on June 12, 2006 in Gatineau, Canada, entitled "Virtual Reality and Pain Reduction," and held at the 11th Annual CyberTherapy 2006 Conference: Virtual Healing: Designing Reality. The purpose of the workshop was to review the current use of virtual reality (VR) for the treatment of pain, and to explore other potential applications of VR in the treatment and prevention of acute and chronic pain. The National Institutes of Health (NIH) Pain Consortium was briefed on the conclusions from this workshop by David Thomas at the June 28th, 2006 Pain Consortium meeting.

Dr. Rao Rapaka, DBNBR, attended the AAPS conference on "Critical Issues in Discovering Quality Clinical Candidates," held in Philadelphia PA, April 24-26,

2006.

Dr. Rapaka conducted 3 scientific sessions at the National Biotechnology Conference of the AAPS, June 18-23, 2006. The 3 sessions were Drug delivery: Filamentous phage for vector-mediated organ targeting, Micro RNAs and drug development, and Caveolae and lipid rafts: Targets for medications development?

Dr. Nancy Pilotte, DBNBR, gave a seminar entitled "Anabolic Steroids and You" at the Jewish Community Center, Rockville, MD in April 2006.

Dr. Allison Chausmer, DBNBR, co-organized and co-chaired two symposia at the World Conference on Tobacco or Health in Washington, D.C., held June 12-15, 2006. The symposia, entitled "Prenatal Nicotine Exposure: What Happens in Adolescence?" and "Nicotine Exposure During Pregnancy: How Does it Relate to Later Behavioral Problems?" represented a collaborative effort between Dr. Chausmer and Dr. Vince Smeriglio of DCNBR.

Ms. Aurora Hutchinson, DBNBR, Dr. Teri Levitin, OEA, Dr. Lisa Onken, DCNBR, and Dr. Cora Lee Wetherington, DBNBR, attended the meeting, "2006 National Conference on Women, Addiction and Recovery: News You Can Use," July 12-14, 2006, in Anaheim, CA. The meeting was jointly sponsored by CSAT/SAMHSA, NIDA, and NIAAA. Drs. Dorynne Czechowicz, Lisa Onken, and Cora Lee Wetherington served on the planning committee. Dr. Wetherington gave a keynote plenary address, "Substance Abuse: Does Gender Matter?"

Dr. Cora Lee Wetherington was an invited "Champion" at the College on Problems of Drug Dependence annual Brunch with Champions event for junior investigators, June 22, 2006, Scottsdale, AZ.

Drs. Tammy Chung, University of Pittsburg, and Cora Lee Wetherington co-organized and co-chaired the symposium, "Adolescent Smoking: Gender-Specific Biological, Social, and Psychological Risk Factors," at the annual meeting of the American Psychological Association, New Orleans, LA, August 10-13, 2006.

Dr. Cora Lee Wetherington delivered the keynote address at the meeting, "Breaking Barriers, Creating Change: Current Thinking on Women and Substance Misuse Across the Lifecycle - Risks and Strengths, Treatment Needs and Outcomes," sponsored by the Kaiser Permanente Division of Research, Oakland, CA, September 15, 2006.

Dr. Minda Lynch, DBNBR, and Dr. David Shurtleff co-organized and chaired a symposium at the American Psychiatric Association 159th Annual Meeting, during May 2006, in Toronto, Ontario. The symposium, entitled "Adolescent Brain Development: Implications for Psychiatric Treatment" was a collaborative effort between DBNBR and DCNBR, with Dr. Larry Stanford serving as discussant for the session. Speakers addressing topics of adolescent brain development, consequences for risk behavior and decision making, and possible interventive approaches, included Drs. Ronald Dahl, Bea Luna, Isabelle Rosso, and Leslie Jacobsen.

Dr. Minda Lynch represented NIDA on the poster session planning committee for NIH's Office of Behavioral and Social Sciences 10th Anniversary Conference at Natcher Auditorium, in June of 2006. Through a coordinated effort from all divisions, offices and programs at NIDA, a poster was prepared on "Reducing the Public Health Burden of Drug Abuse: Behavioral and Social Sciences Research at the National Institute on Drug Abuse." In addition to this display, organized by Dr. Susan Weiss, Dr. Gayathri Dowling, Ms. Anna Staton and Ms. Jennifer Elcano of OSPC, the team also contributed to stories of scientific discovery on the topics of Relapse and Vulnerability, used as accompanying hand-outs to extramural poster presentations by NIDA grantees Drs. Rajita Sinha and Lew Donohugh. NIDA posters were also included in a congressional

reception following the conference, sponsored by the Coalition of Social Sciences Associations.

Drs. Minda Lynch and Nicolette Borek organized and co-chaired a symposium at the American Psychological Association Annual Meeting in New Orleans, LA, during August, 2006. The session, entitled "Environmental influences on brain development - Implications for intervention?" featured presentations and discussion by Drs. Susan Andersen, Megan Gunnar, Michael Debellis and Linda Mayes. The focus of the session was on sensitive periods in brain development, parallel animal and human studies of environmental insult, translational approaches to prevention and intervention, and harnessing neurobiological theories of development to understand functional outcomes and opportunities for optimal therapeutic impact.

Dr. Minda Lynch co-presented a NIH funding talk for the American Psychological Association Science Student Council, with Dr. Ron Abeles from NIH's Office of Behavioral and Social Sciences Research, at the APA annual convention in August, 2006, New Orleans, LA.

Dr. Allison Chausmer, DBNBR, participated on the planning committee for a NIH State-of-the-Science Conference on "Tobacco Use: Prevention, Cessation and Control", held in the Natcher Auditorium June 12-14, 2006.

Dr. Allison Chausmer served on the DHHS Tobacco Work Group that contributed to a Surgeon General's Report on Involuntary Tobacco Exposure, released in June of 2006.

Dr. Paul Schnur, DBNBR, with Dr. William Corrigall (NIDA contractor), completed a site visit with NCDDG project investigators in La Jolla, California on August 14-17, 2006. The meeting involved group presentations from Dr. Henry Lester's group (Cal Tech and Targacept), Dr. Palmer Taylor's group (UCSD) and Dr. Athina Markou's group (UCSD, Scripps).

Dr. Kevin Conway, DCNBR, presented a paper on "Lifetime Comorbidity of DSM-IV Mood and Anxiety Disorders and Specific Drug Use Disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions" at the American Psychiatric Association Meeting, Toronto, Canada, on May 22, 2006.

Dr. Kevin Conway gave a talk entitled "Potential Etiologic Links between Antisocial and Addictive Disorders" at the Mid-America Conference on Co-Occurring Disorders, Indianapolis, Indiana, on June 21, 2006.

Dr. Kevin Conway gave a talk entitled "Epidemiology of Comorbid Antisocial and Addictive Disorders" Mid-America Conference on Co-Occurring Disorders, Indianapolis, Indiana, on June 21, 2006.

Dr. Kevin Conway presented a paper on "Lifetime Comorbidity of DSM-IV Mood and Anxiety Disorders and Specific Drug Use Disorders: Results from the NESARC." College of Problems on Drug Dependence, Scottsdale, Arizona, June 19, 2006.

Dr. Steven Grant and Dr. Melissa Racioppo, DCNBR, co-chaired a symposium titled "What is the Added Value of Social Neuroscience to Drug Abuse Treatment" at the annual meeting of the American Psychological Association held in New Orleans, on August 12, 2006. The participants included Dr. Kevin Ochsner, Columbia University, Dr. Jennifer Beer, University of California, Davis, Dr. Han Brieter, Massachusetts General Hospital and Dr. Gregory Berns, Emory University.

Dr. Laurence Stanford, DCNBR, served as the discussant for a symposium entitled "Adolescent Brain Development: Implications for Psychiatric Treatment, at the annual meeting of The American Psychiatric Association held

in Toronto, Canada on May 22, 2006.

Dr. Steven Grant and Dr. Meyer Glantz, DESPR, co-chaired a symposium titled "Inhibitory Dysregulation and Drug Abuse" at the annual meeting of the American Psychological Association in New Orleans on August 10, 2006. The participants included Dr. Harriet de Wit, University of Chicago, Hallam Hurt, Children's Hospital of Philadelphia, Dr. Martin Paulus, University of California at San Diego, Dr. Ralph Tarter, University of Pittsburgh, and Dr. Roy Baumiester, Florida State University.

Dr. Steven Grant gave a talk entitled "Addiction: The Neurobiology of Free Will Gone Awry" in the Invited Symposium on "Integration of Behavioral and Brain Sciences - Research on the Nature of Addiction" at the annual meeting of the American Psychological Association in New Orleans on August 10, 2006. The other speakers included Dr. Antoine Bechara, University of Southern California, Dr. Warren Bickel, University of Arkansas, and Dr. Charles R. Schuster, Wayne State University.

On June 13, 2006, Dr. Cece Spitznas, DCNBR, was invited to present the CCTN Classroom Series. She gave a talk entitled "Functional Brain Maps Revealed by Independent Component Analysis." Independent Component Analysis (ICA) is a valuable technique for multivariate data-driven analysis of functional magnetic resonance imaging (fMRI) data sets. The session was open to all NIDA staff.

On June 15, 2006, Dr. Joni Rutter, DBNBR, presented the CCTN Classroom Series. She spoke on secondary outcomes analysis on a study testing Buproprion--an antidepressant with modest monoamines uptake inhibition, and mild stimulant effect in animals--for the treatment of methamphetamine dependence. This session was for CCTN staff.

Dr Cece Spitznas, DCNBR, gave a presentation entitled "Community Friendly Treatment: How Can Technology Help" to the Institute through the CTN Classroom, June 13, 2006.

Dr. Cece Spitznas gave a presentation on treatment research at NIDA's National Hispanic Science Network Summer Research Training Institute, on June 16, 2006, at the University of Houston, Houston TX.

Dr. Melissa W. Racioppo, DCNBR, presented at the annual retreat of the K12 trainees of the American Academy of Child and Adolescent Psychiatry (AACAP) in Scottsdale, AZ, June 13 - 16, 2006.

Dr. Lisa Onken, DCNBR, participated in the July 10-11, 2006 NIMH/NIDA/NIAAA meeting of the grantees of the P20 Developing Centers on Suicide in Philadelphia, PA.

Dr. Nicolette Borek, DCNBR, co-chaired a symposium on "Environmental Influences on Brain Development - Implications for Interventions?" at the 2006 American Psychological Association Convention, August 10-13, 2006 in New Orleans. Dr. Borek also spoke on NIDA's Child and Adolescent Funding Opportunities during the session "Practical Guide to Federal Funding for Child-Adolescent Mental Health".

Dr. Karen Sirocco, DCNBR, served as Discussant and Chair of a session on "Imaging Brain Function: Principles, Methods, and Future Directions" at the 2006 Society for Prevention Research Meeting, June 1, 2006, in San Antonio, Texas.

Dr. Joseph Frascella, Director, DCNBR, served as a discussant in the Society for Adolescent Substance Abuse Treatment Effectiveness (SASATE) 5th Annual Meeting entitled "Neuro-Scientific Advances Related to Intervention" held during the CPDD Annual Meeting in Scottsdale, AZ, June 19, 2006.

Dr. Joseph Frascella co-chaired with Dr. Melissa Racioppo a session at the American Psychological Association: "Commonalities between Addiction and Obesity" in New Orleans, August 12, 2006. He also gave a presentation entitled "Common Brain Mechanisms in Addiction and Obesity" in this symposium.

Dr. Joseph Frascella gave a plenary talk at the annual meeting of the National Hispanic Science Network entitled: "The NIH Roadmap's Teams of the Future: Implications for Funding, Training, and Scientific Collaboration" in Scottsdale, AZ, September 13, 2006.

On June 18, 2006, at the College on Problems of Drug Dependence 66th Annual Scientific Meeting, Nathan M. Appel, Ph.D., DPMCDA, co-chaired a symposium entitled: Developments in Methamphetamine Abuse Targets and Pharmacotherapies. The symposium provided an update on several candidate pharmacotherapies that have emerged from different rationales and mechanism-based targets. Dr. Dwoskin reported on lobeline, an alkaloid targeting the vesicular monoamine transporter-2; Dr. Stephen Dewey reported on vigabatrin, an irreversible GABA-transaminase inhibitor; Dr. S. Michael Owens reported on neutralizing monoclonal antibodies directed against methamphetamine; and Dr. Thomas Newton reported on perindopril, an angiotensin converting enzyme inhibitor. Dr. Appel served as the discussant.

On June 20, 2006, at the CPDD Annual Scientific Meeting in Scottsdale, Arizona, Nora Chiang, Ph.D. introduced and chaired the NIDA Medications Workshop: New Opportunities for Chemists and Pharmacologists. David McCann, Ph.D. presented "The Evolution of NIDA's Medications Discovery Programs," Frank Vocci, Ph.D. presented "New Molecular Targets as Potential Pharmacotherapies for Drug Addiction," and Ming Shih, Ph.D. presented "NIDA Resources Supporting Medications Discovery and Development." Rik Kline, Ph.D. served as the discussant.

Dr. Jag Khalsa of the DPMCDA co-chaired a session on Methamphetamine and HIV: A New and Dangerous Epidemic" at the 68th Annual Meeting of the College on Problems of Drug Dependence (CPDD), June 17-22, 2006, Scottsdale, AZ. A combined review paper is in preparation.

Drs. Ivan Montoya, DPMCDA, and Pat Needle co-chaired a workshop during the CPDD International Satellite Conference about opportunities for research collaboration in Latin America.

Drs. Ivan Montoya and Frank Vocci co-chaired a symposium at the American Psychiatric Association meeting in Toronto about smoking cessation in patients with schizophrenia.

Drs. Ivan Montoya and Frank Vocci co-chaired a symposium at the CPDD meeting in Arizona about medications development for marijuana dependence.

Dr. Frank Vocci was the discussant in a symposium entitled "Agonist Pharmacotherapy for Stimulant Abuse and Dependence -- A Viable Option," presented at the Annual Meeting of the American Psychological Association in New Orleans, LA, in August 2006.

On August 31, 2006, Dr. Betty Tai, Director, CCTN, attended the second Organization Meeting of the Principle Investigators for the HIV/AIDS Clinical Trials Networks in Bethesda. The meeting was sponsored by the Division of AIDS, NIAID/NIH.

Dr. Betty Tai attended and presented at the 2006 National Association of State Directors Meeting in Albuquerque, NM on June 3, 2006. Her presentation titled "How does the CTN generate Evidence Based Drug Treatment?"

Two symposia, a workshop, poster and paper were presented at the 27th Annual Meeting of the Society for Clinical Trials by the CCTN. The meeting was

held May 21-24, 2006 in Orlando, Florida: 1) Analytical Issues Unique to Multi-Site Trials: Which Are Resolved and Which Are Still Controversial?; Dr. Paul Wakim, organizer and chair; 2) Group Therapeutic Interventions for Drug Dependence and Mental Health: What Questions to Ask and How to Design Trials to Answer Them?; Dr. Janet Levy, organizer and chair.

Dr. Mary Ellen Michel, Deputy Director, CCTN, was an invited speaker at a workshop on Clinical Trials Networks. She spoke on the sponsor's perspective on networks, including advantages and disadvantages, governance, oversight, budgeting, obstacles and opportunities. Nancy Hamilton, Director of Operation PAR in Florida, and Vice-Chair of the CTN Steering Committee, presented the perspective of a participating clinical center. Michele Straus, Principal Investigator of the Clinical Coordinating Center, EMMES Corporation, presented the role of clinical coordinating centers.

Carmen Rosa, CCTN, presented a poster titled: "Ensuring Good Clinical Practice: A Multi-Level Approach." The poster was co-authored by Royce Sampson (Southern Consortium Node) and Aimee Campbell (Long Island Node).

Dr. Janet Levy, CCTN, presented a paper titled, "Designing Trials to Develop Adaptive Treatment Strategies to Treat Prescription Opioid Dependence." The co-authors are Roger Weiss (Northern New England Node PI) and Carl Pieper (Data and Statistics Center PI).

Dr. Jeng-Jong (JJ) Pan, CCTN, is co-author of the paper entitled "Group Independent Component Analysis Reveals Consistent Resting-State Networks Across Five Sessions", which was presented at the 12th Annual Human Brain Mapping Meeting in Florence, Italy June 11-15, 2006.

Dr. David Liu, CCTN, co-chaired a session at the New Clinical Drug and Evaluation Unit (NCDEU) meeting in Boca Raton, Florida, June 12-15, 2006. The session was entitled, "Pharmacological Treatment of ADHD in Substance-Abusing Adolescents and Adults: New Findings, Research Directions, and Clinical Implications."

Two CTN workshops were held at the College on Problems of Drug Dependence (CPDD) Annual Meeting June 17-22, 2006, in Scottsdale, AZ. The workshops were entitled: 1) HIV/AIDS Research in the NIDA Clinical Trials Network: Emerging Results and 2) Addressing Health Disparities Research in the CTN.

CCTN staff presented a poster and participated in symposia at the American Psychological Association (APA) meeting in New Orleans on August 10, 2006: Dr. Janet Levy presented a poster entitled, "Evolving Clinical Trial and Research Methodology for Studying Drug Dependence."

Dr. Harold Perl, CCTN, participated in two symposia: 1) He chaired the symposium, "Mission to the Gulf: Meeting the Crisis of Hurricane Katrina" and presented a talk entitled, "Responding to Katrina and Rita: Meeting the Mental Health Needs of Evacuees in Central Louisiana." 2) At the second symposium, "Implementation Issues in Evidence Based Practice in Addictions Treatment", he gave a presentation entitled, "Implementation Science and the Adoption of Practice in Addiction Treatment", and served as symposium discussant.

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Media and Education Activities

Press Conference

NIDA Director Dr. Nora D. Volkow and Deputy Director Dr. Timothy Condon joined Chicago Mayor Richard M. Daley, Cook County, Illinois, Chief Judge Timothy Evans, and six individuals in recovery at a July 24, 2006, press conference in Chicago to launch NIDA's Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide. The new publication outlines13 research-based components of successful treatment of drug abusers who have entered the criminal justice system. The press conference was held in Chicago to highlight innovative substance abuse programs underway in the Cook County criminal justice system. These programs include a NIDA-sponsored project that trains judges about the neuroscience of addiction and treatment so they can be better prepared to place addicted defendants in adequate treatment environments. NIDA is planning to expand these trainings to other states as well as part of its commitment to translate research into practice.

Press Releases

July 24, 2006 - NIDA NewsScan #44 - Criminal Justice Issue

- New Research Examines the Relationship Between Greater Punitive Law Enforcement Policies and HIV Prevalence Among Intravenous Drug Users
- Predictors of Unmet Healthcare Needs Among Incarcerated Drug Abusers
- Treatments Enhance Juvenile Drug Court Outcomes
- Incarceration Among Factors That Increase Likelihood of Developing Hepatitis C

July 24, 2006 - NIDA Announces Recommendations to Treat Drug Abusers, Save Money, and Reduce Crime.
The National Institute on Drug Abuse released a landmark scientific report showing that effective treatment of drug abuse and addiction can save communities money and reduce crime. Principles of Drug Abuse Treatment for Criminal Justice Populations outlines some of the proven components for successful treatment of drug abusers who have entered the criminal justice system, leading to lower rates of drug abuse and criminal activity.

July 13, 2006 - Toddlers of Mothers Who Smoked During Pregnancy Show Behavior Problems.
New findings from a study supported by the National Institute on Drug Abuse, suggest that toddlers of women who smoked during pregnancy begin to show a pattern of behavior problems as early as 18-24 months of age. This is the first study to show a link between smoking during pregnancy and child behavior

problems in the first years of life.

June 16, 2006 - NIDA NewsScan #43

- Deficits in Neurocognitive Functions May Affect Outcomes of Preventive Interventions Among Adolescent Boys
- Teens Who Engage in Risky Behaviors Are More Likely To Become Depressed
- Lack of Empowerment on the Job Is Associated With Higher Risk of Drug Abuse
- New Behavioral Intervention Shows Promise in Patients with Co-Occurring Disorders
- PRISM Diagnostic Tool Reliably Diagnoses Substance Abuse, Psychiatric Disorders

May 19, 2006 - NIDA NewsScan #42

- New Research Shows Vaccine May Offer Promising Treatment for Nicotine Addiction
- Psychiatrists Should Be More Alert to Smoking Practices Among Patients in Routine Care
- Numerous Factors Influence Chronic Smoking in Youth, and Many Cross Racial, Ethnic Lines
- Schizophrenics Take In More Nicotine Per Cigarette
- Low-Dose Naltrexone May Help Reduce Weight Gain in Smokers Trying to Quit
- Lifetime Simulation Model Shows Significant Economic Benefits of Methadone Treatment
- Interim Methadone Treatment Increases Likelihood of Future Comprehensive Treatment
- Cocaine Increases Susceptibility to MPTP, a Toxin Known to Cause Symptoms of Parkinson's Disease in Mice

May 15, 2006 - Behaviors May Indicate Risk of Adolescent Depression.
New findings from a study supported by the National Institute on Drug Abuse, show that girls and boys who exhibit high levels of risky behaviors have similar chances of developing symptoms of depression. However, gender differences become apparent with low and moderate levels of risky behaviors with girls being significantly more likely than boys to experience symptoms of depression. The study, which incorporates data from almost 19,000 teens, was published in the May 15, 2006 issue of the *Archives of Women's Mental Health*.

May 11, 2006 - NIDA Research Uncovers the Neurobiology of Dread.
In what is the first brain imaging study of dread, new research supported by the National Institute on Drug Abuse, has shown that people who experience substantial dread about an adverse experience can be biologically distinguished from those who can better tolerate the experience. Understanding how the brains of non-addicted people guide them in selecting what actions to take when the outcome of a decision is unpleasant lays the foundation for further investigations that can compare how drug abusers' brains make such choices. The study was published in the May 5, 2006 issue of the journal *Science*.

April 27, 2006 - 10th Annual PRISM Awards Winners.
Walk The Line," "Without A Trace," "Saturday Night Live," "Reba," "Guiding Light" & "ABC World News Tonight" Received PRISM Nods. The winners of the *10th Annual PRISM Awards* were announced at a gala dinner at the Beverly Hills Hotel. Presented by the Entertainment Industries Council, Inc., in partnership with the National Institute on Drug Abuse, and the FX Network, the *10th Annual PRISM Awards* recognize accurate depictions of drug, alcohol and

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tobacco use and addiction in television, feature film, video, music and comic book entertainment. Donny Deutsch, host of CNBC's "The Big Idea with Donny Deutsch," served as Master of Ceremonies. The *10th Annual PRISM Awards* will air as a one-hour television special on the FX Network at a later date.

Articles of Interest

August 2005, *Ladies Home Journal* - "The Deadliest Drug you've Never Heard Of" - Interview with Joseph Frascella, Ph.D.

July 24, 2006, *Associated Press* - "Drug Experts Urge Better Prison Treatment"—Interview with Nora D. Volkow, M.D.

July 17, 2006, *Wall Street Journal* - "The New Science of Addiction"—Interview with Nora D. Volkow, M.D.

July 4, 2006, *New York Times* - "Scientists Testing Vaccines to Help Smokers Quit"—Interview with Frank Vocci, Ph.D.

June 25, 2006, *New York Times Magazine* - "An Anti-Addiction Pill?"—Interview with Nora D. Volkow, M.D.

June 13, 2006, *Newsday* - "Wired to Overeat? Researchers Study the Anatomy of Food Addiction"—Interview with Nora D. Volkow, M.D.

June 9, 2006, *Washington Post* - "Promise Thrown Away"—Interview with Nora D. Volkow, M.D.

Educational Activities

Heads Up: Real News About Drugs and Your Body.
NIDA and SCHOLASTIC INC. are moving into year 5 of their aggressive outreach to middle school students and teachers in the classroom, with the Heads Up science-based article inserts on drug abuse and addiction. Junior Scholastic, Science World, Up Front, CHOICES, SCOPE, and Action have carried Heads Up articles four times a year since 2003. Each issue is distributed to nearly 2 million students and teachers nationwide in classrooms, with an overall reach of nearly 7 million. In September and October, SCHOLASTIC magazines will be carrying the article The Science of Addiction, once again explaining to a new series of students and reinforcing in others the health risks of abuse and addiction, the disease of addiction, the risks of abusing Vicodin and OxyContin, an individual's risk and protective factors, and prevention resources.

In addition, SCHOLASTIC INC. included a full page spread of NIDA's "chalkboard" print PSA for free in the September 2006 issue of Instructor magazine. This ad directs teachers to NIDA's www.teens.drugabuse.gov website for research-based information for them as well as their students. Instructor has a circulation of 200,000 with a "pass along" readership of 1 million.

Training Judges
NIDA, in collaboration with the Federal Judicial Center, has been involved in an initiative to provide training on addiction and drug abuse to federal judges. Specifically, the training focuses on new approaches to understanding the behavior of drug abusers involved with the criminal justice system and effective ways to treat addiction, including how judges can modify their approach to maximize the benefits of their interventions. Two themes are addressed including: 1) neuroscience research during the past two decades demonstrating that drug abuse is a chronic, relapsing medical condition with characteristic brain and behavioral features, and 2) effective principles of treatment for drug abusers involved with the criminal justice system. NIDA

staff participating in this training include: Dr. Timothy P. Condon, Dr. Wilson Compton, Dr. Redonna K. Chandler, and Dr. Jack Stein.

Conferences/Exhibits

American Psychological Association 114th Annual Convention -- August 10-13, 2006

American Correctional Association 136th Congress Of Correction -- August 12-17, 2006

Latino Behavioral Health Institute 12th Annual Conference -- September 19-21, 2006

American Academy of Family Physicians Scientific Assembly and Exposition -- September 27-October 1, 2006

Society for Neuroscience 36th Annual Meeting -- October 14-18, 2006

NIDA Blending Conference -- October 16-17, 2006

American Academy of Child and Adolescent Psychiatry 54th Annual Meeting -- October 24-29, 2006

American Public Health Association 134th Annual Meeting and Exposition -- November 4-8, 2006

NIDA Conference on HIV -- November 29-29, 2006

Southeast Conference on Alcohol and Drug Addiction 2006 Conference -- November 29-December 2, 2006

American Academy of Addiction Psychiatry Annual Meeting and Symposium -- December 7-10, 2006

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Planned Meetings

NIDA will host "*Blending Addiction Science & Practice: Bridges to the Future*" at the Washington State Convention and Trade Center in Seattle, October 16-17, 2006. This 2-day conference will bring together clinicians and researchers, to examine cutting-edge findings about drug use and addiction and their application to clinical practice.

The National Institute on Drug Abuse (NIDA) is collaborating with the American Psychiatric Association (APA) to hold a major research based track at the APA Annual Meeting in San Diego, CA, May 19-24, 2007. The first major NIDA/APA track was held at the 1998 APA meeting in Toronto and then again at the 2004 APA meeting in New York City. In 2004 NIDA organized 26 sessions, including 7 major lectures. NIDA anticipates another highly successful program at the meeting in 2007.

Eve Reider, Ph.D., Deputy Branch Chief of DESPR's Prevention Research Branch, and Gina R. Hijjawi, Ph.D., AAAS/SRCD Executive Branch Fellow in DESPR, are planning a scientific meeting on Children of Parents in the Criminal Justice System to be held November 6, 2006 in Bethesda, MD. The purpose of this meeting is to bring together scientists who are conducting research on children of parents in the criminal justice system.

Dr. Samia Noursi and colleagues from DESPR are organizing a scientific meeting entitled "Substance Abuse Research and Disaster: A Dialogue" to be held on December 7-8, 2006 in Bethesda, MD. This meeting will focus on reviewing current research that addresses human response to disaster, preparedness, and strategies for service delivery; identifying relevant research findings that are not utilized in service delivery systems; and identifying gaps in existing research findings.

The next CTN DSMB meetings are planned for September 19, 2006, October 6, 2006, November 13, 2006 and November 16, 2006.

The next National CTN Steering Committee Meeting is planned for October 16-20, 2006 in Seattle, Washington.

The CCTN will present a symposium at the 45th Annual Meeting of the American College of Neuropsychopharmacology (ACNP) entitled: "Co-morbid Pain and Addiction - Novel Treatments." The meeting will be held in Hollywood, Florida, December 3-7, 2006. The pain symposium is scheduled for December 4th. Dr. Charles O'Brien will chair the session together with Dr. Petra Jacobs. This symposium will review new findings on the neurophysiology of pain and addiction. Presenters will include Dr. David Borsook, Dr. Nathaniel Katz, Dr. Gavril Pasternak and Dr. Jon-Kar Zubieta. Dr. Walter Ling will be a discussant in the panel as well.

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A CCTN symposium was accepted by the American Academy of Addiction Psychiatry (AAAP) for the 17th Annual Meeting & Symposium. The meeting will be held in St. Pete Beach, Florida, December 7-10, 2006. Dr. Petra Jacobs will co-chair the symposium entitled: "Interface between Pain and Opioids: New Horizons" along with Dr. Roger Weiss. Presenters will include Dr. Howard Heit, Dr. Martin Angst and Dr. Steven Passik. Dr. Walter Ling will be a discussant on this symposium.

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NEW RELEASE!

Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research-Based Guide
NIH Pub. No. 06-5316
A new NIDA publication, Principles of Drug Abuse Treatment for Criminal Justice Populations, drafted by Bennett Fletcher, Ph.D., and Redonna Chander, Ph.D., was introduced at the American Parole and Probation Association meeting in Chicago on July 24. The guidelines are intended to help criminal justice professionals - judges, correctional officers, parole/probation officers, and others in criminal justice who work with substance-abusing offenders - to understand more about abuse and addiction and how to treat it. The guidelines are also intended for treatment providers who work with patients who are involved with the criminal justice system. NIDA Director Dr. Nora Volkow and Deputy Director Dr. Timothy Condon held a press conference to announce the release, and strong media interest was generated through Reuters and AP stories and satellite news broadcasts. As of early August, approximately 3,000 copies of the publication had been distributed and an additional 20,000 requests for copies were on pre-publication order.

Research Report Series: Tobacco Addiction (Rev.)
NIH Pub. No.
This research report describes what tobacco is, presents current epidemiological research data regarding its use, and reports on the medical consequences of tobacco use. The report emphasizes the effects on the brain as well as current research findings about use during pregnancy. Includes treatment approaches.

Serie de Reportes: De Investigación El VIH/SIDA
(Research Report series: HIV/AIDS)
NIH Pub. No.
This research report was designed to highlight the latest NIDA-supported research into the multiple ways in which drugs of abuse contribute to the spread of HIV. It was released to coincide with the launch of NIDA's new public awareness campaign. "Drug Abuse and HIV: Learn the Link." The campaign was created specifically to raise awareness among teens and young adults about the links between drug abuse and HIV, and features nationally televised public service announcements and NIDA's new web site, www.HIV.drugabuse.gov.

National Survey Results from the Monitoring the Future 2005, Volume I: Secondary Students

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NIH Pub. No. 06-5883
Reports on the prevalence of drug use among students in 8th, 10th-, and 12th grades. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.

National Survey Results from the Monitoring the Future 2005, Volume II: College Students and Adults Ages 19-40
NIH Pub. No. 06-5884
Reviews trends in drug use by populations based on gender, college plans, regions of the country, population density, race/ethnicity, and parents' education. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.

Assessing Drug Abuse Within and Across Communities - Rev. 2006
NIH Pub. No. 06-3614
This publication helps communities understand their local drug abuse problems and develop drug abuse epidemiologic surveillance systems to assess local drug patterns and trends.

NIDA Notes

***NIDA Notes* Volume 20 Issue No. 6**
NIH Pub. No. 06-3478
The lead story discusses the effectiveness of legally mandated treatment for drug and alcohol problems. The Director's Perspective looks at the continuing challenges presented by HIV/AIDS, and discusses some factors that contribute to the disproportionate disease burden carried by the African-American community. Other research reports discuss the Recovery Management Checkup system, designed to help patients who are experiencing relapse; the potential role of glial cells in the brain's protective response to methamphetamine; the effects of obesity on nicotine reward; and gender influences on biological response to nicotine, cocaine, and alcohol. Issue 20-6 also features a "NIDA at Work" article, an in-depth look at the Division of Pharmacotherapies and Medical Consequences of Drug Abuse. The Tearoff feature discusses data from the 2004 National Survey on Drug Use and Health. "Research in Brief" highlights recently published, NIDA-funded studies, "What the Numbers Say" provides a data snapshot of the benefits of on-site psychiatric treatment among teens with co-occurring disorders. The issue also carries the full index to NIDA Notes Volume 20.

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.

A patient recruitment brochure was printed and distributed for Protocol CTN 0027, Starting Treatment with Agonist Replacement Therapies (START).

A patient recruitment brochure was printed and distributed for Protocol CTN 0030, Prescription Opioid Addiction Treatment Study (POATS).

CCTN developed a data sharing web site for the public use of CTN clinical data. To support the NIH Roadmap and data sharing policy, CCTN adopted the Clinical Data Interchange Standards Consortium (CDISC) data standards for interoperability and ensured that data met HIPAA's security and privacy requirements.

NIDA International Program

The NIDA International Program issues an *E-News Letter* every other month to

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inform the international drug abuse research community about recent events, funding opportunities, NIDA's the research training and exchange programs for international scientists, and forthcoming meetings.

June 2006 - This issue reported on the NIDA International Forum, the Institute's international research priorities, the NIDA International Program Awards of Excellence, the NIH transition to electronic submission of grant applications, and several new funding opportunities for international researchers.

Other Publications

Compton, W.M., and Volkow, N.D. Drug Alcohol Depend. 83 Suppl 1:S4-7, June 2006. Abuse of Prescription Drugs and the Risk of Addiction. Abuse of several categories of prescription drugs has increased markedly in the United States in the past decade and is now at alarming levels for certain agents, especially opioid analgesics and stimulants. Prescription drugs of abuse fit into the same pharmacological classes as their non-prescription counterparts. Thus, the potential factors associated with abuse or addiction versus safe therapeutic use of these agents relates to the expected variables: dose, route of administration, co-administration with other drugs, context of use, and expectations. Future scientific work on prescription drug abuse will include identification of clinical practices that minimize the risks of addiction, the development of guidelines for early detection and management of addiction, and the development of clinically effective agents that minimize the risks for abuse. With the high rates of prescription drug abuse among teenagers in the United States, a particularly urgent priority is the investigation of best practices for effective prevention and treatment for adolescents, as well as the development of strategies to reduce diversion and abuse of medications intended for medical use.

Dr. Kevin Conway, DCNBR, co-edited a special issue on Novel Approaches to Phenotyping Drug Abuse, which was published as the June 2006 issue of Addictive Behaviors. The papers appearing in this special issue emphasize innovative research that better describes, discriminates, and predicts the complex nature and course of drug abuse so as to offer more precise phenotypic indicators for testing the hypothesized underlying genetic and environmental risks for drug abuse. Conway, K.P., Compton, W.M., and Miller, P.M. Novel Approaches to Phenotyping Drug Abuse. Addictive Behaviors, 31, pp. 923-928, 2006.

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Honors and Awards

NIDA received an NIH Director's Award for "*Drug Abuse and HIV: Learn the Link*," NIDA's latest awareness campaign about the connection between drug abuse and HIV infection. The NIDA team was honored at the 2006 NIH Director's Award Ceremony held on July 12, 2006. The NIDA HIV PSA Campaign Team consisted of Timothy P. Condon, Ph.D., Lucinda Miner, Ph.D., Jan Lipkin, Susan Weiss, Ph.D., David Anderson, Gayathri Dowling, Ph.D. Jennifer Elcano, Lynda Erinoff, Ph.D., Mark Fleming, Sheryl Massaro, Joan Nolan, Jacques Normand, Ph.D., Michelle Person, Anna Staton, M.P.A., and Sara Rosario Wilson.

Dr. Betty Tai, CCTN Director, has been selected to receive the 2006 Meritorious Research Service Commendation of the American Psychological Association. This award honors individuals who have made outstanding contributions to psychological science through their service as employees of the federal government or other organizations. Dr. Tai was chosen for this award due to her energetic leadership and organizational talents in the CTN. The CTN program has evolved into an outstanding proving ground for psychosocial interventions, such as motivational interviewing and motivational incentives, and studies of innovative pharmacotherapy, such as the application of buprenorphine to the problems of drug dependence. She was nominated by several of her scientific peers.

Dr. Harold Perl, CCTN, and the other NIH and SAMHSA personnel who were deployed to the Gulf Coast region last fall received recognition through a 2006 Secretary's Award for Distinguished Service, for "distinguished service in providing increased capacity for mental health and substance abuse treatment services following Hurricanes Katrina, Rita and Wilma in 2005.

Ms. Ana Anders, Senior Advisor on Special Populations, SPO, received an award from "Entre Familia," a residential drug abuse treatment program for Latina mothers and their children in Boston on July 14, 2006. The award was for "Long-standing contributions to research that improves drug abuse treatment and prevention among Hispanics in the U.S. and internationally."

Redonna K. Chandler, Ph.D., DESPR, received the 2006 Health and Human Services Secretary's Award for Distinguished Service.

Dr. Belinda Sims, DESPR, was selected to be an ex officio member of the US Department of Education Safe and Drug-Free Schools and Communities Advisory Committee. This committee advises the Secretary of Education on federal, state, and local programs designed to create safe and drug-free schools, and on issues related to crisis planning.

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Dr. Lisa Onken, DCNBR, received the NIH Director's Award for her work in advancing research on behavioral and integrative treatments for addiction.

Dr. Laurence Stanford, DCNBR, received the NIMH Director's Award for his contribution to the NIH MRI Study of Normal Brain Development.

Drs. Steven Grant and **Laurence Stanford**, DCNBR, received Blueprint Director's Awards for Significant Achievement in recognition of their contributions to the workgroup for the NIH Neuroscience Blueprint Research Training Initiative.

Dr. Laurence Stanford, DCNBR, received the NIH Director's Award for his work in creating a database of normal brain development as a resource for developmental neuroscience communities.

Dr. Laurence Stanford, DCNBR, received a Blueprint Director's Award for Significant Achievement in recognition of his contributions to the Pediatric MRI Study - Diffusion Tensor Imaging Expansion Project Team.

Dr. Rosmarie Nemeth-Coslett, DCNBR, completed the requirements and achieved the level of Advanced Toastmaster's Silver, April 2006. She received the Area 51 President of the Year Award (May 2006) and was presented with the Club President of the Year Award plaque from District 36 on, June 25, 2006.

Dr. Teresa Levitin, Director, OEA, received the NIH Office of the Director Merit Honor Award for being part of an EPMC workgroup that demonstrated "leadership in developing the NIH response to 2004 OHRP Guidance on Research Involving Coded Private Information or Biological Specimens."

Dr. Jag Khalsa, DPMCDA, received the NIH Director's Award for his outstanding contributions to the Trans-NIH Type I Diabetes Research Strategic Plan.

Dr. Jane B. Acri, DPMCDA, was elected to Fellow of Division 28, Psychopharmacology and Substance Abuse, of the American Psychological Association. At the annual meeting of the APA in New Orleans, LA in August, 2006, she gave a New Fellow address entitled "Medication Development for Addictive Disorders: Recent Changes in Preclinical Evaluations."

Dr. Brandon Harvey, Neural Protection and Regeneration Section, IRP, has been promoted to staff scientist.

Drs. Jonathan Katz and **Amy Newman**, IRP, applied for the following patent: Use of benztropine analogues for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), nicotine abuse, and obesity. U.S. Patent pending, EIR Filed, January 19, 2006.

Dr. Amy Newman was invited by Dr. Michael Gottesman to join the NIH Central Tenure Committee in October 2006.

An article (Xi et al. Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-promed relapse in rats: role of glutamate in the nucleus accumbens) from the laboratory of **Dr. Eliot Gardner** was chosen by the editorial board of the *Journal of Neuroscience* for highlighting in the "This Week in The Journal" section of the 16 August 2006 issue.

Staff Changes

Ms. Carol Krause joined the Office of Science Policy and Communications as Chief of the Public Information and Liaison Branch in May 2006. She began her career as a television journalist covering medical and political issues, and won an Emmy Award in the 1980's as a news reporter in Chicago. She wrote a

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nationally published book, *How Healthy is Your Family Tree* (Fireside Books/Simon and Schuster) which resulted in a period of exposure in the national media. As an independent contractor she helped to develop some of the earliest informed consent materials for patients and their families facing choices about genetic testing, and was asked to testify before Congress on this issue. In 1997 she became the first Communications Director of the new HHS Office on Women's Health. There she built a communications staff, and launched the *National Women's Health Information Center*, the government's premiere health Web site for women. She left government service to take a position with a private firm that served as the primary communications contractor for the National Cancer Institute, and was instrumental in launching the *Cancer Bulletin*, a new weekly newsletter from the NCI Director. Carol has recently been a consultant developing strategic communications plans for the U.S. Department of Energy and the FDA Office of Women's Health. Her new role is to lead the health communications efforts for NIDA. Carol has a B.A. in Political Science from George Washington University and an M.A. in Communications and Public Affairs from American University.

Denise Pintello, Ph.D., M.S.W., was recently named as the Special Assistant for the Deputy Director, NIDA. She joined NIDA in 2002 as a Health Scientist Administrator in the Office of Science Policy and Communications. Dr. Pintello has coordinated six NIDA Council Review Work Groups and currently serves as NIDA's Roadmap Deputy Liaison and also as the Project Officer for the NIDA-SAMHSA Blending Initiative. Her research publications have focused on intra-familial child sexual abuse, post-traumatic stress in women and child maltreatment recurrence.

Redonna Chandler, Ph.D. was recently named Branch Chief of the Services Research Branch, Division of Epidemiology, Services and Prevention Research. For six years, prior to joining NIDA, she worked for the Bureau of Prisons administering and implementing substance abuse treatment programs and services for federally sentenced offenders. Dr. Chandler was trained as a psychologist and received her doctoral degree from the University of Kentucky. She has written and published on a range of topics including body image, measuring treatment process and outcomes, treating offenders with co-occurring substance abuse and mental health disorders, and substance abuse problems of adolescent girls. As a licensed psychologist she is an active member in the American Psychological Association and serves as the Treasurer of Division 35, Society for the Psychology of Women.

Dionne J. Jones, Ph.D. is currently the Deputy Branch Chief of the Services Research Branch, Division of Epidemiology, Services and Prevention Research, National Institute on Drug Abuse (NIDA). She joined NIDA in 1998 and manages a grant portfolio that includes women and gender issues, rural services and treatment issues, HIV/AIDS, co-occurring disorders, and health disparities. Before joining the federal government, Dr. Jones served in a number of administrative and research capacities at nonprofit and for profit organizations, including the National Urban League, The Lewin Group, and Pacific Institute for Research and Evaluation. She has published journal articles, book chapters and a monograph in a number of public health-related areas.

Sarah Duffy, Ph.D., a health economist, joined the Services Research Branch, Division of Epidemiology, Services and Prevention Research on July 24, 2006. She will be responsible for the economics portfolio in the Branch. Dr. Duffy has a Ph.D in economics and has been a health economist for 18 years. She comes to NIDA from the Office of Applied Studies, SAMHSA where she worked as a senior research economist for eight years. Her responsibilities at SAMHSA included work on large national data collection projects such as the National Survey on Drug Use and Health (NSDUH) and the Treatment Episode Data Set (TEDS). She was sole or lead author on a number of publications and has been

a reviewer on health economics topics for several leading journals including: *Medical Care, Health Services Research, Eastern Economic Journal, the American Journal of Public Health and the Journal of the American Medical Association*.

Samia Noursi, Ph.D. joined the Division of Epidemiology, Services and Prevention Research (DESPR) in May 2006 as a Special Assistant in the Office of the Director. At DESPR, Dr. Noursi is responsible for coordinating a number of division-wide initiatives including science to service initiatives as well as assisting in the management of the division. Prior to joining NIDA, Dr. Noursi was a Social Science Analyst at the Division of Services and Intervention Research (DSIR) at the National Institute of Mental Health (NIMH) and worked on a variety of projects including efforts to bridge science to services and various Institute-wide activities. Prior to joining NIH, Dr. Noursi held several senior research positions with consulting firms in the Washington DC area among them a senior analyst and trainer of the National Reporting System for the Head Start Bureau and the Research Director for the National Child Welfare Resource Center on Legal and Judicial Issues at the Center on Children and the Law at the American Bar Association. Dr. Noursi holds a Masters and Ph.D. in Applied Developmental Psychology and was awarded a Post-Doctoral Fellowship at the National Institute of Child Health and Human Development (NICHD). Dr. Noursi has published, authored and co-authored several book chapters and articles in peer-reviewed journals.

Marta De Santis, Ph.D., joined the Regulatory Affairs Branch of the NIDA's DPMCDA as a Regulatory Affairs Specialist in May 2006. Dr. De Santis received a Ph.D. in Chemical Science, and a Master in Biochemical Science, from the National University of Cordoba, Argentina. Before coming to NIDA, Dr. DeSantis was a Regulatory Compliance/Medical Writer for Technical Resources International, Inc. Dr. De Santis will be responsible for helping to ensure that DPMCDA supported studies and regulatory submissions are in compliance with pertinent Federal, State, NIDA and NIH regulations and policies.

Elisabeth Davis joined the Science Policy Branch in the Office of Science Policy and Communications in September 2006 as a Program Analyst. She received her Masters of Public Health degree from the University of Michigan School of Public Health. Prior to joining NIDA, Ms. Davis worked at the Annenberg Public Policy Center of the University of Pennsylvania where she was responsible for managing an NICHD-funded adolescent sexual health and media research study for the health communications group. She has worked on numerous other public health issues including prenatal education, childhood obesity, youth violence, recidivism, and women and heart disease.

Usha Charya joined the Science Policy Branch in the Office of Science Policy and Communications in September 2006 as a Program Analyst. Previously, Ms. Charya held a position at MasiMax Resources, Inc., as Project Director on the NIDA Science Meetings Logistical Support project, and as Deputy Project Director on the NIDA State and Local Epidemiology Planning and Information Development contract. Ms. Charya has a BA in Psychology, and a BA in Journalism and Mass Communication. She will continue to be involved in science meeting planning for NIDA, overseeing the science meetings contract.

Vivian Chiu has joined the OEA Staff as Grants Systems Specialist, and she will assume these duties for OEA activities.

Derrick Prather joined the Special Populations Office as a contractor. Derrick has an M.A. in Microbiology from the State University of New York at Buffalo.

Murat Oz, Ph.D., has resigned as a Scientific Review Administrator in OEA as of August 2006.

Douglas Rugh, Ph.D., DESPR, has left NIDA to pursue his research interests in

the private sector.

Jack Stein, Ph.D. Deputy Director in the Division of Epidemiology, Services and Prevention Research (DESPR) left NIDA on August 20, 2006 to assume the position of the Director of the Division of Services Improvement at the Center for Substance Abuse Treatment (CSAT) within the Substance Abuse and Mental Health Services Administration (SAMHSA). Dr. Stein was with NIDA for over 9 years in two major capacities: first he was the Deputy Director in the Office of Science Policy and Communication (OSPC) and for the last 5 years, was the Chief of the Services Research Branch and later the Deputy Director for DESPR. In his new position at CSAT/SAMHSA, Dr. Stein will lead a nationwide services program that has a distinguished record of shaping the drug abuse treatment system in the United States.

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Timothy Baker was awarded the James McKeen Cattell Award for 2006. This award is given by the Association of Psychological Science for lifetime acheievement in the application of psychological research.

Sean David, M.D., D. Phil., was nominated for the Society for Research on Nicotine and Tobacco's New Investigator Award 2006.

David Fiellin received the Nyswander-Dole Award from the American Association of the Treatment of Opioid Dependence (AATOD) in April. The award recognizes extraordinary work and service in the field of opioid treatment.

NIDA grantee, **Sandro Galea, M.D., Dr.P.H.**, Professor of Epidemiology at the University of Michigan's School of Public Health was honored as one of Time Magazine's "Innovators of 2006" in the March 20, 2006 issue. Dr. Galea was described as an epidemiologist forging the future and honored specifically for his pioneering research on the public psychology of emerging diseases and the psychosocial effects of 9/11 on New Yorkers and how Canadians were responding to the 2003 SARS outbreak and quarantines in Toronto. Dr. Galea's current research focuses on the social epidemiology of drug abuse and the characteristics of urban environments as determinants of health outcomes (morbidity, mortality, substance abuse, and related risk behaviors).

Dr. Raul Gonzalez, University of Illinois at Chicago, received travel award to participate in the NIDA Young Investigator session held at the annual meeting of the American Psychological Association in New Orleans on August 11, 2006.

Dr. Sharon Hall, from the University of California San Francisco, will receive the Society for Research on Nicotine and Tobacco (SRNT) Ove Ferno Award for Clinical Research on Nicotine and Tobacco.

Andrew (Andy) Kaplan, M.D., Professor of Medicine and Microbiology and Immunology, and a NIDA grantee, was an invited speaker of the Presidential Advisory Council on HIV/AIDS, held in Washington, D.C. on June 19, 2006. Dr. Kaplan's presentation was entitled "Collateral Damage: Incarceration, HIV, and Vulnerable Communities." Dr. Kaplan died on June 28th.

Dr. Sheppard Kellam, American Institutes for Research, was selected to be a member of the US Department of Education Safe and Drug-Free Schools and Communities Advisory Committee. This committee advises the Secretary of Education on federal, state, and local programs designed to create safe and drug-free schools, and on issues related to crisis planning.

NIDA grantee's **Drs. Alexandros Makriyannis** and **John Huffman**, were joint recipients of the prestigious "Mechoulam Award," given by the International Society for Cannabinoid Research at the Annual Meeting, June 2006, Budapest,

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Hungary.

Dr. Judith J. Prochaska, from the University of California San Francisco, will receive the Society for Research on Nicotine and Tobacco (SRNT) Young Investigator Award. Awards will be presented during SRNT's annual conference, which will be held in Austin, Texas, February 21- 24, 2007.

Dr. Jody Tannabe, University of Colorado Health Science Center, received the Department of Radiology Faculty Research Award, June 2006.

Dr. Linda Teplin, Professor of Psychiatry and Director of Psycho-Legal Studies, at Northwestern University was named Commissioner of the American Bar Association's Commission on Youth at Risk.

Dr. JosŽ Szapocznik, Principal Investigator of the CTN Florida Node at the University of Miami, joined Florida State Governor Jeb Bush, First Lady Columba Bush, and other participants for a reception at the Governor's Mansion on June 6th to launch the Eighth Statewide Drug Control Summit in Tallahassee. On June 7th, drug summit participants, including members of law enforcement, school prevention staff and students, treatment providers, and researchers like Dr. Szapocznik, met in the Capitol for an invitation-only daylong discussion of efforts to implement effective drug control strategies.

Dr. George Woody, CTN Delaware Valley PI, and **Edwin Zvartau**, Vice Rector for Science, Pavlov State Medical University, St. Petersburg, Russia received the 2006 NIDA International Program Award of Excellence in Collaborative Research. This award honors mentors, researchers, bi-national collaborative teams, and individuals whose efforts support the International Program mission. The award recognizes creative or pioneering efforts by bi-national or multinational research teams consisting of at least one NIDA grantee and one non-U.S. research partner who have appreciably improved the mechanisms to foster international collaborative research and/or significantly contributed to scientific knowledge about drug abuse and addiction.

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