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Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Basic Neurosciences Research

α5 Nicotinic Acetylcholine Receptor Subunit mRNA Levels During Brain Development

This study compared pre- and postnatal expression of the α5 nicotinic acetylcholine receptor (nAChR) subunit in rat cortex and hippocampus. Similar to expression of other nAChR subunits, there was transient expression of α5 mRNA during cortical and hippocampal development. During the first two postnatal weeks of development, transient expression was detected mainly in cortical layers V and I/II. In the hippocampus, transiently increased expression was detected in CA1 and CA3 pyramidal neurons and granule cells of the dentate gyrus; areas have low expression levels in the adult. Co-expression of α5 and α7 mRNAs was detected in a subpopulation of hippocampal interneurons. In contrast, in the subiculum, numerous cells exhibited strong hybridization signals for α5 and α7 mRNAs, but co-expression was rarely detected. The investigators concluded that this expression pattern places nicotinic receptors containing the α5 subunit in a position to regulate glutamatergic and GABAergic transmission during the postnatal period. Winzer-Serhan, U.H. and Leslie, F.M. Expression of Alpha5 Nicotinic Acetylcholine Receptor Subunit mRNA During Hippocampal and Cortical Development. Journal of Comparative Neurology, 481(1), pp. 19-30, 2005.

CB2 Cannabinoid Receptor and Mechanisms of Peripheral Analgesia

CB2 cannabinoid receptor-selective agonists are promising candidates for the treatment of pain. CB2 receptor activation inhibits acute, inflammatory, and neuropathic pain responses but does not cause central nervous system (CNS) effects, consistent with the lack of CB2 receptors in the normal CNS. To date, there has been virtually no information regarding the mechanism of CB2 receptor-mediated inhibition of pain responses. Here, Ibrahim and colleagues test the hypothesis that CB2 receptor activation stimulates release from keratinocytes of the endogenous opioid β-endorphin, which then acts at opioid receptors on primary afferent neurons to inhibit nociception. The antinociceptive effects of the CB2 receptor-selective agonist AM1241 were prevented in rats when opioid antagonist naloxone or antiserum to β-endorphin was injected in the hind paw where the noxious thermal stimulus was applied, suggesting that β-endorphin is necessary for CB2 receptor-mediated antinociception. Further, AM1241 did not inhibit nociception in μ-opioid receptor-deficient mice. Hind paw injection of β-endorphin was sufficient to produce antinociception. AM1241 stimulated β-endorphin release from rat skin tissue and from cultured human keratinocytes. This stimulation was prevented by AM630, a CB2 cannabinoid receptor-selective antagonist and was not observed in skin from CB2-cannabinoid receptor-deficient mice. These data suggest that CB2 receptor activation stimulates release from keratinocytes of β-endorphin, which acts at local neuronal mu-opioid receptors to inhibit nociception. Supporting this possibility, CB2 immunolabeling was detected on B-endorphin-containing keratinocytes in stratum granulosum throughout the epidermis of the hind paw. This mechanism allows for the local release of β-endorphin, where CB2 receptors are present, leading to anatomical specificity of opioid effects. Ibrahim, M.M., Porreca, F., Lai, J., Albrecht, P.J., Rice, F.L., Khodorova, A., Davar, G., Makriyannis, A., Vanderah, T.W., Mata, H.P. and Malan, T.P., Jr. CB2 Cannabinoid Receptor Activation Produces Antinociception by Stimulating Peripheral Release of Endogenous Opioids. Proceedings of the National Academy of Sciences, 102, pp. 3093-3098, 2005.

Receptor Affinity Ligands

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The design of ligands as "reporters" of reactivity toward protein receptors, transporters, or channels has frequently been based on covalent modification of amino acids specific to these proteins. Examples of this technique include the isothiocyanate group used in opioid and cannabinoid receptor ligands, and the photo-activated azido group, used in tropane and pyridyl ligands, targeting the dopamine transporter and the nicotinic receptor, respectively. Dr. Philip Portoghese and his collaborators have pursued the approach of targeting appropriately spaced cysteine thiol and lysine amino groups with a ligand produced from naltrexamine and ortho-phthalaldehyde or ortho-naphthaldehyde. These ligands have the following properties: they are capable of labeling mu, kappa, or delta opioid receptor membranes from HEK-293 cells with high affinity, and in an irreversible (wash-resistant) manner. The labeling also produces a fluorescence in the 533-546 nm range when laser excitation of 460-490 nm is used, and the development of this fluorescence can be followed kinetically by flow cytometry. The fluorescence is characteristic of that for a benzoisoindole ring, formed by stepwise reaction of the ligand with a lysine amino group, followed by reaction of the resulting imine with a neighboring cysteine thiol group, to produce a 2-thiobenzoisoindole ring. Background or non-specific fluorescence could be minimized by the inclusion of an antagonist such as naltrexone in the analysis. In the case of the ortho-naphthaldehyde ligand, site-directed mutational analysis of the mu receptor has suggested that the lysine 233 and the cysteine 235 in transmembrane helix five are the reactive sites for this ring formation. Further experiments may include full pharmacological characterization (the cross-linked product should produce receptor antagonism) and confirmation of the reaction sites by digests of various receptor regions. Zhang, Y., McCurdy, C.R., Metzger, T.G., and Portoghese, P.S. Specific Cross-Linking of Lys233 and Cys235 in the Mu Opioid Receptor by a Reporter Affinity Label. Biochemistry, 44, pp. 2271-2275, 2005.

Preparation of Monoclonal Antibodies Reactive to the Endogenous Small Molecule, Anandamide

This report describes the hapten design and carrier molecule strategy that the authors used to generate a panel of monoclonal antibodies (mAB) to the endogenous cannabinoid, anandamide (N-arachidonylethanolamide, AEA) in order to develop an easy and inexpensive immunoassay for measuring this endogenous cannabinoid. These authors designed and successfully prepared a hapten, N-arachidonyl-7-amino-6-hydroxy-heptanoic acid (AHA), which retained the basic characteristic features of anandamide - the carboxamide, the hydroxyl and the lipophilic arachidonyl moiety with its skipped double bond system, while still showing the attachment to protein. In addition, a secondary alcohol structure was added to reduce the potential for biological hydrolysis of the hapten. Because of the diverse responses obtained after coupling this hapten to four different carriers, the authors determined that the type of carrier molecule used was particularly important for generating anti-anandamide antibodies. This report further describes the characteristics of a panel of 11 mAB, generated from four separate fusions, with a range of relative affinities and cross reactivities. Excellent selectivity for anandamide vs. two other endogenous cannabinoids and arachidonic acid was achieved following this strategy (cross reactivities <5%). In addition, at least one mAB maintained specificity for anandamide compared to two very closely related fatty acid amide molecules. However, the IC50 values in a standard enzyme-linked immunosorbent assay (ELISA) format (ca. 2-3 uM) indicated that improvement in antibody affinities or assay format will be required for an immunoassay to measure endogenous levels. Basta, P., Adcock, A.R., Tallent, C.R., Fleming, D.N., Seltzman, H.H., Whisnant, C.C., and Cook, C.E. Preparation of Monoclonal Antibodies Reactive to the Endogenous Small Molecule, Anandamide. Journal of Immunological Methods, 285, pp. 181-195, 2004.

Morphine and Stress Response in Adult Female Offspring

It has been shown that adult female rats react to stressors more intensely than adult male rats and that opioids have an inhibitory effect on the stress response. Furthermore, the response of the hypothalamic pituitary adrenal (HPA) axis to stress is known to be gender specific. In a recent paper, Dr. Ilona Vathy and her associates report that prenatal morphine exposure alters the HPA axis-regulated stress response and the sensitivity of negative feedback that are affected by the fluctuation of ovarian hormones. This study examined the effects of prenatal morphine exposure on ACTH and CORT plasma concentrations before and after restraint stress in proestrus (high estrogen level) and diestrus (low estrogen level) female rats. Prenatal morphine exposure differentially altered the ACTH and CORT responses to stress and the sensitivity of negative feedback of glucocorticoid (GR) probably by affecting the characteristics of GR receptors, and thereby altering the HP axis-controlled stress response. Slamberova, R., Rimanoczy, A., Riley, M.A., and Vathy, I. Hypothalamo-

Pituitary-Adrenal Axis-Regulated Stress Response and Negative Feedback Sensitivity is Altered by Prenatal Morphine Exposure in Adult Female Rats. Neuroendocrinology, 80, pp. 192-200, 2004.

Corticotropin Releasing Factor Antagonism Reduces Cocaine-Induced DA Neuronal Activity and DA Overflow in the Nucleus Accumbens

Corticotropin releasing factor (CRF) is a neuropeptide associated with the integration of the physiological and behavioral responses to stress. More recently, CRF1 receptor antagonists have been shown to decrease cocaine self-administration and inhibit stress-induced reinstatement of cocaine-seeking behavior. The exact mechanisms underlying this effect are not clear. Based on the large literature demonstrating an association between dopaminergic neurotransmission and reward-related behavior, the aim of the present study was to examine the effects of acute vs. chronic CRF1 receptor blockade on mesencephalic dopamine (DA) neuron activity (determined by in vivo extracellular recordings) and extracellular DA levels in the nucleus accumbens (Acb) (using in vivo microdialysis). In addition, the effect of CRF1 receptor antagonism on cocaine-induced DA overflow in the Acb was examined and correlated with DA neuron activity in the ventral tegmental area (VTA). Acute (but not chronic) CRF1 receptor blockade (by CRA-0450) significantly increased DA neuron population activity without affecting burst firing, average firing rate or accumbal DA concentrations. In addition, both acute and chronic CRF1 receptor antagonism significantly reduced cocaine-stimulated DA overflow in the Acb, and this reduction was correlated with an attenuated cocaine-induced inhibition of DA population activity. Taken as a whole, these data demonstrate that, although DA neuron population activity exhibits tolerance to chronic CRF1 receptor antagonism (by CRA-0450), tolerance does not develop to the selective inhibition of cocaine-induced DA release (in the Acb) and as such may be of benefit in the treatment of cocaine addiction. Lodge, D.J., and Grace, A.A. Acute and Chronic CRF1 Receptor Blockade Inhibits Cocaine-induced Dopamine Release: Correlation with Dopamine Neuron Activity. Journal of Pharmacology and Experimental Therapeutics, (epub ahead of publication), March 22, 2005.

Relative Opioid Efficacy is Determined by the Complements of the G Protein-Coupled Receptor Desensitization Machinery

G protein-coupled receptor regulation by G protein-coupled receptor kinases and beta-arrestins can lead to desensitization and subsequent internalization of the receptor. For in vitro and cellular systems, beta-arrestins do not seem to play a major role in regulating mu opioid receptor (μOR) responsiveness. Removal of the beta arrestin2 (βarr2) gene in mice leads paradoxically to enhanced and prolonged μOR-mediated antinociception. The barr2 knockout (βarr2-KO) mice also fail to develop morphine antinociceptive tolerance in the hot-plate test, further indicating that the βarr2 protein plays an essential role in μOR regulation in vivo. In this study, the contribution of βarr2 to the regulation of the μOR was examined in both human embryonic kidney 293 cells and in βarr2-KO mice after treatment with several opiate agonists. A green fluorescent protein tagged barr2 was used to assess receptor-βarr2 interactions in living cells. Opiate agonists that induced robust βarr2-green fluorescent protein translocation produced similar analgesia profiles in wild type and βarr2-KO mice, whereas those that do not promote robust βarr2 recruitment, such as morphine and heroin, produce enhanced analgesia in vivo. In this report, Dr. Laura Bohn presents a rationale to explain the seemingly paradoxical relationship between b-arrestins and μOR regulation wherein morphine-like agonists fail to promote efficient internalization and resensitization of the receptor. Bohn, L.M., Dykstra, L.A., Lefkowitz, R.J., Caron, M.G., and Barak, L.S. Relative Opioid Efficacy is Determined by the Complements of the G Protein-Coupled Receptor Desensitization Machinery. Molecular Pharmacology, 66(1), pp. 106-112, 2004.

Microglial Activation Precedes Dopamine Terminal Pathology in Methamphetamine-Induced Neurotoxicity

Previous studies have demonstrated methamphetamine (METH)-induced toxicity to dopaminergic and serotonergic axons in rat striatum. Although several studies have identified the nature of reactive astrogliosis in this lesion model, the response of microglia has not been examined in detail. In this investigation, Dr. Hastings and her research team at the University of Pittsburgh characterized the temporal relationship of reactive microgliosis to neuropathological alterations of dopaminergic axons in striatum following exposure to methamphetamine. Adult male Sprague-Dawley rats were administered a neurotoxic regimen of methamphetamine and survived 12 h, or 1, 2, 4, and 6 days after treatment. Immunohistochemical methods were used to evaluate reactive changes in microglia throughout the brain of methamphetamine-

treated rats, with a particular focus upon striatum. Pronounced morphological changes, indicative of reactive microgliosis, were evident in the brains of all methamphetamine-treated animals and were absent in saline-treated control animals. These included hyperplastic changes in cell morphology that substantially increased the size and staining intensity of reactive microglia. Quantitative analysis of reactive microglial changes in striatum demonstrated that these changes were most robust within the ventrolateral region and were maximal 2 days after methamphetamine administration. Analysis of tissue also revealed that microglial activation preceded the appearance of pathological changes in striatal dopamine fibers. Reactive microgliosis was also observed in extra-striatal regions (somatosensory and piriform cortices, and periaqueductal gray). These data demonstrate a consistent, robust, and selective activation of microglia in response to methamphetamine administration that, at least in striatum, precedes the appearance of morphological indicators of axon pathology. These observations raise the possibility that activated microglia may contribute to methamphetamine-induced neurotoxicity. LaVoie, M.J., Card, J.P. and Hastings, T.G. Microglial Activation Precedes Dopamine Terminal Pathology in Methamphetamine-Induced Neurotoxicity. Experimental Neurology, 187, pp. 47-57, 2004.

Serotonergic Neurotoxicity Enhances Methamphetamine and Cocaine Conditioned Place Preference

In mice, a neurotoxic regimen of fenfluramine, which selectively damaged their serotonergic axon terminals, enhanced methamphetamine and cocaine-induced conditioned place preference (CPP), while having no effect on lithium-induced aversive conditioning (conditioned place aversion, CPA). In the same study, selective dopaminergic neurotoxicity, induced by methamphetamine in the mice, decreased methamphetamine and cocaine CPP, and had no effect on lithium CPA. Dual dopaminergic/serotonergic neurotoxicity had no apparent effect on CPP; however, CPA was attenuated. An implication for humans is that drug-induced neurotoxicity may modulate, and even may predispose to, further drug abuse. Achat-Mendes, C., Ali, S.F., and Itzhak, Y. Differential Effects of Amphetamines-Induced Neurotoxicity on Appetitive and Aversive Pavlovian Conditioning in Mice. Neuropsychopharmacology, epub advance online publication, 2005.

Thrombospondins are Astrocyte-Secreted Proteins that Promote CNS Synaptogenesis

The proper formation of synapse and neural circuits is essential for the coordination and execution of adaptive behavior. Abnormal development of neural circuit and synaptic connection and abnormalities in the mechanisms underlying synaptic plasticity may underlie neuropsychiatric and addictive disorders. Synapses are tight junctions where a neuron releases a chemical signal, a neurotransmitter, to communicate with a neighboring neuron. Thus, a key question is how synapses form and how they are modified. Recent work by Dr. Ben Barres and his colleagues has found, surprisingly, that glia secrete factors that induce the formation of mature synapses. Mature synapses are characterized by the ability of the transmitting neuron to secrete neurotransmitter and by the ability of the receiving neuron to have receptors inserted into the membrane and clustered closely opposite of the site where neurotransmitter is being released, and the formation of tight junctions. The result that glia play an active role in synapse formation is surprising because glia were thought only to play a housekeeping role by supporting their survival and that neurons were the key players in synapse formation. In the February 11, 2005 issue of Cell, Dr. Ben Barres and his colleagues report the identification of thrombospondin 1 and 2 as some of the factors secreted by glia to promote synapse formation. Mice lacking thrombospondin 1 and thrombospondin 2 have 40 percent fewer synapses. Addition of thrombospondin 1 and 2 to neurons in culture induces the formation of synapse and induces the machinery necessary for transmitter release. However, the synapses are silent because the AMPA receptors are not inserted into the receiving neuron. Because completely functional synapses occur in the presence of glia, at least one other unidentified protein in addition to thrombospondin 1 and 2 is needed to produce a fully functional synapse. In future work, Dr. Barres hopes not only to identify the secreted factor but the receptors to which thrombospondin 1 and thrombospondin bind and induce the formation of "silent synapses." This breakthrough opens new avenues of research. Scientists can now test whether drugs of abuse modulate synapses by altering the amount or function of thrombospondins in glia. This research may also lead to the development of treatments for repair of the nervous system after injury. Christopherson, K.S., Ullian, E.M., Stokes, C.C., Mullowney, C.E., Hell, J.W., Agah, A., Lawler, J., Mosher, D.F., Bornstein, P. and Barres, B.A. Cell 120(3), pp. 421-433, February 11, 2005.

Modulation of Nicotine but not Ethanol Preference by the Mouse Chrna4 A529T Polymorphism

Alcohol and nicotine are commonly abused together. Some evidence suggests that a common set of gene variants underlies addiction to both nicotine and alcohol. Mice carrying a polymorphism of the alpha 4 subunit of the nicotinic acetylcholine receptor (AchR) in which threonine is substituted for an alanine at amino acid 527 in the alpha 4 subunit show increased consumption and preference for both alcohol and nicotine. Dr. Allan Collins and his colleagues determined whether the preference for alcohol and nicotine could be explained solely by the polymorphism in the alpha 4 subunit or could be explained by another gene in close proximity of the alpha 4-receptor gene. Dr. Collins crossed mice carrying the alanine and threonine gene variants of the alpha 4-receptor gene into mice lacking beta2 subunit of the nicotinic receptor. These mice are unable to make functional alpha4 beta2 nicotinic receptors. The increased preference for nicotine in the mice carrying the threonine variant of the alpha4 receptor lacking the beta2 subunit over mice carrying alanine variant of the alpha4 AchR lacking the beta2 is abolished but the difference in alcohol preference is not. Thus threonine substitution in the alpha4 AchR explains nicotine preference because the loss of the receptor eliminates any difference. However, because ethanol preference remains in the absence of functional alpha4 beta2 nicotinic receptors a gene lying in close proximity to the alpha4 receptor gene must exist. This is because genes lying in close proximity are less likely to recombine and segregate independently when eggs and sperm are developing during the process of meiosis. A question for future investigation is the identity of the gene variant underlying the increased preference for ethanol. Butt, C.M., King, N.M., Hutton, S.R., Collins, A.C. and Stitzel, J.A. Behavioral Neuroscience, 119(1), pp. 26-37, 2005.

Nicotinic Acetylcholine Receptor Containing the Beta4 Subunit Mediate Nicotine Withdrawal

Withdrawal from nicotine is one of the greatest obstacles that people addicted to nicotine face when they attempt to quit smoking. The actions of nicotine are mediated by a number of different types of nicotinic acetylcholine receptors in the brain. Two major types of nicotine receptors in the brain are nicotinic receptors that consist of either the alpha-4 subunit and the beta-2 subunit or the alpha-4 subunit and the beta-4 subunit. To determine which nicotine receptor is relevant to withdrawal Dr. Mary Debiasi and her colleagues at Baylor College of Medicine developed a mouse model of withdrawal. Mice were infused with nicotine using a mini-osmotic pump and withdrawal was precipitated with mecamylamine, a nicotine receptor antagonist. Withdrawal in mice is characterized by behavioral symptoms of withdrawal measured as increased grooming, chewing, scratching, shaking, jumping, and leg tremors. Mary Debiasi and her colleagues report in the November 10, 2004 issue of the Journal of Neuroscience that mutant mice lacking the beta2 subunit that are insensitive to the rewarding properties of nicotine still show behavioral signs of withdrawal while mice lacking the beta4 subunit do not show withdrawal symptoms. This result suggests that the alpha4beta4 subunit mediates withdrawal to nicotine and suggests targets for treating nicotine dependence. The results also suggest that gene variants in the beta4 subunit may affect response to nicotine in humans. To test this idea Mary Debiasi in collaboration with John Dani and Arthur Beaudet have identified four human variants of the beta4 subunit: Thr to Ile at codon 91 (T91I), Arg to Trp at codon 136 (R136W), Ser to Gly at codon 140 (S140G), and Met to Val at codon 467 (M467V). Receptors containing the R136W and M467V gene variants for the beta4 subunit were more sensitive to nicotine while T91I mutation was less sensitive to nicotine. All of these mutations showed enhanced desensitization when compared to wild type. The S140G has no effect. Future research will determine whether these gene variants are associated with differences in the severity of nicotine withdrawal. Salas, R., Pieri, F. and De Biasi, M. Journal of Neuroscience, 24(45), pp. 10035-10039, 2004; Liang, Y., Salas, R., Marubio, L., Bercovich, D., De Biasi, M., Beaudet, A.L. and Dani, J.A. Neurogenetics, 6(1), pp. 37-44, 2005.

Lmo Mutants Reveal a Novel Role for Circadian Pacemaker Neurons in Cocaine-Induced Behaviors

Fruit fly genetics provides a powerful approach to identify the molecular mechanisms underlying biological processes without any preconceived ideas. Jay Hirsh at the University of Virginia and Ulricke Heberlein at the University of California have developed genetic screens in the fruit fly drosophila melanogaster to uncover the molecular mechanism underlying the acute affects of cocaine. In the December 2004 issue of PLOS Biology Dr. Ulricke Heberlein and her colleagues describe the discovery of mutations in the LIM-only (LMO), encoding a regulator of LIM-homeodomain

proteins, that alter the response to cocaine. Mutations that increase expression of LMO decrease sensitivity of flies to cocaine while decreased expression of LMO increases the sensitivity of flies to cocaine. Restoring normal levels of LMO in the PDF-expressing ventral lateral neurons (LNvs), the principal neurons that generate circadian rhythms, of mutant flies is sufficient to reestablish normal sensitivity to cocaine. As might be expected flies carrying the mutations LMO also have circadian rhythm defects. Dr. Heberlein and her colleagues were able to separate the role that (LNvs) play in regulating cocaine sensitivity from the role these neurons play in regulating circadian rhythm behavior. The response of flies to cocaine was not altered during any portion of the light dark cycles. Mutations that ablate the expression of PDF peptide in the (LNvs) affected circadian rhythms but not sensitivity to cocaine. Acute inactivation of (LNvs) neurons by transiently expressing tetanus toxin or an inwardly rectifying potassium channel increased sensitivity to cocaine without affecting circadian rhythms. This work together suggests that there is an overlap between neuronal systems that regulate circadian rhythms and cocaine sensitivity. Future studies will determine the relevance of LMO mutations in the mouse. Tsai, L.T., Bainton, R.J., Blau, J. and Heberlein, U. PLoS Biol, 2(12), e408, 2004.

Mapping of a Quantitative Trait Locus (QTL) For Morphine Withdrawal Severity

Chronic morphine exposure results in physical dependence, manifested by physical symptoms during naloxone-precipitated withdrawal. Jumping frequency is widely considered the most sensitive and reliable index of withdrawal intensity in mice. Inbred mouse strains surveyed for naloxone-precipitated withdrawal display large and significant strain differences in jumping frequency, including an approximately tenfold difference between C57BL/6 and 129P3 mice. In the present study, (B6 X 129)F2 hybrid mice were given daily morphine injections for four days using an escalating dosing schedule, and measured naloxone-precipitated withdrawal on day 5. A whole-genome scan for linkage to phenotypic data was performed using polymorphic microsatellite markers. Significant linkage was observed between withdrawal jumping frequencies and 28 cM-wide region of Chromosome 1, accounting for ~20% of the overall phenotypic variance. Two other suggestive QTLs were found on Chromosomes 5 and 10, and an additive model fitting all three loci accounted for ~43% of the total variance. The Chromosome 1 QTL for naloxone-precipitated withdrawal severity in morphine-dependent mice, which was named *Depmq1*, harbors approximately 100 known genes. Although QTL mapping does not indicate which gene(s) are relevant to the phenotype under study, two genes within this region are high priority candidates. These are *Plcd4*, encoding phospholipase C δ4 subunit (PLC) and *Ugt1a1*, encoding an isoform of the UDP-glucoronosyl-transferase family 1. The *Depmq1* QTL is the first to be associated with naloxone-precipitated withdrawal jumping frequency, the most commonly used measure of withdrawal severity in morphine-dependent mice. Kest, B., Palmese, C.A., Juni, A., Chesler, E.J., and Mogil, J.S. Mapping of a Quantitative Trait Locus for Morphine Withdrawal Severity. Mammalian Genome, 15, pp. 610-617, 2004.

Identification of Tyrosine Hydroxylase as a Physiological Substrate for Cdk5

Kinases are enzymes that covalently bind phosphate groups to selected serines, threonines and tyrosines on proteins. The addition of the phosphate group causes dramatic changes in the substrate protein structure or function or both. For example, Dr. Bibb had previously reported that one of the substrates for cyclin-dependent kinase-5 (Cdk5) is Thr75 of the dopamine and cyclic-AMP-regulated phosphoprotein, Mr 32,000 (DARPP-32). Upon phosphorylation of Threonine 75, DARPP-32 is converted to an inhibitor of PKA, another kinase. Tyrosine hydroxylase (TH) is an enzyme involved in cellular synthesis of dopamine, one of the key molecules involved in the pleasurable effects of drugs and natural rewards. In this study, Dr. Bibb and collaborators report evidence that Cdk5 is able to phosphorylate TH directly as well as indirectly by activating another phosphorylation cascade, which ultimately phosphorylates TH. Furthermore, they identified Ser31 as the specific site at which Cdk5 is adding the phosphate group to TH. The effect of phosphorylation at Ser31 is activation of TH. Interestingly, previous studies have shown that acute administration of cocaine causes a decrease in the phosphorylation of TH Ser31. In this study authors observed increased phosphorylation of Ser31 with chronic administration. Chronic cocaine administration has also been shown to increase Cdk5 levels in the same brain regions. This study provides evidence for a mechanism by which Cdk5 may impact dopamine synthesis and furthermore that this mechanism is involved in chronic, but not acute cocaine administration. Kansy, J.W., Daubner, S.C., Nishi, A., Sotogaku, N., Lloyd, M.D., Nguyen, C., Lu, L., Haycock, J.W., Hope, B.T., Fitzpatrick, P.F. and Bibb, J.A. Journal of Neurochemistry, 91(2), pp. 374-384, 2004.

Activation of Peripheral Cannabiniod Receptors Reduces Neuronal Correlates of Pain in Rats

Andrea Hohmann and colleagues has been studying the utility of peripherally administered cannabinoid CB2 receptor agonists in reducing pain in animal models. In the current study, the authors found that peripheral application of CB2-selective cannabinoid agonist AM1241 reduced the activity of spinal wide dynamic range (WDR) fibers, which are involved in pain transmission from the spinal cord to the brain. AM1241 reduced the WDR activity that was produced by electrical stimulation of the hind paw, as well as that produced by paw inflammation. The responses of other non-pain related fibers were not reliably altered by AM1241. These findings demonstrate that the activation of CB2 receptors selectively attenuates the activity of a well-known component of a major pain pathway. These data support the potential efficacy of peripherally acting CB2 receptor agonists in the treatment of pain, an approach that would avoid many of the side effects of centrally-acting cannabinoids. Nackley, A.G., Zvonok, A.M., Makriyannis, A. and Hohmann, A.G. Activation of Cannabinoid CB2 Receptors Suppresses C-fiber Responses and Windup in Spinal Wide Dynamic Range Neurons in the Absence and Presence of Inflammation. J Neurophysiol. 92(6), pp. 3562-3574, December 2004.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Basic Behavioral Research

"Speedball" Abuse May be Motivated by the Attenuation of Cocaine's Negative Aversive Effects

According to epidemiological observations, "speedballing," the combined use of psychostimulants with opiates, is relatively widespread among drug users. Verbal reports suggest that the combination of cocaine and heroin induces a greater euphoria than experienced with either drug alone. These drug combinations also produce higher break points in preclinical studies using progressive ratio schedules to assess relative reinforcement. Heroin also shifts the cocaine reward dose-effect curve to the left, suggesting that heroin enhances cocaine's rewarding effects. However, cocaine also induces a negative affective state that can be measured using runway procedures to detect approach/avoidance responses when animals are trained to run into a goal box for i.v. cocaine. In this paradigm, the dependent measure of avoidance is the number of "retreats" en route to the goal box. Dr. Aaron Ettenberg, has been studying aversive properties of cocaine and recently found that either a low (.025 mg/kg), or a high (.100 mg/kg), dose of heroin reduces the number of retreats in animals trained to traverse a runway for 1.0 mg/kg i.v. cocaine. Three groups of rats were trained to run the runway for cocaine and were matched prior to testing with heroin on mean number of retreats over 14 days of training. Seven trials were conducted with groups reinforced for running to the goal box, either with cocaine only, or cocaine + one of the heroin doses. While it is also possible that heroin produces its effects by enhancing the reinforcing effects of this dose of cocaine (thus, the "approach" component of responding), the groups showed no difference in latency to leave the runway start box. Also, the low dose of heroin used does not produce a conditioned place preference on its own. The authors argue that these observations support the interpretation that heroin attenuates the ambivalence or conflict experienced over entering the goal box for a cocaine injection. Guzman, D. and Ettenberg, A. Heroin Attenuates the Negative Consequences of Cocaine in a Runway Model of Self-Administration. Pharmacology, Biochemistry and Behavior, 79, pp. 317-324, 2004.

Chronic Cocaine Enhances the Strength of Conditioning to Sexual Stimuli

Repeated psychostimulant administration induces behavioral sensitization to the locomotor activating effects of these drugs, and is associated with greater drug-induced dopamine release than acute drug treatment. This sensitization has been proposed to be responsible for enhanced incentive motivational properties of drug-related stimuli that induce craving in addiction. For example, in animal studies, behavioral sensitization increases drug self-administration and drug seeking after abstinence. Cross-sensitization has also been demonstrated; drug sensitization facilitates responding for other classes of reinforcers, such as natural rewards including sucrose, and for sexual stimuli. Psychostimulant-sensitized animals also form stronger associations in Pavlovian conditioning, and it has been suggested that increased dopamine enhances learning. Dr. Chana Akins and colleagues have been using a well-studied sexual conditioning paradigm in Japanese quail to measure approach behaviors for stimuli previously paired with copulatory experience. In a recent study, cocaine-treated animals received 10mg/kg i.p. daily for six days and were tested for locomotion after each injection. After a 10-day withdrawal period, 10 conditioning trails were conducted with a discrete visual stimulus in the test box introduced 30 sec before availability to interact with a female conspecific. Time spent in proximity of this conditioned stimulus (CS) was recording for drug or saline injected animals that were exposed to this stimulus paired or unpaired with access to a female. On tests of locomotor activity, cocaine injected animals had greater

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activation, in comparison with saline injected controls, over all six sessions. While both paired groups showed a successive increase in amount of time spent near the CS, this effect was greater for cocaine CS-paired animals than for the other three groups, suggesting enhanced conditioning as a result of the prior cocaine treatments. Cocaine-treated animals conditioned with a paired CS also demonstrated a shorter latency to copulate and had more cloacal contacts with the female than saline-treated animals with the CS conditioned to a female. These findings suggest that prior repeated cocaine exposure may strengthen the ability of sex-related stimuli to acquire incentive motivation properties that can elicit approach behavior, and also may increase unconditioned sexual behaviors. As cocaine use has been associated with high-risk sexual behaviors, these findings may suggest a neurobiological mechanism for cross-sensitization to the vulnerability for sexual behaviors. Levens, N. and Akins, C.K. Chronic Cocaine Pretreatment Facilitates Pavlovian Sexual Conditioning in Male Japanese Quail. Pharmacology, Biochemistry and Behavior, 79, pp. 451-457, 2004.

Analogous Changes in Striatal Gene Expression Follow Sexual Experience or Exposure to Drugs of Abuse

It has been suggested that drugs of abuse "hijack" neural systems that evolved to support natural motivated behaviors. Thus, an understanding of the neural control of natural behaviors can help us understand the specific pathology of drug abuse. Motivated behaviors that exhibit properties such as sensitization — an increase in behavioral response with repeated exposures to motivating stimuli — are of particular interest in this regard. Repeated sexual experiences, like repeated drug use, produce long-term changes including sensitization of dopamine release in the nucleus accumbens and dorsal striatum. Previously, Drs. Katherine Bradley and Robert Meisel showed that amphetamine-stimulated locomotor activity was sensitized by previous sexual experience in female Syrian hamsters. They are now collaborating with Dr. Paul Mermelstein to investigate the molecular mechanisms underlying neuroadaptations produced by sexual experience. In this study, they used DNA microarray techniques to identify genes differentially expressed within the nucleus accumbens and dorsal striatum between sexually experienced and sexually naïve female hamsters. For these experiments, female hamsters were ovariectomized and hormonally primed. Half of them were then exposed to a stimulus male once a week for six weeks, while the other half remained naïve. On week seven, the two groups were subdivided, with one half of each exposed to a stimulus male. In comparison with sexually naïve animals, sexually experienced hamsters that received a stimulus male on week seven exhibited an increase in a large number of genes. Conversely, sexually experienced females that did not receive a stimulus male on week seven exhibited a reduction in the expression of many genes compared to naïve animals. The data for the nucleus accumbens and dorsal striatum were similar in terms of directional changes and the categories of genes regulated by the experimental conditions. However, the specific genes exhibiting changes in expression differed between these two brain areas. The investigators also observed that many of the gene classes and specific genes regulated by sexual experience overlapped with those previously reported to be regulated by chronic administration of drugs of abuse, and that many of these genes are involved in forms of neuronal plasticity such as changes in excitability or dendritic growth. These experiments are among the first to profile genes regulated by sexual behaviors in brain areas (the mesolimbic and nigrostriatal dopamine pathways) involved in long term neuroadaptive changes underlying addiction. And, importantly, studies like this may help us understand why, unlike drug use, natural motivated behaviors do not, in general, progress to an uncontrolled, compulsive state. Bradley, K.C., Boulware, M.B., Jiang, H., Doerge, R.W., Meisel, R.L. and Mermelstein, P.M. Sexual Experience Generates Distinct Patterns of Gene Expression Within the Nucleus Accumbens and Dorsal Striatum of Female Syrian Hamsters. Genes, Brain and Behavior, 4, pp. 31-44, 2005.

Opioid Receptor Activation of the Mesolimbic System by Sexual Behavior and Associated Environmental Cues

The mesolimbic system plays an important role in the regulation of both pathological behaviors such as drug addiction and normal motivated behaviors such as sexual behavior. In this study, Dr. Lique Coolen and her colleagues, investigated the mechanism by which this system is endogenously activated during sexual behavior in male rats. Specifically, they studied the effects of sexual experience and sex-related environmental cues on the activation of several components of the mesolimbic system, which consists of a dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Previous studies suggest that these neurons are under tonic inhibition by local GABA interneurons, which are in turn modulated by mu opioid receptor (MOR) ligands. To test the hypothesis that opioids are acting in

the VTA during sexual behavior, the investigators measured MOR internalization in VTA as a marker for ligand-induced activation of the receptor. They observed significant increases in MOR internalization following copulation or exposure to sex-related environmental cues alone (the test cage). A second experiment was designed to determine if sexual behavior activates dopamine neurons in the VTA, using tyrosine hydroxylase as a marker for dopaminergic neurons and Fos-immunoreactivity as a marker for neuronal activation. They found significant increases in the percentage of activated dopaminergic neurons following copulation or exposure to sex-related environmental cues. In addition, mating and sex-related cues activated a large population of nondopaminergic neurons in VTA and neurons in both the NAc core and shell. This study is the first to provide direct functional neuroanatomical evidence that the mesolimbic system is activated by both sexual behavior and exposure to sex-related environmental cues. Opioid addiction is, at least in part, mediated by activation of these same MORs, which inhibit the firing of GABA neurons in the VTA, releasing the dopamine neurons from inhibition. Studies like this one from Dr. Coolen's laboratory will help us understand how these brain systems are regulated in their normal function and become dysregulated in drug addiction. Balfour, M.E., Yu, L., and Coolen, L.M. Sexual Behavior and Sex-Associated Environmental Cues Activate the Mesolimbic System in Male Rats. Neuropsychopharmacology, 29, pp. 718-730, 2004.

Early Life Stress Enhances Relapse in an Animal Model

Observations from clinical studies on cocaine abusers show that both psychological and physical stress elicit drug craving. Moreover, risk for drug use has been associated with adverse life events and chronic stress. Thus, stress may contribute to the vulnerability for drug abuse behavior and to the propensity to maintain this behavior or to relapse. A vast preclinical literature has modeled deleterious effects of physical and social stressors on acquisition, maintenance and reinstatement of drug seeking. Animal models of early life stress employ neonatal isolation procedures that involve prolonged separation from the mother for one hour per day over post-natal days 2 through 12. Neonatal stress has previously been shown to enhance vulnerability for acquisition of cocaine self-administration, but subsequent effects on relapse after self-administration has been extinguished are unknown. In the present study, the investigators compared male and female rats that were subjected to neonatal isolation with controls that were only handled and returned to the litter. All animals were trained for cocaine i.v. self-administration at 90 days of age, under a fixed ratio 1 schedule of reinforcement. They were then subjected to seven consecutive sessions of a 24-hr discrete trial procedure that provides extended access to drug and has been used to develop excessive, uncontrollable intake. This was followed by 10 days of extinction during which time animals did not receive drug infusion for operant responses in the chamber. After the tenth session, rats were tested in a single one-hour reinstatement session in the presence of cues previously paired with i.v. drug delivery. Group comparisons revealed that during acquisition, female rats took more cocaine than males, replicating findings of many prior preclinical studies on gender differences in cocaine intake. During extinction responding, females also tended to respond at higher levels during initial extinction sessions than males, and isolated rats responded at much higher levels than handled controls. Similarly, neonatally isolated rats responded at much higher levels during cue-induced reinstatement testing — making approximately 48% more responses in the presence of drug-associated cues. The findings of this study indicate that early stress may enhance the vulnerability for relapse to cocaine-seeking behavior in adulthood, when cues previously associated with drug reinforcement are encountered. Lynch,W.J., Mangini, L.D., and Taylor, J.R. Neonatal Isolation Stress Potentiates Cocaine-Seeking Behavior in Adult Male and Female Rats. Neuropsychopharmacology, 30, pp. 322-329, 2005.

Sucrose Intake Enhances Behavioral Sensitization Produced by Cocaine

Prior research has revealed interactions between an animal's history with sweet solutions and psychostimulant drug self-administration. For example, access to a sweet solution can prevent acquisition, and decrease the continued maintenance of cocaine self-administration. Dr. Blake Gosnell from the Neuropsychiatric Research Institute has now shown that experience with sucrose can sensitize animals to the locomotor-activating effects of cocaine. For 38 days, three groups of rats had daily 1-hr access either to sucrose, ground rat chow, or alternating daily access to either chow or sucrose. On the following two days, respectively, rats were given an i.p cocaine injection and an i.p saline injection. In response to the cocaine injection, rats pre-exposed to sucrose exhibited an elevated, although non-significant, locomotor response compared to the other two groups. Next, for five days, rats were given an

injection of cocaine and immediately returned to their home cage. Then one and 15 days after the final cocaine injection they were tested for their locomotor response to cocaine. On the first day, all rats exhibited a sensitized locomotor response to cocaine with the sucrose group exhibiting the greatest sensitization. When tested 15 days after the last cocaine injection, sensitization was still present and was greater in the previously exposed sucrose group than the other two. These outcomes indicate that repeated, intermittent intake of a palatable food can potentiate the effect of cocaine on locomotor behavior, and are consistent with other studies showing that food reward and drug reward are subserved by overlapping neural circuits. This area of investigation may contribute to understanding high rates of comorbidity between eating disorders and substance abuse, especially in females. Gosnell, B.A. Sucrose Intake Enhances Behavioral Sensitization Produced by Cocaine. Brain Research, 1031, pp. 194-201, 2005.

Pharmacokinetics of Intravenous Cocaine Across the Menstrual Cycle in Rhesus Monkeys

Numerous rodent studies have demonstrated that cocaine sensitivity is greater in females than in males and that this sensitivity varies with the estrus cycle. Laboratory-based studies in humans have also documented sex differences and menstrual cycle differences in the subjective effects of cocaine thus raising questions about possible fluctuations in cocaine pharmacokinetics during the menstrual cycle. Drs. Suzette Evans and Richard Foltin addressed this issue by studying the rhesus monkey, which has a menstrual cycle similar in length and hormonal fluctuations to that in humans. They examined cocaine pharmacokinetics in five female rhesus monkeys given acute i.v. doses of 0, 0.25, 0.50 and 1.0 mg/kg cocaine during four phases of the menstrual cycle: menses, midfollicular, periovulatory and midluteal. Plasma levels of cocaine and cocaine metabolites benzoylecgonine (BZE) and ecgonine methyl ester (EME) were measured at multiple time points during 90 min following each cocaine injection. The researchers found that peak plasma levels of cocaine increased as a function of dose, but did not vary with the menstrual cycle. There were also no menstrual cycle differences in either the time to achieve peak plasma levels of cocaine or the half-life of cocaine. On the other hand, levels of cocaine metabolites did vary with the menstrual cycle. Plasma levels of BZE and EME were greatest during the luteal phase particularly following the highest cocaine dose. In an analysis of their data from a prior study in which plasma cocaine metabolite levels were collected in women who received repeated doses of 12 mg smoked cocaine during the follicular and luteal phases (Evans et al., 2002), Drs. Evans and Foltin also found that BZE plasma levels were higher in the luteal phase than in the follicular. The present findings, along with the similarity of the menstrual cycle in rhesus monkey and in humans, point to the feasibility of the rhesus monkey model to further our understanding of the role of the menstrual cycle in acute and chronic effects of cocaine. Evans, S.M., and Foltin, R.W. Pharmacokinetics of Intravenous Cocaine Across the Menstrual Cycle in Rhesus Monkeys. Neuropsychopharmacology, 29, pp. 1889-1900, 2004.

Impulsivity (Delay Discounting) as a Predictor of Acquisition of IV Cocaine Self-Administration

Studies in humans have shown a relationship between drug abuse and impulsivity as measured by delayed discounting. Cigarette smokers, crack/cocaine abusers, and opioid dependent individuals, for example, discount delayed rewards more than non-drug users, although it is not clear whether the impulsivity precedes the development of drug abuse or is a consequence. This question was addressed by researchers at the University of Minnesota and University of Wisconsin-Eau Claire using an animal model in which they compared acquisition of cocaine self-administration in female rats that differed in baseline level of impulsivity, as measured by choice for an immediate small reinforcer (one 45 mg food pellet) over a delayed larger reinforcer (three 45 mg food pellets). The researchers found that acquisition of cocaine self-administration occurred in a greater percentage of the rats that exhibited high levels of baseline impulsivity compared to those that exhibited low levels of baseline impulsivity. These data are consistent with and extend prior research showing that rats that exhibited high impulsive choices consumed more ethanol than those that exhibited medium or low impulsive choices (Poulos et al., 1995) and therefore point to impulsivity as a factor that may predispose one to drug abuse. The authors caution, however, that the relationship between impulsivity and drug use may not be unidirectional, citing findings from an earlier study (Richards et al., 1999) in which rats receiving chronic methamphetamine showed increased delay discounting. Perry, J.L., Larson, E.B., German, J.P., Madden, G.J., and Carroll, M.E. Impulsivity (Delay Discounting) as a Predictor of Acquisition of IV Cocaine Self-Administration in Female Rats.

Psychopharmacology, 178, pp. 193-201, 2005.

Binge Self-Administration and Deprivation Produces Sensitization to the Reinforcing Effects of Cocaine

Recently there has been heightened interest in using animal behavioral paradigms of drug self-administration to model compulsive drug use in humans. One such model has been described by Dr. David Roberts and colleagues at Wake Forest University (Roberts et al., 2002). These investigators use a procedure in which rats receive access to cocaine for 24 hr per day in 4 discrete trials (DT4) per hour, (thus permitting a maximum of four infusions per hour), for 10 days followed by 7-days of cocaine deprivation. This procedure results in an enhanced reinforcing efficacy of cocaine as measured by breakpoints (BP) on a progressive ratio schedule (PR). [In a PR schedule, the number of responses required for reinforcement progressively increases after each reinforcer until a "breakpoint" is reached where responding ceases]. In the present study, these researchers sought to identify features of the DT4 procedure that are critical for producing an enhancement of cocaine's reinforcing efficacy. Four separate groups of rats were tested under the DT4 procedure for 10 days with cocaine self-administered doses of 0.38, 0.75, 1.5, or 3.0 mg/kg per infusion. A fifth group, the Matched FR group, self-administered 1.5 mg/kg per infusion according to a fixed ratio one (FR 1) schedule and received the average number of daily cocaine infusions that was self-administered by the DT4 1.5 mg/kg group. A sixth group also self-administered 1. 5-mg/kg but received a 1-day drug-free period before PR assessment instead of a 7-day period. Responding on an FR1 schedule and on a PR schedule was measured prior to the 10 days of cocaine self-administration, and then again following the 7 days, or one day, of drug abstinence. Results indicated that following the DT4 procedure and 7 drug-free days, there was not an increase in BP for all four dose groups; but instead, BPs were increased for groups receiving 1.5 and 3.0 mg/kg per per infusion, but not for groups receiving the lower doses. By contrast, experience with the DT4 procedure followed by 7 drug-free days did not alter responding on a FR1 schedule. The Matched FR group failed to show any change in BP following the DT4 procedure, indicating that the daily pattern of self-administration is an important determinant in development of enhanced reinforcing efficacy. Although these groups were matched on the absolute amount of drug received over 24 hours, it is significant that self-administration in the Matched FR group occurred largely in the first eight hours of cocaine availability and at a high frequency, thus permitting high blood levels of cocaine, whereas in the DT4 groups self-administration could not occur at similarly high rates and was spaced over far more hours per day. Thus, the pattern of drug intake may be an important variable in the changing efficacy of cocaine produced by the DT4 schedule. Also, as the group receiving only one drug-free day failed to exhibit an increase in BP following the DT4 procedure, exposure to an extended drug-free deprivation period may be another variable that is important in the development of enhanced drug reinforcement efficacy. The results of this study illustrate the utility of this protocol for identifying factors that may contribute to a shift from casual to compulsive use of abused drugs. Morgan, D., Smith, M.A. and Roberts, D.C.S. Binge Self-Administration and Deprivation Produces Sensitization to the Reinforcing Effects of Cocaine in Rats. Psychopharmacology, 178, pp. 309-316, 2005.

Effects of D-amphetamine on Cognition and Response Inhibition

Stimulant drugs such as d-amphetamine and methylphenidate (RitalinTM) are often used to improve performance in humans and, in fact, are prescribed to treat behavioral and cognitive impairments associated with ADHD and disorders of self-control. Moreover, illicit use of stimulants, such as d-amphetamine and cocaine, might be motivated by self-medication of behavioral and/or cognitive deficits. Research by NIDA grantee Mark Fillmore and his colleagues tested the effects of d-amphetamine on working memory and inhibitory control in a group of healthy adults with no reported history of illicit stimulant use or drug dependence. The study used well-documented and reliable measures of working memory (the rapid information processing task, RIP) and inhibitory control (the stop signal task). Three doses of oral d-amphetamine (0, 7.5 and 15 mg/70kg) were administered double blind in a randomized, within-subject design. In addition to the two dependent variables of primary interest, the study also measured subjective (12-item, visual analogue scale) and physiological (HR and BP) effects of this drug. Results indicated that RIP rates increased 2 hr following the two active doses and the increase was maintained at 3 hr. By contrast, d-amphetamine had no effect on response inhibition. Active doses of the drug increased BP and HR up to 3 hr after drug administration and subjective effects of the drug were seen at 2 and 3 hrs. These findings indicate that a stimulant drug can enhance aspects of cognitive functioning without producing a concomitant

improvement in inhibitory control of behavior. Failure to observe a stimulant-induced enhancement of inhibitory control in healthy adults might appear at odds with previous reports that d-amphetamine improved inhibitory control in this population. However, the facilitating effects in those studies were confined to individuals who displayed poor levels of response inhibition at baseline. Poor inhibition was determined in those studies by a median split of subjects into high and low baseline inhibition levels. That evidence, along with findings of stimulant-induced inhibitory facilitation in children with ADHD, could suggest that stimulant-induced enhancement of response inhibition might be selectively induced in individuals with poor basal levels of inhibitory control. The present findings contribute to a growing understanding of how stimulant drugs affect behavioral control in humans. The findings also highlight the complex nature of stimulant effects on human behavior and the utility of performance tasks as models of complex behavioral and cognitive functions. Fillmore, M.T., Kelly, T.H., and Martin, C.A. Effects of D-amphetamine in Human Models of Information Processing and Inhibitory Control. Drug and Alcohol Dependence, 77, pp. 151-159, 2005.

Repeated Maternal Separation in Mice: Sex Differences in Cocaine-Induced Behavioral Sensitization in Adulthood

Experimental protocols in rats have documented that repeated maternal separation (MS) of the neonate can produce changes in the dopamine system and in the hypothalamic-pituitary-adrenal axis (HPA axis), including enhancement of cocaine-induced increases in ventral striatal dopamine levels and elevated basal levels of circulating glucocorticoids and glucocorticoid response to mild stress. Dr. Klaus Miczek and colleagues now report the effects of MS on cocaine-induced sensitization, on glucocorticoid receptors in the hippocampus, and on the dopamine transporter in the nucleus accumbens in male and female neonatal mice. MS occurred for 1 hour per day on postnatal days (PD)1-13. Induction of sensitization occurred during PD 50-59 with mice receiving daily i.p. injections of 10-mg/kg cocaine. The development of locomotor sensitization was assessed on PD 50, 54, and 59. Expression of sensitization was assessed on PD 69 or 71 and on PD 99 by measuring the locomotor response to 7.5 mg/kg i.p. cocaine injections. On PD 50, the locomotor response to cocaine was greater in MS females than in non-MS females, MS males, and non-MS males. On PD 54 and 59, all MS mice exhibited enhancement of cocaine-induced locomotion. Assessment of the expression of cocaine locomotor sensitization on PD 69 or 71 and on PD 99 indicated an enhancement of sensitization in MS males, but not in females. This study is the first to report a relationship between MS and cocaine reactivity in mice. Whereas prior studies of MS rats have shown down-regulation of hippocampal glucocorticoid receptor expression and increased accumbal dopamine transporter binding, in the present study neither of these measures were affected by MS; however, but both measures were greater in females than males. Possible explanations for these discrepancies between MS rats and MS mice include differences in maternal care in rats and mice and differences in the daily length of MS used in this study and prior studies with rats. Kikusui, T., Faccidomo, S., and Miczek, K.A. Repeated Maternal Separation: Differences in Cocaine-Induced Behavioral Sensitization in Adult Male and Female Mice. Psychopharmacology, 178, pp. 202-210, 2005.

Activation of Metabotropic Glutamate Receptors Blocks Enhanced Amphetamine Self-Administration

Central glutamatergic (GLU) systems participate in the development and expression of psychostimulant sensitization. Sensitization is observed when repeated amphetamine or cocaine administration produces enhanced behavioral activation, (i.e., greater hyperactivity than seen with acute drug administration), paralleled by increases in dopamine (DA) and GLU release from subcortical mesolimbic regions. Sensitized animals also take more drug when available in i.v. self-administration paradigms. Ionotropic GLU receptors have been demonstrated to contribute importantly to the development and expression of sensitization. However, metabotropic group II GLU receptors negatively regulate GLU release and therefore may be in a position to "gate" sensitization by controlling transmitter available at the synapse for activating ionotropic receptors. Dr. Paul Vezina and colleagues at the University of Chicago have tested a recently developed GLU agonist, with high potency for metabotropic GLU receptors, in tests of behavioral sensitization, DA and GLU release, and self-administration for the psychostimulant, amphetamine. Rats were sensitized with five injections of either saline or 1mg/kg amphetamine (AMPH), with injections given every 2-3 days. Two weeks later they were tested for locomotor stimulation with i.p. saline, AMPH, the GLU agonist LY379268 (LY), or AMPH + LY. Animals receiving prior amphetamine injections showed the expected sensitized

response to AMPH and also had enhanced DA and GLU release from the nucleus accumbens core. However, co-administration of LY greatly attenuated this behavioral sensitization, and the increase of AMPH-induced neurotransmitter release. Animals were also implanted with jugular catheters and trained for i.v. self-administration of AMPH after the sensitization procedure. After training on fixed ratio schedules of reinforcement, all rats were tested on a progressive ratio schedule to determine "how hard" animals were "willing to work" to receive the drug. Animals previously sensitized with AMPH made more operant responses to receive drug on the PR schedule than those with a history of repeated saline injections, but when LY was present in the i.v. solution, this increase in AMPH's reinforcing efficacy was blunted. Together these observations support the hypothesis that activation of II mGluRs can "gate" the neurochemical and behavioral expression of psychostimulant sensitization, including the escalation of drug seeking and drug-taking seen under progressive ratio requirements. Thus, these receptors may be a potential target for pharmacotherapeutic intervention in cocaine addiction. Kim, J-H., Austin, J.D., Tanabe, L., Creekmore, E. and Vezina, P. Activation of Group II mGlu Receptors Blocks the Enhanced Drug Taking Induced by Previous Exposure to Amphetamine. European Journal of Neuroscience, 21, pp. 295-300, 2005.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Behavioral and Brain Development Research

Motor Development During the First 18 Months of Life in Children with Prenatal Cocaine Exposure

In a recent report from the multi-site Maternal Lifestyle Study, Miller-Loncar and colleagues examined patterns of motor development during the first 18 months of life in children with in utero exposure to cocaine. Motor development was examined at 1, 4, 12, and 18 months of age. The children were divided into two groups: 392 cocaine-exposed and 776 comparison. Exposure status was determined by meconium assay and maternal self-report. Relationships between level of exposure and motor development were also analyzed. Motor skills were assessed at 1 month using the NICU Network Neurobehavioral Scale (NNNS), at 4 months using the posture and fine motor assessment of infants (PFMAI), at 12 months using the Bayley Scales of Infant Development-Second Edition (BSID-II), and at 18 months using the Peabody Developmental Motor Scales (PDMS). Hierarchical linear modeling (HLM) was used to analyze change in motor skills from 1 to 18 months of age. Children with prenatal cocaine exposure showed low motor skills at their initial status of 1 month but displayed significant increases over time. Both higher and lower levels of tobacco use related to poorer motor performance on average. Heavy cocaine use related to poorer motor performance as compared to no use, but there were no effects of level of cocaine use on change in motor skills. Miller-Loncar, C., Lester, B.M., Seifer, R., et al. Predictors of Motor Development in Children Prenatally Exposed to Cocaine. Neurotoxicology and Teratology, 27(2), pp. 213-220, 2005.

Gender and Alcohol Exposure Influence Prenatal Cocaine Effects on Child Behavior at 7 Years of Age

A Wayne State University study research team has reported findings from analyses intended to provide new information on how gender and prenatal exposure to alcohol affect relationships between prenatal cocaine exposure and behavior problems at school age. This report is based on assessments conducted when the children were 7 years of age (a total of 499 children, 214 of which were exposed prenatally to cocaine). Analyses of teacher-reported child externalizing behavior problems data were stratified by gender and prenatal alcohol exposure status, and controlled for significant pre- and postnatal confounders. Results indicated that among boys with prenatal alcohol exposure, those with persistent cocaine exposure throughout pregnancy had significantly higher levels of delinquent behavior compared to boys with no cocaine exposure. Boys with any prenatal cocaine exposure were twice as likely as unexposed boys to have clinically significant externalizing behavior scores. However, no association was found between prenatal cocaine exposure and scores on externalizing behavior and specific syndromes for boys with no prenatal alcohol exposure. Among girls with no prenatal alcohol exposure, those with persistent cocaine exposure had significantly higher levels of externalizing behaviors and aggressive behaviors compared to girls with no prenatal cocaine exposure, and were almost five times as likely to have clinically significant externalizing behavior scores. However, for girls with prenatal alcohol exposure, no association between prenatal cocaine exposure and scores on externalizing behavior and specific syndromes was found after control for confounding. The investigators state that the current findings support gender- and alcohol-moderated effects of prenatal cocaine exposure on school-age teacher-reported child behavior problems. They also note that these findings are similar to what they have reported for independent parent-reported behaviors. Nordstrom Bailey, B., Sood, B.G., Sokol, R.J., et al. Gender and Alcohol Moderate Prenatal Cocaine Effects on Teacher-report of Child Behavior. Neurotoxicology and Teratology, 27(2), pp. 181-189, 2005.

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Grantee Honors

In Memoriam

Attentional Functioning and Impulse Control in 10-Year-Old Children Exposed to Cocaine in Utero

University of Pennsylvania investigators examined the question of whether children with gestational cocaine exposure may be at risk for difficulties in attentional functioning and impulse control. They administered the Gordon Diagnostic System (GDS) and subtests of the Halstead-Reitan Battery to inner-city children with and without gestational cocaine exposure at age 10 years. The GDS involves a visual computerized task battery that measures impulsivity and sustained attention through three tasks of increasing stress arousal. The subtests of the Halstead-Reitan Battery used were the Trail Making Test (a measure of visual attention) and the Seashore Rhythm Test (a measure of auditory attention). These assessments involved 40 exposed and 40 non-exposed children, a subset of the original study cohort. Subtle differences were found between the prenatally cocaine-exposed children and those not exposed to cocaine during gestation (on the GDS Delay and Distractibility Tasks). With these two exceptions, children had similar performance, with both groups performing poorly. Attentional functioning and impulse control were also assessed in school. Teachers did not distinguish between exposed and non-exposed children, although both groups presented behavioral problems. The researchers concluded that gestational cocaine exposure may be associated with subtle problems in attention and impulse control, putting exposed children at higher risk of developing significant behavioral problems as cognitive demands increase. They also noted that these analyses involved a small sample, and that there is need for continued investigation of the interplay between school performance and attentional regulation and impulse control in order to more fully develop knowledge of long-term effects of gestational cocaine exposure. Savage, J., Brodsky, N.L., Malmud, E., et al. Attentional Functioning and Impulse Control in Cocaine-Exposed and Control Children at Age Ten Years. Developmental and Behavioral Pediatrics, 26(1), pp. 42-47, 2005.

Youth Tobacco and Marijuana Use Relative to Prenatal Cigarette and Marijuana Exposure

As part of their long-term follow-up of prenatal marijuana and tobacco exposure, researchers at Carleton University have examined whether maternal cigarette smoking and marijuana use during pregnancy were associated with an increased risk of initiation and daily/regular use of tobacco and marijuana among one hundred fifty-two 16- to 21-year-old adolescent offspring. The participants were from a low risk, predominately middle-class sample participating in an ongoing, longitudinal study. Findings indicated that offspring whose mothers reported smoking cigarettes during their pregnancy were more than twice as likely to have initiated cigarette smoking during adolescence than offspring of mothers who reported no smoking while pregnant. Offspring of mothers who reported using marijuana during pregnancy were at increased risk for both subsequent initiation of cigarette smoking (OR=2.58) and marijuana use (OR=2.76), as well as daily cigarette smoking (OR=2.36), as compared to offspring of whose mothers did not report using marijuana while pregnant. There was also evidence indicating that dose-response relationships existed between prenatal exposure to marijuana and offspring use of cigarettes and marijuana. These associations were found to be more pronounced for males than females, and remained after consideration of potential confounding variables. The authors note that these results suggest that maternal cigarette smoking and marijuana use during pregnancy are risk factors for later smoking and marijuana use among adolescent offspring, and add to the weight of evidence supporting the importance of programs aimed at drug use prevention and cessation among women during pregnancy. Porath, A.J. and Fried, P.A. Effects of Prenatal Cigarette and Marijuana Exposure on Drug Use Among Offspring. Neurotoxicology and Teratology, 27(2), pp. 267-277, 2005.

Suicidal Behavior, Drug Use and Depressive Symptoms After Detoxification: a 2-Year Prospective Study

Individuals with substance-related disorders are at increased risk for suicidal behavior. This study examined factors associated with drug-related suicidal behavior using multivariable regression analyses in a 2-year prospective study of 470 inpatients enrolled from an unlocked, detoxification unit. Suicidal behavior included suicidal ideation (SI) and suicide attempt (SA). Lifetime prevalence for SI was 28.5%, and for SA, 21.9%. During the 2-year follow-up, 19.9% of the sample endorsed suicidal ideation and 6.9% reported a suicide attempt. Correlates of lifetime suicidal behavior included younger age, female, Hispanic, greater depressive symptoms, past sexual abuse, and problem sedative or alcohol use. Factors associated with suicidal

behavior at follow-up included past suicidal behavior, more depressive symptoms, and more frequent benzodiazepine and alcohol use. Cocaine and heroin use did not reach statistical significance. Differences in "suicide potential" may exist between drug categories with CNS depressants increasing the risk. These findings highlight the importance of addressing the recurrent 'suicide risk' of patients with substance-related disorders and regular monitoring for changes in depressive symptoms and drug use. Based on the prevalence and severity of this problem, the role of universal suicide screening of individuals with substance-related disorders merits greater attention. Wines, J.D. Jr., Saitz, R., Horton, N.J., Lloyd-Travaglini, C., and Samet, J.H. Drug and Alcohol Dependence. 76, Supplement 1, pp. S21-S29, 2004.

Evaluation of Behavioral Measures of Risk Taking Propensity with Inner City Adolescents

This study examined the utility of behavioral measures of risk-taking propensity in the assessment of self-reported real-world risk-taking behaviors using a sample of 51 high-school-aged inner-city adolescents. Results indicated that performance on one behavioral measure, the balloon analogue risk task (BART), accounted for unique variance in self-reported delinquency/safety risk behaviors as well as substance use risk behaviors, above and beyond that provided with demographics and self-report measures of risk-related constructs (i.e., impulsivity and sensation seeking). These results suggest the potential utilization of BART as part of a multimethod assessment to measure risk-taking propensity in adolescents. Aklin, W.M., Lejuez, C.W., Zvolensky, M.J., Kahler, C.W., and Gwadz, M., Behaviour Research and Therapy, 43(2), pp. 215-228, 2005.

Predictors of Infection with Chlamydia or Gonorrhea in Incarcerated Adolescents

This cross-sectional study examined the prevalence, multiple correlates, and gender differences in chlamydia and gonorrhea infections among adolescents, aged 13 to 18, incarcerated in a youth detention center in the southern region of the United States. Rates of undiagnosed chlamydia were 24.7% for incarcerated girls and 8.1% for boys. Gonorrhea was detected in 7.3% of the girls and 1.5% of the boys. Predictors of STD positivity differed for boys and girls. Demographic characteristics (gender, race, and age) account for 52% of the total variance in STD infections; youths' behavior accounts for approximately one third of the total variance, and psychological and family variables account for 8.6% and 7.2% of the total variance, respectively. Sexual activity while under the influence of alcohol was associated with a greater likelihood of testing positive for an STD. Beliefs about alcohol and other drugs regarding loss of control and enhancement of sex were not associated with testing positive. This study demonstrates that an approach that considers psychological and social influences on adolescent sexual behavior is useful for identifying potential risk and protective factors of adolescent STD/HIV risk that are amenable to intervention. Robertson, A.A., Thomas, C.B., St Lawrence, J.S., and Pack, R. Sexually Transmitted Diseases, 32(2), pp. 115-122, 2005.

Contributions of Amygdala and Striatal Activity in Emotion Regulation

Understanding how emotion influences cognitive processes is critical for understanding both normal and atypical behavior. Dr. B.J. Casey and her colleagues have used functional magnetic resonance imaging to probe the role of the amygdala and the striatum in processing emotional information in a paradigm in which individuals were instructed to respond to the presentation of a happy or fearful face. They found that reaction time when presented with fearful faces was longer than when presented with happy faces and that the increased reaction time was correlated with increased activation in the right amygdala. Activation in the right caudate nucleus was increased when a subject was successful in not responding to a happy face when instructed to do so, implicating this structure in behavioral inhibition or impulse control. These findings, in normal subjects, can be used to probe the possible alterations in brain responses that may accompany drug use or abuse. Hare, T.A., Tottenheim, N, Davidson, M.C., Glover, G.H. and Casey, B.J., Biol. Psychiatry 57, pp. 624-632, 2005.

T-maze Performance after Developmental Exposure to F-19 Tagged 5-HTP in Chicks

Many neurotransmitter systems that are known to be affected by drug use and drug exposure are present in the central nervous system in quantities that are undetectable by conventional neuroimaging techniques. Dr. Sherry Dingman and her colleagues have synthesized a 5-hydroxytryptophan molecule (5-HTP) tagged with

multiple fluorine atoms that should allow for the visualization of the serotonin neurotransmitter pathway using magnetic resonance spectroscopy. To determine whether the introduction of this molecule during development would affect serotonin function, it was injected into the airsac of chick eggs prior to hatching. Three days after hatching, the chicks that had been injected with the tagged 5-HTP were compared with chicks that had been injected with a control solution on a t-maze task selected for its sensitivity to serotonin function. No differences were found between the groups, indicating that performance on this task was unimpaired by the presence of the fluorine tagged molecule. Dingman, S., Nash, L., Hogan, J. and Branch, C., Perceptual and Motor Skills 99(3), pp. 793-798, 2004.

Alcoholism Risk, Tobacco Smoking, and P300 Event-related Potential

The amplitude of the P300 event-related potential has been reported to be smaller in children of alcoholic parents, i.e., in children at high risk for developing alcoholism, in some studies while other studies have not reported a difference. In this study, the amplitude of the P300 in response to a visual discrimination task was compared among young adults at low and high risk for the development of alcoholism that also differed on whether they smoked cigarettes. The results indicated that more of the variance in P300 amplitude was linked with smoking status than the risk for development of alcoholism. Since it has been suggested that alterations in P300 amplitude may be related to genetic risk for other disorders, the results of this study emphasize the need for taking smoking status into account in interpreting the results of studies using event-related potentials. Polich, J. and Ochoa, C.J., Clinical Neurophysiol. 115, pp. 1374-1383, 2004.

Small Tip Angle Three-Dimensional Tailored Radiofrequency Slab-Select Pulse for Reduced B1 Inhomogeneity at 3T

High field strength imaging systems have the advantages of increased signal-to-noise and signal-to-contrast ratios. Along with these advantages, however, is an increase in image artifacts due to inhomogeneities in the field. Dr. Stenger and his colleagues have developed a protocol that uses tailored radio frequency pulses and, in this report, provide evidence that the use of this protocol greatly reduces artifacts in high field strength images due to inhomogeneity while maintaining a reasonably short acquisition time. Saekho, S., Boada, F.E., Noll, D.C., and Stenger, V.A., Magnetic Resonance in Medicine 53, pp. 479-484, 2005.

Effects of Smoking and Smoking Abstinence on Cognition in Adolescent Tobacco Smokers

There is considerable evidence that exposure to nicotine during early development can have neurotoxic effects. In this study, Dr. Leslie Jacobsen and her colleagues sought to determine whether exposure to nicotine during adolescence had demonstrable cognitive effects. Behavioral data from 41 adolescent smokers and 32 non-users were obtained on a number of cognitive tasks. Abstinence from smoking, for both male and female adolescent nicotine users, significantly decreased their performance on a test of verbal learning. In a memory task, smokers performed less accurately than non-smokers; this difference was greater when the smokers were abstinent. Whether abstinent or not, the magnitude of the performance difference between smokers and non-smokers was positively correlated with smoking history (number of pack-years). In tests of visual and auditory attention, smokers were found to perform as accurately as non-smokers, but their reaction times were slower. Finally, in terms of gender effects, male smokers were found to perform less accurately than female smokers. Male smokers, however, tended to have smoked longer than female smokers and to have started smoking earlier, which may account for at least part of the difference. These findings strongly suggest that nicotine exposure during adolescence has deleterious effects. Jacobsen, L.K., Krystal, J.H., Mencl, W.E., Westerveld, M., Frost, S.J., and Pugh, K.R. Biol. Psychiatry pp. 56-66, 2005.

Early Development of Subcortical Regions Involved in Non-Cued Attention Switching

Being able to change one's focus between tasks, or among salient cues, is an important element in our cognitive repertoire that becomes more refined with age. In the series of experiments reported on here, Dr. B.J. Casey and her colleagues monitored brain activation patterns using fMRI as subjects of different ages switched from discriminating among stimuli based on shape or color. The results showed that both children and adults activated the caudate nuclei bilaterally when switching tasks (i.e., from a color-based discrimination to a shape-based discrimination or vice-

versa). Adults, however, had quicker reaction times and were more accurate in performing the task. The quicker reaction time was correlated with decreased activation of the caudate nuclei and increased activation in prefrontal and parietal cortical regions. These results suggest that subcortical regions are important in attention-switching and that the task increasingly involves cortical regions as the individual becomes older. Casey, B.J., Davidson, M.C., Hara, Y., Thomas, K.M., Martinez, A., Galvan, A., Halperin, J.M., and Tottenham, N. Developmental Science 7(5), pp. 534-542, 2004.

Imaging the Developing Brain: What Have We Learned About Cognitive Development

Dr. B.J. Casey and her colleagues authored an article in a special issue of Trends on Cognitive Sciences entitled "Cognitive Development: At the Crossroads" in which they reviewed the neuroimaging literature on the neurobiology of cognitive development. A general principle in cognitive development is the ability to filter and suppress irrelevant information and attend to relevant information. As this capacity increases with age activation of areas of association cortex becomes less diffuse and more focal and anatomical evidence suggests a concurrent refinement in the connections of these areas. In general, imaging studies of the developing human nervous system indicate that basic functions, such as motor and sensory processing, mature first followed by areas involved in control of actions and that this maturation process is accompanied by a more refined and specific pattern of brain activation. Casey, B.J., Tottenham, N., Liston, C., and Durston, S. Trends in Cognitive Sciences 8(3), pp. 104-110, 2005.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Clinical Neuroscience Research

Smoking Topography and Mood: Effects of Trauma-Related Recall Versus Recall of Neutral Experiences in Trauma Survivors with PTSD

Researchers at Duke Medical Center measured smoking topography in trauma survivors with and without posttraumatic stress disorder (PTSD) after recalling trauma-related and neutral experiences. Analysis of covariance was performed on puff topography and mood measures using nicotine dependence scores and current major depressive disorder as covariates. Puff volumes were higher in the PTSD group than in the non-PTSD group. The PTSD group exhibited stable puff onset intervals while the non-PTSD group exhibited significantly shorter intervals following trauma recall. These findings support a "ceiling effect" hypothesis in which individuals with PTSD perpetually smoke in such a way as to maximize nicotine delivery, possibly reducing the potentially reinforcing effects of increased smoke delivery in negative affect-inducing situations. McClernon, F.J., Beckham, J.C., Mozley, S.L., Feldman, M.E., Vrana, S.R. and Rose, J.E. Addictive Behaviors, 30, pp. 247-257, 2005.

Additive Effects of HIV and Chronic Methamphetamine Use on Brain Metabolite Abnormalities

Dr. Linda Chang and associates sought to determine whether HIV coupled with a history of chronic methamphetamine (METH) use might have additive or interactive effects on brain metabolite abnormalities. 1H-MRS was performed in 68 HIV-positive subjects (24 with a history of chronic METH use with a lifetime exposure of a mean of 2,167 g and last use a mean of 4.9 months earlier and 44 HIV+ individuals with no history of drug abuse) and compared to 1H-MRS in 75 HIV-negative subjects (36 with a history of chronic METH use with a lifetime exposure of a mean of 8,241 g and last use a mean of 6.3 months earlier; 39 had no history of drug abuse). Results showed decreased N-acetylaspartate and increased myo-inositol in subjects with chronic METH use and in subjects infected with HIV. Chronic METH users who were HIV- showed lower concentrations of N-acetylaspartate in the frontal white matter and basal ganglia and higher concentrations of choline compounds and myo-inositol in the frontal cortex, relative to subjects with no history of drug abuse. HIV+ status was associated with lower concentrations of N-acetylaspartate and creatine in the frontal cortex and higher concentrations of myo-inositol in the white matter, compared with HIV- status. The combined effects of HIV and chronic METH use were consistent with an additive model, suggesting additional neuronal injury and glial activation due to the comorbid conditions. Chang, L., Ernst, T., Speck, O. and Grob, C.S. American Journal of Psychiatry, 162, pp. 361-369, 2005.

Decreased Brain Dopaminergic Transporters in Patients With HIV-Associated Dementia

Since HIV has a propensity to invade subcortical regions of the brain, which may lead to a subcortical dementia termed HIV-cognitive motor complex, NIDA investigators assessed whether dopamine (DA) D2 receptors and transporters (DAT) are affected in the basal ganglia of subjects with HIV, and how these changes relate to dementia status. Fifteen HIV subjects (average age 44.5; mean CD4 185mm) and 13 seronegative controls (average age of 42) were evaluated with PET to assess availability of DAT ([11C]cocaine) and DA D2 receptor ([11C]raclopride). HIV patients with associated dementia (HAD), but not those without dementia (ND) had significantly lower DAT availability in putamen and ventral striatum compared with seronegative controls. Higher plasma viral load in the HIV dementia patients correlated with lower DAT in the caudate and putamen. DA D2 receptor availability,

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however, showed mild and non-significant decreases in HIV patients. These results provide the first evidence of DA terminal injury in HIV dementia patients, and suggest that decreased DAT may contribute to the pathogenesis of HIV dementia. The greater DAT decrease in the putamen than in the caudate parallels that observed in Parkinson's disease. The inverse relationship between viral burden and DAT availability further supports HIV-mediated neurotoxicity to dopaminergic terminals. Wang, G.J., Chang, L., Volkow, N.D., Telang, F., Logan, J., Ernst, T. and Fowler, J.S. Brain, 127, pp. 2452-2458, 2004.

Neurocognitive Performance of Methamphetamine Users Discordant for History of Marijuana Exposure

Abuse of the stimulant drug methamphetamine (METH) is associated with neural injury and neuropsychological (NP) deficits, while the residual effects of marijuana use remain uncertain. Researchers at UCSD sought to determine if methamphetamine dependent persons who also met criteria for marijuana abuse or dependence evidenced different NP performance than those with dependence for METH alone. Three groups that did not differ significantly on important demographic factors were tested: (1) subjects with a history of METH dependence and history of marijuana (MJ) abuse/dependence (METH+/MJ+, n=27); (2) METH dependent subjects without history of MJ abuse/dependence (METH+/MJ-, n=26); (3) a control group with minimal or no drug use (n=41). A comprehensive NP battery was administered and performance was quantified for five cognitive ability areas. The METH+/MJ- group generally demonstrated the greatest NP impairment, with statistically significant differences observed between the METH+/MJ- and control group in learning, retention/retrieval, and a summary score of global NP performance. The METH+/MJ+ group did not differ significantly from the control or METH+/MJ- group on any NP ability. However, there was a significant linear trend in the global NP score suggesting that the METH+/MJ+ performed intermediate to the control and METH+/MJ- groups. Based on these findings, the authors cannot conclude that there is a protective effect of marijuana use in METH users; however, MJ use clearly did not appear to exacerbate METH neurotoxicity. Further investigations are needed to determine if the emerging literature, suggesting that certain cannabinoids might have neuroprotective actions, is generalizable to community-dwelling substance abusers. Gonzalez, R., Rippeth, J.D., Carey, C.L., Heaton, R.K., Moore, D.J., Schweinsburg, B.C., Cherner, M. and Grant, I.. Drug and Alcohol Dependence, 76, pp. 181-190, 2004.

Route of Administration of Methamphetamine in Men Who Have Sex With Men Uncovers Psychosocial Differences, Risk Behaviors

Dr. Grant and colleagues at UCSD compared injection and non-injection users of METH in terms of background characteristics, drug use patterns, health and social problems, sexual risk behavior, and psychosocial factors. The sample consisted of 194 HIV+Men who have Sex with Men (MSM) who were enrolled in a sexual risk reduction intervention for METH users. Men who injected METH were significantly more likely to be Caucasian, bisexual, homeless, divorced/separated, with lower educational attainment as compared to non-injectors. Injectors also reported more years of METH use, greater frequency and amount of METH, more social and health problems, including higher prevalence of STDs and Hepatitis C, and more sexual risk behaviors. In terms of psychosocial factors, injection users of METH scored significantly higher on measures of impulsivity and experiences of rejection, and lower on a measure of emotional support. A multivariate logistic regression revealed that educational attainment and experiences of rejection were the factors that best discriminated between injection and non-injection users of METH. The unique characteristics of injection METH users are discussed in relation to the development of effective HIV prevention programs for the target population. Semple, S.J., Patterson, T.L. and Grant, I. Drug Alcohol Dependence, 76, pp. 203-212, 2004.

Neurocognitive and Emotional Differences in Abstinent Drug Abusers Compared to Non Users

NIDA researchers undertook a study to compare the performance of abstinent drug abusers (n = 21) and nonuser control participants (n = 20) in neurocognitive and emotional functions by use of the Rogers Decision Making Task, Gambling Task, Emotional Stroop, impulsivity continuous performance task (CPT), and vigilance CPT. Skin conductance (SC) and heart rate (HR) monitoring was synchronized with task performance. Groups showed similar performance for vigilance, impulsivity, and emotional interference; however, drug abusers showed stronger SC responses. Drug abusers performed more poorly on the Gambling and Rogers Decision Making Tasks. When making risky decisions, drug abusers showed significantly less increase in SC activity than controls and exhibited lower HRs throughout performance on all tasks. In

conclusion, complex tasks involving decision making, sensitivity to consequences, and emotional regulation discriminated between drug abusers and controls. Fishbein, D., Hyde, C., Eldreth, D., London. E.D., Matochik, J., Ernst, M., Isenberg, N., Steckley, S., Schech, B. and Kimes A. Experimental Clinical Psychopharmacology, 13, pp. 25-40, 2005.

Nicotine Temporarily Normalizes Smooth Pursuit Eye Movement Deficits in Schizophrenia

Dr. Tanabe and colleagues used functional magnetic resonance imaging (fMRI) to examine changes in brain hemodynamic response associated with nicotine administration during a smooth pursuit eye movement task in subjects with schizophrenia. Nine subjects with schizophrenia performed the eye movement task while undergoing fMRI. Subjects were then given nicotine (pilocrilex) or placebo and repeated the task while being scanned. Subjects repeated the procedure the following week, receiving the counterbalanced condition. Compared with placebo, nicotine was associated with greater activity in the anterior and posterior cingulate gyri, precuneus, and area MT/MST and less activity in the hippocampus and parietal eye fields. Changes in area MT/MST and the cingulate gyrus are consistent with an improvement in perception and attention to moving stimuli. The most important observed difference between nicotine and placebo--less activation of the hippocampus after nicotine than after placebo administration--is consistent with nicotinic receptor mediation of inhibitory neuronal dysfunction in schizophrenia. Tregellas J.R., Tanabe J.L., Martin L.F. and Freedman R. American Journal of Psychiatry, 162, pp. 391-393, 2005.

Cognitive Mechanisms Underlying Deficits in Episodic Verbal Memory in Methamphet-amine (METH) Abusers

Dr. Igor Grant and colleagues at UCSD evaluated a component process model of episodic verbal memory in 87 persons with METH dependence (METH+) and 71 demographically similar non-METH-using controls (METH-). Compared with METH-controls, METH+ participants demonstrated deficient overall learning, free recall, and utilization of semantic clustering, as well as higher rates of repetitions and intrusions. No between-groups differences were evident on measures of serial clustering, retention, or recognition discrimination. Taken together, these findings indicate that METH dependence is associated with deficient strategic (i.e., executive) control of verbal encoding and retrieval, which is consistent with the sequelae of METH-related prefronto-striatal circuit neurotoxicity. Woods, S.P., Rippeth, J.D., Conover, E., Gongvatana, A., Gonzalez, R., Carey, C.L., Cherner, M., Heaton, R.K. and Grant, I. Neuropsychology, 19, pp. 35-43, 2005.

Transverse Relaxation Rate Can Compromise fMRI Results

Several modern MRI techniques, such as functional MRI (fMRI), rely on the detection of microscopic changes in magnetic susceptibility. However, differences in magnetic susceptibility between brain tissue, bone, and air also produce local magnetic field gradients that may interfere with the contrast of interest, particularly at high field strengths. Since the magnetic field distribution depends on the orientation of the human head in the MRI scanner, head rotations can change the effective transverse relaxation rate (R(2)*) and confound fMRI studies. The size of the R(2)* changes produced by small head rotations was estimated from a brain-shaped gel-phantom at 4 T, by measuring the signal decay at 96 different echo times. Similar measurements were carried out in a human study. Rotations larger than 2 degrees changed R(2)* more than 1.5 Hz in the phantom, and indicate that even small rotations may compromise fMRI results. Caparelli, E.C., Tomasi, D. and Ernst, T. Neuroimage, 15, pp. 1164-1169, 2005.

Neurotoxic Effects of Prenatal Methamphetamine (METH) Exposure on the Developing Brain and on Cognition

Dr. Linda Chang and associates at the University of Hawaii examined Meth-exposed children (n=13) and unexposed controls (n=15) with MRI in a pilot study to examine neurotoxic effects of prenatal METH exposure. Global brain volumes and regional brain structures were quantified. Ten METH-exposed and nine unexposed children also completed neurocognitive assessments. METH-exposed children scored lower on measures of visual motor integration, attention, verbal memory and long-term spatial memory. There were no differences among the groups in motor skills, short delay spatial memory or measures of non-verbal intelligence. Despite comparable whole brain volumes in each group, the METH-exposed children had smaller putamen bilaterally (-17.7%), smaller globus pallidus (left: -27%, right: 30%), smaller

hippocampus volumes (left: -19%, right: -20%) and a trend for a smaller caudate bilaterally (-13%). The reduction in these brain structures correlated with poorer performance on sustained attention and delayed verbal memory. No group differences in volumes were noted in the thalamus, midbrain or the cerebellum. In summary, compared with the control group, children prenatally exposed to METH exhibit smaller subcortical volumes and associated neurocognitive deficits. These preliminary findings suggest that prenatal METH exposure may be neurotoxic to the developing brain. Chang, L., Smith, L.M., LoPresti, C., Yonekura, M.L., Kuo J., Walot, I. and Ernst, T. Psychiatry Research, 132, pp. 95-106, 2004.

New Measures of Corpus Callosum Size Are Related To Drug Abuse and To Childhood Neglect and Abuse

While many neuroimaging studies focus on deficits in cortical gray matter in patients with drug abuse or with cognitive deficits, Dr. Moeller and associates at the University of Texas Health Science Center, Houston, have used recent technology in Diffusion Tensor Imaging (DTI) and found reduced white matter integrity in areas of the corpus callosum in cocaine-dependent subjects. In addition, tests of impulsivity showed significant (negative) correlations with callosal integrity. It should be noted, however, that not the entire callosum showed a difference between cocaine-dependent subjects and controls; differences were found only in the genu and rostral body and are likely related to cross-connecting areas in the prefrontal cortex. Moeller, F.G., Hasan, K.M., Steinberg, J.L., Kramer L.A., Dougherty, D.M., Santos, R.M., Valdes, I., Swann, A.C., Barratt, E.S. and Narayan, P.A. Neuropsychopharmacology, 30, pp. 610-617, 2005.

Childhood Neglect Is Associated With Reduced Corpus Callosum Area

Dr. Teicher and colleagues at McLean Hospital reported reduced corpus callosum area in children who were neglected or abused. This is important because early physical or sexual abuse is likely associated with later drug abuse. However, the affected areas were posterior to those found by Moeller and associates. Nevertheless, these data may help understand the effect of early events in brain development and their impact on drug abuse liability. Teicher, M.H., Dumont, N.L., Ito, Y., Vaituzis, C., Giedd, J.N and Anderson, S.L. Biological Psychiatry, 56, pp. 80-85, 2004.

Specific Brain Regions Are Activated Following Script-Induced Emotions In Cocaine Users and in Non-Using Individuals

Dr. Sinha at Yale University has found limbic and other brain structures to be activated as measured by fMRI in cocaine users and in non-using subjects as they listen personalized scripts designed to induce heightened emotions. In non-using subjects, increases were observed in limbic and midbrain regions such as the striatum, and thalamic regions, caudate, putamen, hippocampus, parahippocampus and posterior cingulate. In some of these areas, left activation was greater. In cocaine users, stress tended to activate temporal areas in addition to medial and superior frontal gyri and anterior cingulate. Of most interest, women seemed to have the greater activation. Sinha, R., Lacadie, C., Skudlarksi, P. and Wexler, B.E., Annals of the New York Academy of Science, 1032, pp. 254-257, 2004; Li, C-S.R., Koston, T.R. and Sinha, R. Biological Psychiatry, 57, pp. 487-494, 2005.

Allelic Variants within the GABAB Receptor Subunit 2 (GABAB2) Gene Significantly Associated with Nicotine Dependence

Dr. Li and colleagues at University of Texas Health Science Center conducted a detailed study on Gamma-aminobutyric acid type B receptor subunit 2 (GABAB2) that is mapped to the linkage area on Chromosome 9. It was investigated with single nucleotide polymorphisms (SNPs) and associated haplotypes in a sample of European Americans (EA) and African Americans (AA). Significant associations to nicotine dependence were found for four of the twelve SNPs in the pooled sample and two SNPs in the AA sample and four in the EA sample. In addition, haplotypes made up of some of these SNPs were also significant, and in two cases, highly significantly associated with nicotine dependence. These results indicate that GABAB2 may be associated with nicotine dependence even though these gene variants themselves were not likely to be responsible for dependence. In addition it is clear there are ethnic differences in the associations. The authors conclude that "the study not only confirms molecular and pharmacological data about the importance of the family of GABA receptor genes in addictive/behavioral trains, but it also provides new information on the genetics of nicotine dependence." Beuten, J., Ma, J.Z., Payne, T.J., Dupont, R.T., Crews, K.M., Somes, G., Williams, N.J., Elson, R.C. and Li, M.D. American Journal of Human Genetics, 76, pp. 859-864, 2005.

Susceptibility Loci and Gene Variants (Including One Within A GABAB2

Subunit) Associated With Nicotine Dependence

Dr. Li and colleagues at the University of Texas Health Science Center, San Antonio, report linkages and suggestive linkages to various chromosome regions and markers from two separate cohorts. One includes permutation linkage analysis of the well-known Framingham Heart Study cohort. Using "cigarettes per day" as the best (highest correlative) measure of nicotine dependence, linkages were found on chromosomes 1,3,4,7,8,9,11,16,17, and 20; the highest significance was for 1 and 4. Most of these have been reported by other nicotine studies and therefore provide good candidate regions for further study. Wang, D., Ma, J.Z. and Li, M.D. The Pharmacogenomics Journal, e-publication, 2005.

Neurophysiology of Motor Function following Cannabis Discontinuation in Chronic Cannabis Smokers: An fMRI Study

Dr. Yurgelun-Todd and her colleagues at McLean Hospital used fMRI to investigate whether attentional areas related to motor function as well as primary and supplementary motor cortices would show diminished activation in chronic cannabis smokers. Nine cannabis smokers and 16 controls were scanned using a 1.5 T scanner during a finger sequencing task. Cannabis users, tested within 4-36 hr of discontinuation, exhibited significantly less activation than controls in the anterior cingulate (BA 24 and 32) and pre-motor cortex (BA 6). There were no statistically significant group differences in BA 4. None of these regional activations correlated with urinary cannabis concentration and verbal IQ for smokers. These results suggest that recently abstinent chronic cannabis smokers produce reduced activation in motor cortical areas in response to finger sequencing compared to controls. Pillay, S.S., Rogowska, J., Kanayama, G., Jon, D.I., Gruber, S., Simpson, N., Cherayil, M., Pope, H.G. and Yurgelun-Todd, D.A. Drug and Alcohol Dependence 76, pp. 261-271, 2004.

Dissociation in Attentional Control in Methamphetamine Dependence

Dr. Ruth Salo and colleagues at the University of California, Davis investigated whether task-shifting, selective inhibition, or both processes were impaired in long-term but currently abstinent methamphetamine-dependent individuals. Methamphetamine-dependent subjects (n=34) and nonsubstance abusing controls (n=20) were tested on an alternating-runs switch task with conflict sequences that required subjects to switch tasks on every second trial (AABBAABB). Methamphetamine-dependent individuals committed more errors on trials that required inhibition of distracting information compared with controls (methamphetamine = 17%, controls = 13%, p =.02). By contrast, error rates did not differ between the groups on switch trials (methamphetamine = 7%, controls = 6%, n.s.). These results indicate that selective inhibition, but not task switching , is selectively compromised by methamphetamine. Salo, R.., Nordahl, T.E., Moore, C., Waters, C., Natsuaki, Y., Galloway, G.P., Kile, S. and Sullivan, E.V. Biological Psychiatry 57, pp. 310-313, 2005.

Role of the Amygdala and the Medial Temporal Lobe Memory System in Retrieving Emotional Memories One Year Later

Dr. Kevin LaBar and colleagues at Duke University used fMRI to investigate the contribution of emotion on memory-enhancing retrieval processes after lengthy retention intervals. In the present study, event related fMRI was used to measure neural activity during the retrieval of emotional and neutral pictures after a retention interval of 1 yr. Retrieval activity for emotional and neutral pictures was separately analyzed for successfully (hits) vs. unsuccessfully (misses) retrieved items and for responses based on recollection vs. familiarity. Recognition performance was better for emotional than for neutral pictures, and this effect was found only for recollection-based responses. Successful retrieval of emotional pictures elicited greater activity than successful retrieval of neutral pictures in the amygdala, entorhinal cortex, and hippocampus. In the amygdala and hippocampus, the emotion effect was greater for recollection than for familiarity, whereas in the entorhinal cortex, it was similar for both forms of retrieval. These findings suggest that the amygdala and the medial temporal lobe memory regions play a role in recollection and familiarity of memories with emotional content after lengthy retention intervals, such as with events associated with drug use. Dolcos, F., LaBar, K.S. and Cabeza, R. Proceedings of the National Academy of Sciences of the United States of America 102, pp. 2626-2631, 2005.

Anger and Depression in Cocaine Addiction: Association with the Orbitofrontal Cortex

Dr. Rita Goldstein and colleagues at Brookhaven National Laboratories investigated

whether anger, impulsivity and violence is related to the compromise of higher-order inhibitory control neurocognitive processes mediated by frontal brain regions in cocaine addiction. The Minnesota Multiphasic Personality Inventory-2 (MMPI-2) anger content scale was used as a personality measure of inhibitory control. This scale was examined for correlations with glucose metabolism in the lateral orbitofrontal gyrus (LOFG) at rest as measured by positron emission tomography with 2-deoxy-2[F-18]fluoro-D-glucose (PET (18)FDG) in 17 recently abstinent cocaine-dependent subjects and 16 comparison subjects. Three additional variables-the MMPI-2 depression content scale, metabolism in the medial orbitotrontal gyrus (MOFG) and the anterior cingulate (AC) gyrus were also examined. When level of education was statistically controlled for, the LOFG was significantly associated with anger within the cocaine group. No other region was associated with anger within the cocaine-dependent group. The LOFG did not correlate with depression within any of the study groups. The present study confirms earlier reports in demonstrating a positive association between relative metabolism at rest in the LOFG and cognitive-behavioral and personality measures of inhibitory control in drug addiction: the higher the metabolism, the better the inhibitory control. Goldstein, R.Z., Alia-Klein, N., Leskovjan, A.C., Fowler, J.S., Wang, G.J., Gur, R.C., Hitzemann, R. and Volkow N.D. Psychiatry Research-Neuroimaging 138, p. 13, 2005.

Frontal Networks for Learning and Executing Arbitrary Stimulus - Response Associations

Dr. Mark D'Esposito at the University of California, Berkeley used fMRI to investigate the role of the prefrontal cortex in flexible rule learning, such as the formation of arbitrary stimulus-response (S-R) associations. Since humans learn these rules very quickly, fMRI scans were acquired while normal, healthy subjects learned by trial and error to associate sets of abstract visual stimuli with arbitrary manual responses. Successful learning of this task required discernment of a categorical type of S-R rule in a block design expected to yield sustained rule representation. Our results show that distinct components of the dorsolateral, ventrolateral, and anterior PFC, lateral premotor cortex, supplementary motor area, and the striatum are involved in learning versus executing categorical S-R rules. Boettiger, C.A. and D'Esposito, M. Journal of Neuroscience 25, pp. 2723-2732, 2005.

Brain Metabolite Abnormalities in Methamphetamine Users in Sustained Abstinence

Dr. Thomas Nordahl and colleagues at the University of California, Davis used proton magnetic resonance spectroscopy (MRS) to determine whether methamphetamine abusers (n=8) continue to exhibit abnormalities in brain neurochemistry after 1 year of abstinence compared to recently abstinent methamphetamine abusers (n=16). Absolute levels of creatine (Cr) did not differ between methamphetamine abusers and normal controls. Compared to controls, both recent and long-term abstinent methamphetamine abusers had low levels of n-acetylaspartate-creatine to phosphocreatine ratios (NAA/Cr) in the anterior cingulate cortex. These differences were specific to the frontal cortex in that no differences were seen in NAA/Cr ratios between controls and methamphetamine abusers in the primary visual cortex. On the other hand, choline-creatine to choline-N-acetylaspartate (Cho/NAA) ratios were abnormally elevated in the anterior cingulate of recently abstinent methamphetamine abusers, but were at normal levels in the methamphetamine abusers who had been abstinent for a year. These results indicate that following one year of abstinence from methamphetamine, some, but not all, measures of brain neurochemistry show evidence of recovery. Nordahl, T.E., Salo, R. Natsuaki, Y., Galloway, G.P., Waters, C., Moore, C.D., Kile, S. and Buonocore, M.H. Archives of General Psychiatry 62, pp. 444-452, 2005.

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Research Findings - Epidemiology and Etiology Research

Drug Use as a Complex Phenotype: A Review

Drug use is a complex behavior influenced by multiple biological, family, and socio-cultural factors. The concurrent use/misuse of multiple drugs is often seen and drug use also co-occurs with other psychiatric conditions. Behavior and molecular genetic studies support an important posited role of genes in drug use. This posited genetic risk does not appear to be conferred by one or two major genes manifesting large effects, but rather by a number of genes manifesting smaller effects. Genetic factors explain, on average, only about half of the total variability in drug use, with the remaining variability influenced by environmental factors. Also, genetic risk may be differentially expressed in the presence vs. absence of particular environmental conditions. Thus, investigation of environmental factors and their interaction with genetic risk is a necessary component of genetic research. While the full potential of genetic investigations for the prevention of drug misuse has yet to be realized, an example of the impact of risk factor modification under various conditions of gene-environment interaction is provided, and the implications for use of genetic information in drug-misuse prevention are discussed. The multifactorial nature of drug use necessitates coordinated investigation from multiple disciplines and timely dissemination of scientific findings. In addition, this work demands adherence to the highest standards of confidentiality and ethical use of genetic information to best inform future prevention efforts. Lessov, C.N., Swan, G.E., Ring, H.Z., Khroyan, T.V. and Lerman, C. Genetics and Drug Use as a Complex Phenotype. Substance Use and Misuse 39, pp. 1515-1569, 2004.

Cognitive and Contextual Mediators of Substance Use

This study examined the cognitions thought to mediate the impact of context on adolescent substance use and also the extent to which context moderates the relations between these cognitions and use. Risk cognitions and behaviors were assessed in a panel of 746 African American adolescents (M age 10.5 at Wave 1, 12.2 at Wave 2). Results indicated that adolescents living in high-risk neighborhoods were more inclined toward substance use and more likely to be using at Wave 2. These context effects were mediated by the adolescents' risk cognitions, their risk images, willingness to use, and intentions to use. Also, context moderated the relation between willingness and use (the relation was stronger in high-risk neighborhoods) but it did not moderate the intentions to use relation. Gibbons, F.X., Gerrard, M., Lune, L.S.V., Wills, T.A., Brody, G. and Conger, R.D. Context and Cognitions, Environmental Risk, Social Influence, and Adolescent Substance Use. Personality and Social Psychology Bulletin 30, pp. 1048-1061, 2004.

Caregiver Factors Buffer Effects of Violence Exposure on Adjustment Problems

This short-term, longitudinal interview study used an ecological framework to explore protective factors within the child, the caregiver, the caregiver-child relationship, and the community that might moderate relations between community violence exposure and subsequent internalizing and externalizing adjustment problems and the different patterns of protection they might confer. Participants included 101 pairs of African American female caregivers and one of their children (56% male, M = 11.15 yrs, SD = 1.28) living in high-violence areas of a mid-sized southeastern city. Child emotion regulation skill, felt acceptance from caregiver, observed quality of caregiver-child interaction, and caregiver regulation of emotion each were protective, but the pattern of protection differed across level of the child's ecology and form of adjustment.

Kliewer, W., Cunningham, J.N., Diehl, R., Parrish, K.A., Walker, J.M, Atiyeh, C., Neace, B., Duncan, L., Taylor, K. and Mejia, R. Violence Exposure and Adjustment in Inner-city Youth: Child and Caregiver Emotion Regulation Skill, Caregiver-child Relationship Quality, and Neighborhood Cohesion as Protective Factor. J Clin Child Adolesc Psychol. 33(3), pp. 477-487, 2004.

Shared Environment, Genetics and Sibling Social Connectedness Predict Adolescent Smoking

Using a genetically informative sample of adolescents, this study assessed whether sibling effects on smoking reflect social rather than genetic processes. A combined twin-sibling design, with 1421 sibling pairs, was employed to disentangle genetic and non-genetic effects. These sibling pairs represent a spectrum of genetic relatedness and include monozygotic twins, dizygotic twins, biological siblings, half-siblings and unrelated siblings. Main effects of both shared environment and genetics were found on adolescent smoking frequency. Social connectedness between siblings moderated shared environmental influences on smoking frequency at each time period, as well as on change in smoking frequency. Shared environmental effects were more pronounced when siblings reported high levels of social connectedness. These environmental sibling effects on smoking were significant after controlling for parent and peer smoking. This report extends prior research on sibling effects on smoking by identifying specific relationship dynamics that underlie transmission of risk within sibships and providing evidence that such relationship dynamics represent social rather than genetic processes. Slomkowski, C., Rende, R., Novak, S., Lloyd-Richardson, E. and Niaura, R. Sibling Effects On Smoking In Adolescence: Evidence For Social Influence From A Genetically Informative Design. Addiction 100(4), pp. 430-438, 2005.

Effects of Parent and Peer Support on Adolescent Substance Use

This research tested comparative effects of parent and peer support on adolescent substance use (tobacco, alcohol, and marijuana) with data from 2 assessments of a multiethnic sample of 1,826 adolescents, mean age 12.3 years. Multiple regression analyses indicated that parental support was inversely related to substance use and that peer support was positively related to substance use, as a suppression effect. Structural modeling analyses indicated that effects of support were mediated through pathways involving good self-control, poor self-control, and risk-taking tendency, parent and peer support had different patterns of relations to these mediators. The mediators had pathways to substance use through positive and negative recent events and through peer affiliations. Effects for gender and ethnicity were also noted. Mechanisms of operation for parent and peer support are discussed. Wills, T.A., Resko, J.A., Ainette, M.G. and Mendoza, D. Role of Parent Support and Peer Support in Adolescent Substance Use, A Test of Mediated Effects. Psychology of Addictive Behaviors 18, pp. 122-134, 2004.

Positive Adult Behavior Predicts Crime and Substance Use

Drawing on diverse approaches to the study of youth development and adult functioning, as well as social capital and citizenship, this investigation identified measures of positive adult behavior, which has been given less attention in research. Analyses included 765 participants from the Seattle Social Development Project interviewed at age 21. Seven measures of positive adult behavior were identified: volunteerism, group involvement, neighborliness, interpersonal connection, constructive engagement, financial responsibility, and honesty. Measures related to distal social relationships (group involvement and neighborliness) had relatively weak associations with crime and substance use. In contrast, the measures of constructive engagement, financial responsibility, and honesty had significant negative associations with multiple measures of crime and substance use. Results indicate that the seven measures provide relatively independent variables useful for assessing positive adult behavior. These measures can be used to assess positive outcomes in adulthood of intervention studies, or to assess the prevalence of positive adult behavior in different populations or groups. Kosterman, R., Hawkins, J.D., Abbott, R.D., Hill, K.G., Herrenkohl, T.I. and Catalano, R.F. Measures of Positive Adult Behavior and their Relationship to Crime and Substance Use. Prevention Science 6(1), pp. 21-33, 2005.

Neighborhood Social Disorder as a Determinant of Drug Injection Behaviors

Neighborhood environments are increasingly recognized as a contextual determinant of health, behaviors, and disease; however, the pathways through which neighborhood characteristics impact health behaviors are poorly understood. This

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article examines pathways to elucidate how neighborhood social disorder may lead to HIV transmission. Data are from a baseline survey of 701 IDUs from the Self-Help in Eliminating Lethal Diseases (SHIELD) Study, an HIV prevention intervention in Baltimore. Structural equation modeling was used to examine the pathways among social disorder, psychological distress, and drug injection behaviors. The relationship between disorder and injection behaviors in the models tested suggests that psychological distress is higher in more socially disordered neighborhoods; that distress leads to greater injection frequency and equipment sharing; and that injection frequency predicts equipment sharing. Latkin, C., Williams, C. and Wa. J. Neighborhood Social Disorder as a Determinant of Drug Injection Behaviors: A Structural Equation Modeling Approach. Health Psychology, 24(1), pp. 96—100, 2005.

Gang Membership Associated with Increased Drug Involvement

This study examined whether gang membership is associated with higher levels of delinquency and drug involvement because boys predisposed to delinquent activity are more likely than others to join. Ten years of longitudinal data from 858 participants of the Pittsburgh Youth Study were used to identify periods before, during and after gang membership. This study builds on prior research by controlling for ages and calendar time, by better accounting for gang memberships that occurred before the study began, and by using fixed effects statistical models. Findings show that boys who join gangs are more delinquent before entering the gang than those who do not join. Even with such selective differences, however, studies replicate prior research showing that drug selling, drug use, violent behaviors and vandalism of property increase significantly when a youth joins a gang. The delinquency of peers appears to be one mechanism of socialization. These findings are clearest in youth self-reports, but are also evident in reports from parents and teachers on boys' behavior and delinquency. After adjusting for time trends, the increase in delinquency is temporary and delinquency falls to pre-gang levels when boys leave gangs. Gordon, R.A., Lahey, B.B., Kawai, E., Loeber, R., Stouthamer-Loeber, M. and Farrington, D.P. Antisocial Behavior and Youth Gang Membership, Selection and Socialization. Criminology, 42, pp. 55-87, 2004.

Trends in Recall and Appraisal of Anti-smoking Advertising among American Youth: National Survey Results, 1997-2001

Data from the Monitoring the Future Study (MTF) were analyzed to provide (a) a description of the overall extent of exposure to anti-smoking media among American youth from 1997 to 2001, (b) an appraisal of general youth reactions to such advertising, and (c) an examination of how exposure levels and reactions vary by socio-demographic characteristics. MTF data were collected each year from nationally representative school samples of 8th, 10th, and 12th grade students (N = 29,724; 24,639; and 12,138, respectively). Self-reported levels of recalled exposure to both electronic and print anti-smoking advertising were measured, as well as the judged impact and perceived exaggeration of such advertising. Data indicate that significant increases in overall exposure to anti-smoking advertising occurred over the study time period. These increases were associated with (a) increases in the self-reported likelihood that anti-smoking advertising diminished the probability of individual smoking behaviors, and (b) increases in the perceived level to which anti-smoking advertising exaggerates the risks associated with smoking. Further, these trends were significantly associated with various characteristics-most notably, ethnicity, smoking behaviors, and residence in a state with an ongoing tobacco-control program having a media component. The findings of this study suggest that current anti-smoking media efforts may be positively impacting youth behaviors, however the ramifications of the level to which ads are perceived to exaggerate behavior risks are not clear. Johnston, L.D., Terry-McEllrath, Y.M., O'Malley, P.M. and Wakefield, M. Prevention Science 6(1), pp. 1-19, 2005.

The Internet and Substance Abuse Among Adolescents

Recognizing that the Internet contains a large amount of information on the use of psychoactive substance, the investigators analyzed preliminary data from a cross-sectional survey of adolescents to examine the effect of the Internet on their drug-use knowledge, attitudes, and behaviors. Of 12 patients (9 male, 3 female) who had used the Internet to learn about psychoactive substances, 100% reported that Internet-based information had affected the ways in which they had used psychoactive substances. Eight of the respondents described adopting behaviors intended to minimize the risks associated with psychoactive substance use. Respondents also reported changes in the use of a wide variety of illicit substances as well as over-the-counter and prescription pharmaceuticals. Analysis of respondents' knowledge, attitudes and behaviors towards drugs suggested that the youth were influenced by

Internet information. These preliminary findings suggest that Web-based data on psychoactive substances may influence a broad range of drug-use behaviors in adolescents. The authors conclude that information on the ways in which the Internet is being used by adolescents should be considered in the design of Web sites to prevent the initiation and use of psychoactive substances. Boyer, E.W., Shannon, M. and Hibberd, P.L. The Internet and Psychoactive Substance Use among Innovative Drug Users. Pediatrics 115(2), pp. 302-305, 2005.

The Influence of Substance Abuse on Desistance in Antisocial Behavior among Young Adults

Using data collected at ages 18, 21, and 26 from male participants in the Dunedin Multidisciplinary Health and Development Study (N=406), the "snares" and "launch" hypotheses about the developmental relation between substance abuse and individual differences in desistance from antisocial behaviors during young adulthood were examined. The "snares" hypothesis posits that substance abuse should result in time-specific elevations in antisocial behavior relative to an individual's own developmental trajectory of antisocial behavior, whereas the "launch" hypothesis posits that substance abuse early in young adulthood slows an individual's overall pattern of crime desistance related to the population norm during his developmental period. Based on latent trajectory analyses, significant individual variability was found in initial levels and rates of change in antisocial behavior over time as well as support for both the snares hypothesis and the launch hypothesis as explanations for the developmental relation between substance abuse and crime desistance in young men. Hussong, A.M, Curran, P.J., Moffitt, T.E., Caspi, A and Carrig, M.M. Substance Abuse Hinders Desistance in Young Adults' Antisocial Behavior. Development and Psychopathology 16, pp. 1029-1046, 2004.

Support for Contextual Models of Smoking Onset

This is a study examining smoking — specific and contextual models of smoking onset. Data was collected in 4 waves from a sample of 1,364 adolescents. Cluster analysis identified experimenters and abstainers, as well as early (7th grade), intermediate (9th grade), and late (10th grade) smoking onset groups. Predictor variables derived from stress-coping, social influence, and problem-behavior theories discriminated smokers from abstainers. The onset groups were discriminated by Group X Time interactions, showing differential changes in risk and protective factors, which occurred just prior to smoking onset. Findings support a contextual model of the smoking onset process. Wills, T.A., Resko, J.A., Ainett, M.G. and Mendoza, D. Smoking Onset in Adolescence: A Person-centered Analysis with Time-varying Predictors. Health Psychology 23, pp. 158-167, 2004.

Familial Aggregation of Alcohol, Drug, and Psychiatric Disorders: Evidence of Shared Vulnerability

This study analyzed data from the family collection of the Collaborative Study on the Genetics of Alcoholism to quantify familial aggregation of substance use disorders and other psychiatric disorders. Age-corrected lifetime morbid risk was estimated in adult first-degree relatives of affected probands and control subjects for selected disorders. Diagnostic data were gathered by semistructured interview (the Semi-Structured Assessment for the Genetics of Alcoholism) family history, and medical records. Rates of illness were corrected by validating interview and family history reports against senior clinicians' all sources best estimate diagnoses. Sex ethnicity, comorbidity, cohort effects, and site of ascertainment were also taken into account. Results from data from 8296 relatives of alcoholic probands and 1654 controls indicate lifetime risk rates of 28.8% and 14.4% for DSM-IV alcohol dependence in relatives of probands and controls, respectively, respective rates were 37.0% and 20.5% for the less stringent DSM-III-R alcohol dependence, 20.9% and 9.7% for any DSM-III-R diagnosis of nonalcohol nonnicotine substance dependence, and 8.1% and 5.2% for antisocial personality disorder. Rates of specific substance dependence were markedly increased in relatives of alcohol-dependent probands for cocaine, marijuana, opiates, sedatives, stimulants, and tobacco. Aggregation was also seen for panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and major depression. These results suggest that the risk of alcohol dependence in relatives of probands compared with controls is increased about 2-fold, and shared familial vulnerability with antisocial personality disorder, drug dependence, anxiety disorders, and mood disorders. Nurnberger, J.I., Wiegand, R., Bucholz, K., O'Connor, S., Meyer, E.T., Reich, T., Rice, J., Schuckit, M., King, L., Petti, T., Bierut, L., Hinrichs, A.L., Kuperman, S., Hesselbrock, V. and Porjesz, B. A Family Study of Alcohol Dependence - Coaggregation of Multiple Disorders in Relatives of Alcohol-dependent Probands. Archives of General Psychiatry 61, pp. 1246-1256, 2004.

Attenuated P300 Amplitude and Substance Use Disorders

This investigation examined whether P300 amplitude in late childhood is a predictor of SUD outcome by age 19, and whether neurobehavior disinhibition (ND) mediates this association. Boys (aged 10-12) were recruited through proband biological fathers with either a lifetime DSM-III-R diagnosis of SUD (N = 67) or no adult psychiatric disorder (N = 94). P300 amplitude was recorded during an auditory oddball task. Neurobehavior disinhibition was evaluated using tests of executive cognitive function, behavior undercontrol, and emotion dysregulation. Results indicate that substance use disorder by age 19 was significantly predicted by P300 amplitude and ND score measured at age 10 to 12. P300 amplitude also significantly correlated with ND severity. Low P300 amplitudes were observed in children who succumbed to SUD by age 19. These results suggest that ND mediates the association between attenuated P300 amplitude in childhood and SUD at age 19, however, P300 amplitude is not a specific childhood marker of SUD. Habeych, M.E., Charles, P.J., Sclabassi, R.J., Kirisci, L. and Tarter, R.E. Direct and Mediated Associations Between P300 Amplitude in Childhood and Substance Use Disorders Outcome in Young Adulthood. Biological Psychiatry 57, pp. 76-82, 2005.

Cognitive Distortions, Neurobehavior Disinhibition, and Substance Use Disorders

Previous research has demonstrated that neurobehavior disinhibition increases the risk for a diagnosis of substance use disorder (SUD). This investigation tested the hypothesis that a deficiency in the capacity to appraise the effects of alcohol and drugs and interpret social interactions mediates the relation between neurobehavior disinhibition in childhood and SUD by early adulthood. Boys with fathers having lifetime SUD (N = 88) and no SUD or other psychiatric disorder (N = 127) were prospectively tracked from ages 10-12 to 19 years. Neurobehavior disinhibition was evaluated at baseline followed by assessments of cognitive distortions and substance use involvement in early and mid-adolescence. SUD outcome was evaluated up to age 19 years. Results showed that cognitive distortions (age 12-14 years) mediated the association between neurobehavior disinhibition (age 10-12 years) and marijuana use (age 16 years) which, in turn, predicted SUD by age 19 years. Cognitive distortions in early adolescence did not directly predict SUD by young adulthood. These results indicate that cognitive processes, in conjunction with psychological self-regulation, comprise important components of the individual liability to SUD. Kirisci, L., Tarter, R.E., Vanyukov, M., Reynolds, M. and Habeych, M. Relation Between Cognitive Distortions and Neurobehavior Disinhibition on the Development of Substance Use during Adolescence and Substance Use Disorder by Young Adulthood, A Prospective Study. Drug and Alcohol Dependence 76, pp. 125-133, 2004.

Initial Sensitivity to the Pharmacological Effects of Nicotine

To validate reports of early experiences with nicotine, this study assessed 34 smokers who had contributed retrospective data on early experiences with smoking. Half had reported experiencing a buzz from smoking their first cigarette (the "yes" group), the other half had not (the "no" group). To simulate initial sensitivity to nicotine, participants were asked to remain abstinent from smoking for 5 days to allow for the dissipation of tolerance. They then participated in a laboratory session in which they were reexposed to nicotine in an unfamiliar form (nicotine nasal spray) and asked to indicate pleasurable responses by depressing a foot pedal if and when they experienced a "pleasurable buzz." Smokers in the "yes" group were marginally more likely to be male. The two groups did not differ significantly on age or race. The "yes" group smoked significantly more cigarettes/day than the "no" group. When the two groups were compared for response to nasal spray following 5 days' abstinence, smokers in the "yes" group were marginally more likely to have signaled experiencing at least one pleasurable buzz and rated "pleasurable sensation from spray" on a 100-mm visual analogue scale administered 10 min after nicotine dosing significantly higher than were those in the "no" group. To the extent that several days' abstinence can serve as a model for initial sensitivity to nicotine, findings validate retrospective reports of pleasurable sensations upon early smoking experimentation. Pomerleau, O.F., Pomerleau, C.S., Mehringer, A.M., Snedecor, S.M. and Cameron, O.G. Validation of Retrospective Reports of Early Experiences with Smoking. Addictive Behaviors 30, pp. 607-611, 2005.

Reliability of Proxy Reports of Parental Smoking

To investigate the accuracy of offspring assessments of parental smoking status, this study assessed 116 parents and 151 adult children (276 parent-child dyads) who provided data on both their own and their parents' smoking status. All currently

smoking and all ex-smoking parents were correctly classified as ever-smokers by their offspring (n=79 and 100, respectively). Of the 97 offspring who reported on never-smoking parents, 88 correctly classified their parents as never-smokers. Thus, sensitivity for detecting ever-smoking in parents was 100%, and specificity, 91%. Because all incorrect classifications involved never-smoking parents, further analyses focused on this group. Too few parents were misclassified to permit testing of parental characteristics. Offspring who misclassified their parents were significantly older than those who did not; neither sex nor smoking status of the offspring was associated with the increased likelihood of misclassification. No significant differences were discovered for dyadic factors (concordance/discordance for sex; parent-offspring age difference). Overall, these results support the utility of proxy reports of parental smoking phenotype by adult informants when self-report is unavailable. Pomerleau, C.S., Snedecor, S., Ninowski, R., Gaulrapp, S., Pomerleau, O.F. and Kardia, S.L. Differences in Accuracy of Offspring Assessment Based on Parental Smoking Status. Addictive Behaviors 30, pp. 437-441, 2005.

Reliability of Retrospective Reports of Nicotine Dependence

Information about levels of nicotine dependence in ex-smokers when they smoked, or in current smokers at an earlier date, is useful for clinical and research purposes. To estimate the accuracy of retrospective reports of dependence, 28 individuals who completed either the Fagerstrom Tolerance Questionnaire (FTQ) or Fagerstrom Test for Nicotine Dependence (FTND) in smoking cessation trials conducted 5 to 12 years earlier were asked to respond again to the same questions, thinking back to their smoking behavior just prior to their on-study quit attempt. Concordance and Kappa values for the items ranged from 50.0% to 95.0% and 0.00 to 0.92, respectively. The mean difference between the baseline and follow-up total scale scores was 0.05 for the FTQ and 0.38 for the FTND, and the correlation between these assessments was 0.62 for the FTQ ($p<0.005$) and 0.72 for the FTND ($p<0.05$). These preliminary results suggest that retrospectively assessed FTQ/FTND scale scores have acceptable reliability. Suchanek Hudmon, K., Pomerleau, C.S., Brigham, J., Javitz, H. and Swan, G.E. Validity of Retrospective Assessments of Nicotine Dependence: A Preliminary Report. Addictive Behaviors 30, pp. 613-617, 2005.

Identifying Venues for Purposive Sampling of Hard-to-reach Latino Youth

This study of recruitment venues in a Latino neighborhood was designed with the following objectives: (1) to identify venues where Latino youth at risk for unintended pregnancies and sexually transmitted infections (STIs) could be reached; (2) to describe different youth crowds, and (3) to investigate how and where youth meet their sex partners. Based on neighborhood venues mapped using Map-Info, and ethnographic interviews conducted with 62 youth recruited primarily from street sites, 3 types of "crowds" were identified, including gang related "regulars," individuals affiliated with street economy, and females. Findings suggest that gang members dominate venues in The Mission and that street sites are important venues to meet sexual partners. This qualitative assessment produced insights into research planning, outreach, and interventions with Latino youth who are at disproportionate risk for unintended pregnancies and STIs. Auerswald, C.L., Greene, K., Minnis, A., Doherty, I., Ellen, J. and Padian, N. Qualitative Assessment of Venues for Purposive Sampling of Hard-to-reach Youth. Sexually Transmitted Diseases 31, pp. 133-138, 2004.

School-level Clustering of Youthful Drug Involvement in Seven Latin American Countries

This study estimated the occurrence and school-level clustering of drug involvement among school-attending adolescent youths in each of seven countries in Latin America. During 1999-2000, anonymous self-administered questionnaires on drug involvement and related behaviors were administered to a cross-sectional, nationally representative sample that included a total of 12,797 students in the following seven countries, Costa Rica (n = 1,702), the Dominican Republic (n = 2,023), El Salvador (n = 1,628), Guatemala (n = 2,530), Honduras (n = 1,752), Nicaragua (n = 1,419), and Panama (n = 1,743). (The PACARDO name concatenates PA for Panama, CA for Centroamerica, and RDO for Republica Dominicana). Estimates for exposure opportunity and actual use of alcohol, tobacco, inhalants, marijuana, cocaine (crack/coca paste), amphetamines and methamphetamines, tranquilizers, ecstasy, and heroin were assessed via responses about questions on age of first chance to try each drug, and first use. Cumulative occurrence estimates for alcohol, tobacco, inhalants, marijuana, and illegal drug use for the overall sample were, respectively, 52%, 29%, 5%, 4%, and 5%. In comparison to females, males were more likely to use alcohol, tobacco, inhalants, marijuana, and illegal drugs, the odds ratio estimates were 1.3, 2.1, 1.6, 4.1, and 3.2, respectively. School-level clustering was noted in all

countries for alcohol and tobacco use. It was also noted in Costa Rica, El Salvador, Guatemala, and Panama for illegal drug use. This report sheds new light on adolescent drug experiences in Panama, the five Spanish-heritage countries of Central America, and the Dominican Republic, and presents the first estimates of school-level clustering of youthful drug involvement in these seven countries. Placed in relation to school survey findings from North America and Europe, these estimates indicate lower levels of drug involvement in these seven countries of the Americas. For example, in the United States of America 70% of surveyed youths had tried alcohol and 59% had smoked tobacco. By comparison, in these seven countries, only 51% have tried alcohol and only 29% have smoked tobacco. Future research will help to clarify explanations for the observed variations across different countries of the world. In the meantime, strengthening of school-based and other prevention efforts in the seven-country PACARDO area may help these countries slow the spread of youthful drug involvement, reduce school-level clustering, and avoid the periodic epidemics of illegal drug use that have been experienced in North America. Dormitzer, C.M., Gonzalez, G.B., Penna, M., Bejarano, J., Obando, P., Sanchez, M., Vittetoe, K., Gutierrez, U., Alfaro, J., Meneses, G., Diaz, J.B., Herrera, M., Hasbun, J., Chisman, A., Caris, L., Chen, C.Y. and Anthony, J.C. The PACARDO Research Project, Youthful Drug Involvement in Central America and the Dominican Republic. Pan American Journal of Public Health 15, pp. 400-416, 2004.

Difference between Ever- and Never-Smokers

This study examined whether 52 same-sex sibling pairs discordant for ever-smoking differed on psychiatric cofactors, alcohol and caffeine use, and responses to initial exposure to smoking. Ever-smokers scored significantly higher on measures of novelty seeking, depression, and childhood ADHD, and on alcohol dependence, alcohol intake, and caffeine intake. They reported significantly more pleasurable experiences, dizziness, "buzz," and relaxation upon initial exposure to smoking and significantly fewer displeasurable sensations, nausea, and cough than did nicotine-exposed, never-smoking siblings. Ever-smokers had significantly fewer years of education than their never-smoking siblings, suggesting that the concentration of smokers in lower socioeconomic strata may be partly due to downward mobility among smokers, possibly because of the observed elevation in psychiatric cofactors, which may interfere with academic performance. These findings are consistent with differences previously identified in unrelated ever- and never-smokers. Because same-sex siblings typically share a large set of common environments during childhood, the findings could be due either to genetic differences among siblings and/or (excepting educational level and responses to early exposure) to differences in adult environments. Pomerleau, C.S., Pomerleau, O.F., Snedecor, S.M., Gaulrapp, S. and Kardia, S.L.R. Heterogeneity in Phenotypes Based on Smoking Status in the Great Lakes Smoker Sibling Registry. Addictive Behaviors 29, pp. 1851-1855, 2004.

HPA-axis Dysregulation among Smokers with and without Depression

To determine whether smokers with a history of depression are differentially susceptible to smoking withdrawal, depressed mood induction and/or hypothalamic-pituitary-adrenal (HPA) axis dysregulation during smoking abstinence, 24 women smokers with and without such a history were studied. During one 5-day interval, participants smoked ad libitum, during a second they abstained. On day 4, the participants were exposed to the Velten mood induction procedure (VMIP). Participants were then instructed to take 1 mg dexamethasone at 11 pm. At 4 pm on day 5, blood samples were withdrawn to determine the cortisol and ACTH response. Despite lower baseline cotinine levels, history-positive participants displayed more pronounced overall withdrawal distress than did history-negative participants, regardless of condition. The VMIP increased depression as well as negative responses on other profile of mood states subscales. Despite many overall group differences, no significant main effects for smoking condition nor interaction effects emerged. All participants evinced cortisol suppression in response to dexamethasone during both conditions, but the degree of suppression did not differ as a function of either abstinence or depression history. In history-positive smokers, however, ACTH levels trended toward overall elevation and showed almost no suppression during abstinence, thus exacerbation of HPA dysregulation in history-positive smokers during smoking abstinence cannot be ruled out. Pomerleau, O.F., Pomerleau, C.S., Snedecor, S.M., Gaulrapp, S., Brouwer, R.N. and Cameron, O.G., Depression, Smoking Abstinence and HPA Function in Women Smokers. Human Psychopharmacology-Clinical and Experimental 19, pp. 467-476, 2004.

Impact of September 11 Attacks on Young Adult Drug Abuse

The authors took advantage of their ongoing longitudinal study to assess the impact

of the September 11 attacks on psychopathology in young adults who lived far from New York City. During that year, 730 rural 19-21 year olds were re-assessed, one third after the attacks. Findings differed by gender and by level of prior stress. Although men showed slightly more tendency to have one or more symptoms of posttraumatic stress disorder, their rates of substance use disorder after September 11 were lower, regardless of prior use history. Women showed increased rates of substance use and abuse after the attacks. The attacks also proved a greater stressor for those under low to moderate levels of stress than for those already under significant stress. No other psychiatric disorders showed an increase after September 11 in this sample. This "natural experiment" suggests that, if confirmed in other studies, even those who are geographically removed from a traumatic event may be vulnerable, and that interventions for those at greater risk may be indicated to prevent further costs in event of such an attack. Costello, E.J, Erkanli, A., Keeler, G., and Angold, A. Distant Trauma: A Prospective Study of the Effects of September 11th on Young Adults in North Carolina. Applied Developmental Science 8, pp. 211-220, 2004.

Elementary School Intervention Demonstrates Long-Term Effects

This study explored long-term effects of the Seattle Social Development intervention. This nonrandomized controlled trial followed up participants to 21 years of age, 9 years after the intervention ended. The investigators compared 3 intervention conditions (a full 6-year intervention (grades 1 through 6); a late 2-year intervention (grades 5 and 6 only); and a no-treatment control condition) in a sample of 605 participants. Broad significant effects on functioning in school and work and on emotional and mental health were found. Fewer significant effects on crime and substance use were found at 21 years of age. Most outcomes had a consistent dose effect, with the strongest effects in subjects in the full-intervention group and effects in the late-intervention group between those in the full-intervention and control groups. This work suggests that a theory-guided preventive intervention that strengthened teaching and parenting practices and taught children interpersonal skills during the elementary grades had wide-ranging beneficial effects on functioning in early adulthood. Hawkins, J.D., Kosterman, R., Catalano, R.F., Hill, K.G. and Abbott, R.D. Promoting Positive Adult Functioning Through Social Development Intervention in Childhood: Long-term Effects from the Seattle Social Development Project. Arch Pediatr Adolesc Med. 59(1), pp. 25-31, 2005.

COMMUNITY EPIDEMIOLOGY WORK GROUP: January 2005

The CEWG is composed of researchers from 21 metropolitan areas of the United States who meet semiannually to report on patterns and trends of drug abuse in their respective areas, emerging drugs of abuse, vulnerable populations and factors that may place people at risk for drug abuse, and negative health and social consequences. Reports are based on a variety of drug abuse indicator data such as morbidity and mortality information, treatment data and local and State law enforcement data. Additional sources of information include criminal justice, correctional, medical and community health data, local and State survey information, and findings from qualitative research studies.

Cocaine continued to be a widely abused illicit stimulant drug in 2003—2004. Cocaine abuse indicators remained high in 19 of the 21 CEWG areas. The exceptions were Honolulu and San Diego where methamphetamine indicators remained high. In CEWG areas in FY 2004, cocaine accounted for more than 40 percent of the drug items analyzed by police forensic labs (National Forensic Laboratory Information System) compared with 11 percent for methamphetamine. Treatment admission data show that primary cocaine admissions exceeded those for methamphetamine/amphetamine in 15 of the 20 metropolitan CEWG areas. In most CEWG areas, high percentages of primary heroin admissions reported cocaine as their secondary drug of abuse, including in New York City (35 percent). Treatment data showed that crack was the most common type of cocaine abused. In 11 of 17 reporting CEWG areas, more than 75 percent of the primary cocaine treatment admissions had smoked the drug.

In 2003—2004, **methamphetamine** abuse indicators increased in five CEWG areas ——Atlanta, Denver, Los Angeles, Minneapolis/St. Paul, and Phoenix. In Minneapolis/St. Paul, 61 percent of the items tested by police forensic labs in FY 2004 included methamphetamine. Methamphetamine abuse indicators were stable at high or relatively high levels in four metropolitan CEWG areas——Honolulu, San Diego, San Francisco, and Seattle, with very high proportions of primary methamphetamine treatment admissions (excluding alcohol admissions) in Hawaii (58.6 percent) and San Diego (54.4 percent). Methamphetamine indicators remained at very low levels in

11 areas. Methamphetamine/amphetamine treatment admissions represented less than 1 percent of illicit drug admissions in six northeastern/Mid-Atlantic areas, Detroit, Miami, and New Orleans. Only 1 percent or less of the items analyzed by forensic labs in Baltimore, Boston, Chicago, Detroit, Miami, New Orleans, Newark, New York City, Philadelphia, and Washington, DC, included methamphetamine.

Methylenedioxymethamphetamine (MDMA or ecstasy) abuse indicators decreased in four CEWG metropolitan areas (Boston, Miami, Seattle, and St. Louis) and school surveys showed ecstasy use decreasing among students in two States (Minnesota and Texas). Most CEWG members reported that MDMA was still used primarily by White youth and young adults, but there were reports from four areas (Chicago, New York City, St. Louis and Texas) that the abuse of this drug was spreading to, or increasing in minority communities. In eight areas, there was insufficient indicator data to draw conclusions regarding changes in MDMA patterns and trends. MDMA indicators remained stable at low levels in Atlanta, Denver, and Phoenix.

Prescription Drug Abuse differs by geographic area and population group and type of drug. **"Other opiate"** (excluding heroin) treatment admissions increased in many CEWG areas but remained at low levels. The proportions of other opiate admissions (excluding alcohol) in 2004 were highest in Texas (6.8 percent) and Boston (6.0 percent), and between 4.1 and 4.4 percent in Detroit, Baltimore, Colorado, and New Orleans. In FY 2004, forensic labs identified 7,319 opiate/opioid items in CEWG areas. More than 35 percent of the items were hydrocodone, 23 percent were oxycodone, 19 percent were methadone, and the remainder were mostly codeine and morphine. There were 6,604 forensic lab (NFLIS) reports of **benzodiazepine**-type items analyzed across 18 CEWG areas and the combined 13 sites in Texas. Most (63.8 percent) of the items were alprazolam, 18.2 percent were clonazepam items, 14.7 percent were diazepam, and 3.3 percent were lorazepam items.

Heroin indicators increased in only one area and were stable or mixed (some up and some down) in 15 areas. However, heroin indicators (especially heroin treatment admissions) remained very high in nine of these areas. For example, high proportions of 2004 treatment admissions were reported in Newark (82.6 percent), Boston (74.2 percent), Baltimore (59.8 percent), Detroit (46.0 percent), San Francisco (42.8 percent), New York City (42.1 percent), Philadelphia (36.0 percent), Los Angeles (30.1 percent), and Seattle (27.0 percent). In addition, 51.2 percent of the 2003 (2004 data were not yet available) treatment admissions in Washington, DC reported heroin as their primary drug of abuse.

Marijuana abuse indicators continued at high levels in all CEWG areas. The drug is reported to be widely available. Cannabis items accounted for between 51 and 53 percent of all drug items analyzed by forensic labs in San Diego, New Orleans, and St. Louis; between 45 and 47 percent of the items in Detroit, Boston, and Chicago; and 20 to 29 percent of the items in New York, Miami, Los Angeles, Atlanta, Texas, and Baltimore. Primary marijuana admissions (excluding alcohol) were highest in Minneapolis/St. Paul (42.1 percent) and New Orleans (39.5 percent).

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Research Findings - Prevention Ressearch

Predicting Early Adolescent Gang Involvement from Middle School Adaptation

This study examined the role of adaptation in the first year of middle school (Grade 6, age 11) to affiliation with gangs by the last year of middle school (Grade 8, age 13). The sample consisted of 714 European American (EA) and African American (AA) boys and girls. Specifically, academic grades, reports of antisocial behavior and peer relations in 6th grade were used to predict gang involvement by 8th grade, measured through self-, peer, teacher, and counselor reports. Unexpectedly, self-report measures of gang involvement did not correlate highly with peer and school staff reports. The results, however, were similar for other and self-report measures of gang involvement. Analysis of means revealed statistically reliable differences in 8th-grade gang involvement as a function of the youth gender and ethnicity. Structural equation prediction models revealed that peer nominations of rejection, acceptance, academic failure, and antisocial behavior were predictive of gang involvement for most youth. These findings suggest that the youth level of problem behavior and the school ecology (e.g., peer rejection, school failure) require attention in the design of interventions to prevent the formation of gangs among high-risk young adolescents. Dishion, T.J., Nelson, S.E. and Yasui, M. Journal of Clinical Child and Adolescent Psychology 34(1), pp. 62-73, 2005.

Maternal Stress and Distress Increase Disruptive Behavior Problems in Boys

This study examined how self-reported maternal stress and distress are associated with child disruptive behaviors, based on mother and teacher ratings of child disruptive behavior problems (attention problems, aggression, and delinquency) collected for 215 boys between 9 and 12 years of age. Participating mothers also provided self-report data on socioeconomic status (SES), parenting stress, and distress (depression and anxiety/somatization). Low SES was significantly associated with both mother- and teacher-reported child disruptive behavior problems. In addition, the relation between parenting stress and mother-reported child disruptive behavior problems was found when SES was controlled. A significant relation between maternal distress and mother-reported child disruptive behavior problems (particularly attention problems), also was observed when both SES and parenting stress were controlled. Maternal stress and distress were not significantly related to teacher-reported child disruptive behavior problems. Although the lack of an association between teacher-reported behavior problems and maternal stress and distress might be interpreted as a rater bias by these mothers, it may be that the mothers' symptoms are associated with a stressful home environment, thus exacerbating child disruptive behavior problems and eventually leading to a reciprocal relation between symptomatology in mothers and children. Barry, T.D., Dunlap, S.T., Cotton, S.J., Lochman, J.E. and Wells, K.C. The Influence of Maternal Stress and Distress on Disruptive Behavior Problems in Boys. Journal of the American Academy of Child and Adolescent Psychiatry 44(3), pp. 265-273, 2005.

The Influence of Partner Type and Risk Status on the Sexual Behavior of Young HIV+ Men who have Sex with Men

Partner type (primary/regular vs. single-time or casual) and risk status (HIV+, HIV- but IV drug use, HIV- and low risk) each affect the sexual behavior of young men living with HIV (YMLH) who have sex with men but the interaction of these risk factors on sexual risk behavior is not know. This study assessed the sexual behavior and sexual partner characteristics of 217 YMLH recruited from adolescent care clinics in 4

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AIDS epicenters. Using generalized linear modeling the authors analyzed the effect of partner type and partner risk status on unprotected sex acts. Sixty-two percent of YMLH reported multiple partners, 26% reported 1 sexual partner, and 12% reported abstinence in the past 3 months. Approximately 34% of polygamous and 28% of monogamous youth engaged in unprotected sex. Monogamous youth were most likely to have unprotected sex with HIV-positive partners. Polygamous youth were most likely to have unprotected sex with HIV-positive partners, irrespective of whether the partner was regular or casual. For polygamous YMLH unprotected sex did not differ among single-time/new partners with different risk levels, suggesting that partner characteristics and perception of their partner's risk influence the condom use behavior of YMLH. These findings suggest that partner characteristics influence the condom use behavior of YMLH. These young men are practicing safer sex with partners who they do not want to infect and not using condoms with partners with whom transmission risk is less concerning. However, it is questionable whether the youth can truly know a partner's risk or HIV status and these young men are still at significant risk for infection with an STD. Preventive interventions must include skills for acquiring accurate information about partner risk status and education regarding the health risks of unprotected sex with HIV seroconcordant partners. Lightfoot, M., Song, J., Rotheram-Borus, M.J. and Newman, P. The Influence of Partner Type and Risk Status on the Sexual Behavior of Young Men who have Sex with Men Living with HIV/AIDS. JAIDS-Journal of Acquired Immune Deficiency Syndromes 38(1), pp. 61-68, 2005.

Prospective Prediction of Alternative High School Graduation Status at Emerging Adulthood

Most studies that examine the prediction of graduation status among teens have examined those who attend regular high schools. This study reports the prediction of high school graduation status five years later among 646 youth who attended alternative (continuation) high schools at baseline. Those youth at baseline who: (a) reported less intention to use cigarettes, alcohol, or marijuana during the next year; (b) suffered relatively few drug-related consequences during the last year; (c) were relatively less likely to have carried a weapon (knife or gun) in the last year; (d) reported feeling relatively hopeful about the future; and (e) were more likely to self-report having graduated continuation high school 5 years later. These results suggest that the consequences of drug use, not drug use per se, other illegal behavior, and a sense of well-being are important predictors of graduation among groups of high-risk teens. Sussman, S., Rohrbach, L.A., Skara, S. and Dent, C.W. Prospective Prediction of Alternative High School Graduation Status at Emerging Adulthood. Journal of Applied Social Psychology 34(12), pp. 2452-2468, 2004.

Tobacco and Alcohol Use as an Explanation for the Association between Externalizing Behavior and Illicit Drug Use among Delinquent Adolescents

Substance use among adolescents is frequently comorbid with other psychiatric disorders. Most studies of these comorbidities use samples of middle or high school students or draw from inpatient settings. Less is known about substance use and psychiatric comorbidity among delinquent adolescents. The present study examined data from two cohorts of juvenile offenders collected over a 2-year period (n=245, n=299). Participants reported frequency of cigarette, alcohol, marijuana, and other substance use. Participants' parents completed a measure of behavior problems. Path analyses suggested that parental reports of externalizing problems were significantly related to self-reported substance use while parental reports of internalizing problems were not. These findings suggest that smoking and alcohol use act as mediators between externalizing problems and marijuana and other drug use. Although there were some mean differences by gender, the pattern of relationships among the variables did not differ by gender. Helstrom, A., Bryan, A., Hutchison, K.E., Riggs, P.D. and Blechman, E.A. Tobacco and Alcohol Use as an Explanation for the Association between Externalizing Behavior and Illicit Drug Use among Delinquent Adolescents. Prevention Science 5(4), pp. 267-277, 2004.

Vulnerability of Children of Incarcerated Addict Mothers: Implications for Preventive Intervention

This preliminary report examined the characteristics, experiences, and behavior of 88 primarily African-American adolescents with incarcerated addict mothers. The age, gender, and risk factor profiles with the children's adjustment status, based on self-reported questionnaire information and selected personality/behavioral assessment inventories, indicated that in spite of the incarceration of their substance-abusing mothers, the majority of these children were neither especially deviant nor maladjusted. All but a small percentage had successfully avoided substance abuse

and the adoption of a deviant lifestyle at this point in their development. In most cases, mother surrogates (usually a grandmother or other family member) had functioned as primary caregivers of the children for many years prior to the incarceration of their birth mothers, possibly attenuating the negative impact ordinarily associated with a mother's absence from the home. However, there was a general indication of problematic school behavior and vulnerability to deviant peer influences that should be addressed in efforts aimed at preventing the escalation of deviant activity in such children. In almost all cases the child's caregiver needed caseworker support services. Hanlon, T.E., Blatchley, R.J., Bennett-Sears, T., O'Grady, K.E., Rose, M. and Callaman, J.M. Vulnerability of Children of Incarcerated Addict Mothers: Implications for Preventive Intervention. Children and Youth Services Review 27(1), pp. 67-84, 2005.

The Characteristics and Vulnerability of Incarcerated Drug-Abusing Mothers

Although the number of drug-addicted incarcerated mothers has grown substantially in recent years, there is little information on their unique characteristics and vulnerabilities. This study examined data on 167 incarcerated drug-abusing mothers from Baltimore City who had volunteered for a parenting program offered at a Maryland correctional facility. Prior to entering this program, these mothers completed a battery of assessment measures including an extensive interview covering their early developmental and current experiences and standardized tests of psychological adjustment and parenting satisfaction. Analyses of these data focused on the link between risk/protective factors drawn from the early development experiences of these and their current adjustment status. There were significant relationships between higher risk levels and less favorable current adjustment suggesting the need to develop both prevention and clinical intervention efforts targeting both mothers and their children. Hanlon, T.E., O'Grady, K.E., Bennett-Sears, T. and Callaman, J.M. Incarcerated Drug-Abusing Mothers: Their Characteristics and Vulnerability. American Journal Of Drug And Alcohol Abuse 31(1), pp. 59-77, 2005.

Sensation Seeking Contributes Directly and Indirectly to Adolescent Drug Use

This study sought to examine whether sensation seeking contributes to the likelihood of drug use by adolescents both directly as well as indirectly through the way it shapes social interactions with peers in the context of drug use. In addition, it examined whether other risk or protective factors affect the likelihood of adolescent drug use by influencing either sensation seeking, association with deviant peers or frequent pro-drug discussions with peers. The analysis was based on cross-sectional data from youth 12 to 18 (N=5,141) collected as part of the evaluation of the National Youth Anti-Drug Media Campaign. The findings support the study's hypotheses that sensation seeking had a significant correlation with association with deviant peers, frequency of pro-drug discussions and intention to use marijuana. Association with deviant peers was also significantly correlated with frequent pro-drug discussions with peers and intention to use marijuana. A hierarchical regression analysis of the contribution of sensation seeking, the frequency of association with peers and pro-drug discussions to intention to use marijuana as well as other risk and protective factors strongly supported the hypothesis that all three contribute independently to intention to use marijuana and that additional risk and protective factors also affected intentions. In the models sensation seeking alone accounted for between a third and a half of the explained variance in the dependent variables suggesting its importance in understanding adolescent drug use. In addition, different factors may protect high sensation-seeking adolescents from using drugs or engaging in such activities as associating with deviant peers which in turn increases their risk for drug use. These findings suggest the importance of studying both direct and indirect influences of variables on drug use and clarifying the links among these factors. Yanovitzky, I. Sensation Seeking and Adolescent Drug Use: The Mediating Role of Association with Deviant Peers and Pro-drug Discussions. Health Communication 17(1), pp. 67-89, 2005.

New Measure of Positivity Offset and Negativity Bias Relates to Sensation Seeking Substance Use

This article investigates links among motivation, sensation seeking, and substance use by extending conceptualizations of sensation seeking as a function of resting activation in the appetitive and aversive motivational systems. The goal was to develop a measure of positivity offset and negativity bias. Positivity offset is the degree to which the appetitive system is more active than the aversive system in a neutral environment. Negativity bias is the speed with which the aversive system responds to negative stimuli of increasing intensity. Four types of individuals would

include those with a large positivity offset and a small negativity bias, called risk takers; those with a large positivity offset and a large negativity bias, called coactives; those with a small positivity offset and a small negativity bias, called inactives; and those with a small positivity offset and a large negativity bias, called risk avoiders. Participants (64 college students of average age 20), viewed and rated a series of pictures ranging in valence and arousal and completed questionnaires assessing sensation seeking and substance use. These new measures had reasonable intercorrelations and correlated with sensation seeking and substance use. Although both positivity offset and negativity bias were related to sensation seeking, substance use was primarily related to positivity offset. Hierarchical regression analyses showed that positivity offset and negativity bias can predict significant variance in substance use, and the variance explained by these measures is different than that explained by sensation seeking alone. Risk takers did indeed score high on sensation seeking and were high substance users. Risk avoiders scored very low on sensation seeking and were low substance users. The coactives and inactives were in the middle. Measures of positivity offset and negativity bias may allow us to define the motivation type most likely to experiment with and become substance users. Lang, A., Shin, M. and Lee, S. Sensation Seeking, Motivation, and Substance Use: A Dual System Approach. Media Psychology, 7, pp. 1-29, 2005.

Racial and Gender Differences in Patterns of Adolescent Sexual Risk Behaviors

Sexual and substance use behaviors co-vary in adolescence. There also are racial and gender differences in the prevalence of HIV and other sexually transmitted diseases (STDs). These differences in subgroup risk behavior differences have not been systematically investigated with nationally representative data. Using cluster analysis 13,998 non-Hispanic black and white participants in the National Longitudinal Study of Adolescent Health, Wave 1, were grouped according to self-reported substance use and sexual behavior. Multinomial logit analyses examined racial and gender differences by cluster. Among 16 clusters, the two defined by the lowest risk behaviors (sexual abstinence and little or no substance use) comprised 47% of adolescents; fewer than 1% in these groups reported ever having received an STD diagnosis. The next largest cluster-characterized by sexual activity (on average, with one lifetime partner) and infrequent substance use-contained 15% of participants but nearly one-third of adolescent with STDs. Blacks were more likely than whites to be in this group. Black males also were more likely than white males to be in three small clusters characterized by high-risk sexual behaviors (i.e., having had sex with a male or with at least 14 partners, or for drugs or money). Although Black females generally were the least likely to be in high-risk behavior clusters, they were most likely to report STDs. Thus, adolescents' risk behavior patterns vary by race and gender, and do not necessarily correlate with their STD prevalence. Halpern, C.T., Hallfors, D., Bauer, D.J., Iritani, B., Waller, M.W. and Cho, H. Implications of Racial and Gender Differences in Patterns of Adolescent Risk Behavior for HIV and Other Sexually Transmitted Diseases. Perspectives on Sexual and Reproductive Health 36(6), pp. 239-247, 2004.

Development of a Life Skills Curriculum for Young South African Adults

This article describes the development of an international collaborative effort designed to reduce risky behavior (e.g., substance use, risky sexual behavior) and its consequences (e.g., HIV/AIDS, pregnancy, and addictions) among a sample of South African youth. Because many of these risky behaviors occur in free time, a major part of the effort was leisure education to promote positive use of free time. The HealthWise program described here was pilot tested and is currently underway as a larger-scale, randomized trial in the Province of the Western Cape in South Africa. The article explains how the HealthWise curriculum was conceptualized revised, in close collaboration with the Western Cape Education Department, and how the on-going randomized trial was implemented. Caldwell, L.L., Smith, E., Wegner, L., Vergnani, T., Mpofu, E., Flisher, A. and Matthews, C. HealthWise South Africa: Development of a Life Skills Curriculum for Young Adults. World Leisure Journal, 46(3), pp. 4-17, 2004.

Development and Validation of a Gender-Balanced Measure of Aggression-Relevant Social Cognition

This study examined the psychometric properties of the Social-Cognitive Assessment Profile (SCAP), a gender-balanced measure of social information processing (SIP) in a sample of 371 (139 girls, 232 boys) 2nd- to 4th-grade children. The SCAP assesses 4 dimensions of SIP (Inferring Hostile Intent, Constructing Hostile Goals, Generating Aggressive Solutions, and Anticipating Positive Outcomes for Aggression) in the context of peer conflict involving relational and overt provocation. Confirmatory factor

analyses indicated that the 4 latent factors provided a good fit to the data for girls and boys and for African American and non-African American children. Regression analyses in which teacher and peer evaluations of aggression and peer evaluations of social competencies were regressed on each of the 4 SCAP scales supported the test's convergent and discriminant validity. These results suggest that the SCAP is an easily administered and brief measure of SIP that is appropriate for racially diverse populations of elementary boys and girls. Hughes, J.N., Meehan, B.T., and Cavell, T.A. Journal of Clinical Child and Adolescent Psychology 33(2), pp. 292-302, 2004.

Exposure to PTSD in the General Population after Mass Terrorist Incidents

Several epidemiological studies were conducted in the aftermath of the September 11th attacks that made use of standardized assessment measures to allow comparability across studies that included design variations permitting comparison of different segments of the US and New Your City area populations. These studies found elevated prevalence of PTSD in the general population in the first months after the attacks. In New York City post-traumatic stress was similar among those who were and those who were not directly exposed to the attacks. Debate about the exact array of symptoms that constitute PTSD and whether that diagnosis is best characterized as a categorical or dimensional variable continue. The general population data suggest that it is likely that a wide range of experiences beyond those currently considered extreme traumatic events by DSM-IV are capable of producing PTSD symptoms. Galea, S. and Resnick, H. Posttraumatic Stress Disorder in the General Population After Mass Terrorist Incidents; Considerations about the Nature of Exposure. CNS Spectrums 10(2), pp. 107-115, 2005.

TV Watching and Mental Health in the General New York City Population after 911

The September 11, 2001 terrorist attacks were watched on television by millions. Using data from a telephone survey of New York City residents in January 2002 (N=2001), this study explored the relationships between TV watching and probably posttraumatic stress disorder (PTSD) after the attacks. Among persons directly affected by the attacks or those who had prior traumatic experiences, watching television was associated with probably PTSD. Experiencing a peri-event panic reaction accounted for some of the association between TV watching and probably PTSD. In this era of constant TV news coverage of global events, the potential impact of watching disasters, wars, terrorism and other traumatic events on television is a growing concern requiring research on the mechanisms behind the observed associations between TV watching and posttraumatic stress to better prepare for the effects of future disasters. Ahern, J. Galea, S., Resnick, H. and Vlahov, D. Television Watching and Mental Health in the General Population of New York City After September 11. Journal of Aggression, Maltreatment and Trauma, 9(1/2), pp. 109-124, 2004.

Intervention Implications of a Theory-Based Understanding of Marijuana Use Intentions

Using an integrated model of behavior change (Fishbein et al. 2001), the authors predict intentions to use marijuana occasionally and regularly in a national sample of youth 12-18 (N=600) and delineate choices in intervention foci and message selection. Predictors include psychosocial and structural factors such as beliefs about consequences of marijuana use, attitudes, norms and self-efficacy. Respondents were recruited at 18 malls and completed anonymous touch-screen surveys on a desktop computer. Respondents who reported never using marijuana answered questions either about occasional or regular use; prior users were assigned to the set of questions about regular use. Respondents who had never used marijuana expressed strong intentions to avoid use in the future; prior users were significantly more likely to intend future use. This suggests that planners must assess whether to use limited resources to focus on the former group. For both occasional and regular use, youths' own attitudes toward marijuana use are stronger predictors of their intentions than norms or self-efficacy. This suggests that attitude and its underlying beliefs should be the focal point of interventions with a focus on norm perception a secondary concern. Examination of the relationship of outcome expectancies and attitudes can help to identify priorities for targeting particular beliefs and attitudes on which there is variation and where beliefs may plausibly be changed. Sayeed, S., Fishbein, M., Hornik, R., Cappella, J. and Ahern, R.K. Adolescent Marijuana Use Intentions: Using Theory to Plan an Intervention. Drugs, Education, Prevention & Policy 12(1), pp. 19-34, 2005.

Correlates of HIV Status among Injection Drug Users in a Border Region of

Southern China and Northern Vietnam

This article examines the correlates of HIV status among samples of injection drug users (IDUs) in Lang Son Province, Vietnam (n = 348), and Nina Ming County, Guangxi Province, China (n = 294), who were interviewed and tested for HIV antibody just before the start of a peer-based HIV prevention intervention in this border region. Participants were largely male, in their 20s, and single. Logistic regression analysis suggests that among Chinese IDUs, border-related factors (e.g., living closer to the border, buying drugs across the border more frequently) and younger age are the best predictors of HIV positivity. In Vietnam, HIV status seems to drive behavior (e.g., some risk reduction practices are predictive of HIV positivity). These differing patterns may reflect the fact that the intertwined epidemics of heroin injection and HIV began earlier and HIV prevalence has reached significantly higher levels in Lang Son than across the border in Ning Ming. Although border-related factors emerge as predictors in Ning Ming, more IDUs in Lang Son are HIV-positive and may be reacting behaviorally to that status. Their greater likelihood of engaging in risk reduction measures may reflect some combination of a belief that risk reduction can slow disease progression and an altruistic desire to avoid infecting others. Hammett, T.M., Johnston, P., Kling, R., Liu, W., Ngu, D., Tung, N.D., Binh, K.T., Dong, H.V., Hoang, T.V., Van, L.K., Donghua, M., Chen, Y., and Jarlais, D.C.D. Correlates of HIV Status among Injection Drug Users in a Border Region of Southern China and Northern Vietnam. JAIDS-Journal of Acquired Immune Deficiency Syndromes 38(2), pp. 228-235, 2005.

Cigarette Smoking More Prevalent and More Frequent Among Whites

Studies of adolescents consistently show that smoking prevalence rates are higher for Whites than for African-Americans. Yet, while White adults report a higher prevalence of lifetime smoking, African-American adults report a higher prevalence of current smoking. Moreover, African-American adults seem to experience higher rates of smoking-related health problems, especially lung cancer. These contradictory findings have been explained by the fact that African-Americans begin smoking later, have lower cessation rates, and smoke higher tar yield brands than Whites. However, many of the common assumptions about cigarette use, such as that most adult smokers report their first use during childhood or adolescence have been based on samples comprised primarily of Whites and may not be generalizable to African-Americans. This study examined racial differences in onset, prevalence and developmental trajectories of cigarette smoking from childhood into young adulthood using the Pittsburgh Youth Study, a prospective, longitudinal study of 562 African American and 421 White high-risk males. Three trajectory groups emerged for both races: nonsmokers, light/occasionally smokers, and heavy/regular smokers. Significantly more Whites were in the heavy/regular smoker group and more African-Americans were in the nonsmoker group. White heavy/regular smokers began smoking earlier and reached higher mean quantities of cigarettes per day. Race remained a significant predictor of cigarette use even after controls for socioeconomic status. White, H.R., Nagin, D., Replogle, E. and Stouthamer-Loeber, M. Racial Differences in Trajectories of Cigarette Use. Drug and Alcohol Dependence 76, pp. 219-227, 2004.

Drug Use may be Mediated through Low Hostile Anger Control

The relationships among selected predictors of violence, including victimization, low conflict management efficacy, hostile anger and drug use were examined using data on 8th-, 10th-, and 12th-grade adolescents. The secondary analysis used population-based, cross-sectional survey of health behaviors (N = 3922). For each grade cohort, it was hypothesized that victimization and low conflict management efficacy would predict low hostile anger control, which would predict gateway drug use, and the subsequent development of hard drug use and violence. Overall model fit and the magnitude of specific paths were expected to increase across grades. Using structural equation modeling (SEM), results indicated acceptable model fit for 8th-grade (CFI = .95), 10th-grade (CFI = .93) and 12th-grade (CFI = .94) cohorts. Results suggest that the influence of relational victimization and conflict management efficacy on hard drug use may be mediated through low hostile anger control and gateway drug use. Weiner, M.D., Pentz, M.A., Skara, S.N., Li, C., Chou, C.P. and Dwyer, J.H. Relationship of Substance Use and Associated Predictors of Violence in Early, Middle, and Late Adolescence. Journal of Child & Adolescent Substance Abuse 13(4), pp. 97-117, 2004.

School District Personnel Hold the Keys to Implementation of Effective Prevention

An important issue in drug abuse prevention programming is the relative roles of

school district and school-level decision-makers in the implementation of effective substance use prevention curricula. Drawing on a "Site-Based Management" approach to effective decision-making, it was hypothesized that schools whose personnel played active decision-making roles would be more likely to implement effective curricula than those in which decision-making was the prerogative of school district personnel. Study data comprised 1,369 questionnaires completed by a representative national sample of both district-level prevention coordinators and middle school-based lead prevention teachers. From the perspective of the lead prevention teachers, the school district-level prevention coordinator was more influential than school staff in selecting effective prevention curricula. However, they did find some support for their hypothesis from the district-level informants, who indicated that community groups and advisory committees also play a modest role in the selection of such curricula. Ringwalt, C., Ennett, S.T., Vincus, A.A., Rohrbach, L.A. and Simons-Rudolph, A. Who's Calling the Shots?: Decision-Makers and the Adoption of Effective School-Based Substance Use Prevention Curricula. Journal of Drug Education 34(1), pp. 19-31, 2004.

Training Youth to Use Leisure Time Wisely Works

The -TimeWise: Learning Lifelong Leisure Skills' curriculum aims to increase positive use of free time, thereby mitigating/ preventing the initiation of substance use. The intervention was delivered to 634 middle school youth in a rural area in eastern United States. Self-report data after one year indicate that students who received TimeWise reported less lack of motivation and more identified and subconscious forms of motivation. TimeWise students reported being better able to restructure boring situations into something more interesting; having higher levels of decision making skills, initiative, community awareness; and participating in new interests, sports, and nature-based activities. Caldwell, L.L., Baldwin, C.K., Walls, T. and Smith, E. Preliminary Effects of a Leisure Education Program to Promote Healthy Use of Free Time. Journal of Leisure Research 36(3), pp. 310-335, 2004.

Infusion-LST Compared to LST as Usual

Findings from the first two years of a study to compare a standard Life Skills Training (LST) program with an infused (I-LST) approach was conducted in 9 small, rural school districts that were randomly assigned to LST, I-LST, or control conditions. Male and female subjects were in grade seven. The LST program significantly reduced alcohol use, binge drinking, marijuana use, and inhalant use after one year for females, and the I-LST program significantly reduced smoking, binge drinking, and marijuana use for females. At the end of the second year the I-LST program continued to impact female smoking, but all other results were non-significant. There were no effects on males at either time point. Smith, E.A. Evaluation of Life Skills Training and Infused-Life Skills Training in a Rural Setting: Outcomes at Two Years. Journal of Alcohol & Drug Education 48(1), pp. 51-70, 2004.

Cost Comparison of LST and Infusion-LST

A cost-effectiveness comparison of the Life Skills Training (LST) to a LST curriculum infusion approach (I-LST) was conducted. Male and female seventh graders from nine rural schools (2 intervention conditions and control) were followed for two years. After one year, significant effects were observed only for females on alcohol, marijuana, and inhalant use in LST condition and for tobacco, alcohol, and marijuana use for I-LST females. After year two, only the I-LST program affected female smoking. Costs for the two programs included actual expenditures for training and materials as well as estimates of teachers' salaries for their project time were calculated. Both programs were almost equally effective after one year, but LST was more cost-effective. I-LST cost more to implement, but sustained effects into year two and was therefore more cost-effective overall. Swisher, J. D. A Cost-Effectiveness Comparison of Two Approaches to Life Skills Training. Journal of Alcohol & Drug Education 48(1) pp. 71-78, 2004.

Effects of Dosage on Outcomes

The present study assessed the ability of the Early Risers "Skills for Success" program to maintain program effects one year post intervention. Participants were kindergarten and first grade children (N=327) who screened positive for aggressive behavior and were randomized to program and control conditions. Program children participated in two continuous years of active intervention followed by one year of no formal intervention activities. Following the active intervention phase, program children, compared to controls, showed significant gains in school adjustment and social competence, but not in academic achievement. At the one-year follow-up

program effects were not maintained using intent-to-intervene analyses. Level-of-dosage analyses, however, revealed that there were significant relationships between children's level of participation and measures of their social competence, externalizing problems, and academic achievement. August, G.J., Lee, S.S., Bloomquist, M.L., Realmuto, G.M. and Hektner, J.M. Maintenance Effects of an Evidence-Based Prevention Innovation for Aggressive Children Living in Culturally Diverse, Urban Neighborhoods: The Early Risers Effectiveness Study. Journal of Emotional and Behavioral Disorders 12(4), pp. 2004.

Perceived Life Chances and Alcohol Use

The relationship between low perceived chances for success in life and binge drinking was examined in a sample of economically disadvantaged, predominantly black and Hispanic students, urban adolescents (N = 774) from 13 inner-city schools. Subjects completed confidential questionnaires in the 7th, 8th, and 9th grades. Eight items measured students' estimation of achieving certain adaptive life goals. Students who reported that they typically drink five or more drinks per drinking occasion were identified as binge drinkers. Results indicated that rates of binge drinking increased and perceived life chances decreased for both boys and girls from the 7th to 9th grade. Moreover, higher perceived life chances in the 7th grade predicted less binge drinking in the 8th grade, whereas binge drinking in the 8th grade predicted lower perceived life chances in the 9th grade, controlling for change over time in both variables. Griffin, K.W., Botvin, G.J., Nichols, T.R. and Scheier, L.M. Low Perceived Chances for Success in Life and Binge Drinking among Inner-city Minority Youth. Journal of Adolescent Health, 34, pp. 501-507, 2004.

Self-esteem and Alcohol Use

Prior studies have found inconsistent relationships between measures of self-concept and adolescent alcohol use. This study explored whether the link between various measures of self-concept and alcohol use depends on gender and whether negative rather than positive self-esteem (i.e., self-derogation) might be more useful in predicting alcohol use. Students (N = 1459) attending 22 middle and junior high schools in New York City completed surveys that included measures of efficacy, self-derogation, and alcohol use. Participants completed surveys at baseline, 1-year follow-up, and 2-year follow-up. Findings indicate that lower efficacy was related to greater self-derogation a year later across gender. Increased self-derogation predicted higher alcohol use for girls but not boys. These findings are congruent with a literature highlighting the importance of negative thoughts about the self in drinking behavior for women but not men. Epstein, J.A., Griffin, K.W. and Botvin, G.J. Efficacy, Self-derogation, and Alcohol Use among Inner-city Adolescents: Gender Matters. Journal of Youth & Adolescence 33, pp. 159-166, 2004.

Influence of Parents on Child Anti-social Behavior

This study examined the unique influence of mothers and fathers on their children's antisocial behavior using a sample of 325 families with sixth grade children. Multiple-group comparisons were conducted to identify differences in the relationships for mothers and fathers with daughters versus sons. Results suggested that, while the relationships were often similar for both parents and for both daughters and sons, mothers and fathers uniquely influenced their child's antisocial behavior depending on the child's gender. Overall, cross-gender influence appeared to be particularly important for fathers' control of their daughters' antisocial behavior. Kosterman, R., Haggerty, K.P., Spoth, R. and Redmond, C. Unique Influence of Mothers and Fathers on their Children's Antisocial Behavior: A Social Development Perspective. Journal of Marriage and Family 66(3), pp. 762-778, 2004.

Does Perception of Behavior Affect Behavior?

This research examined whether parents' and children's perceptions have reciprocal self-fulfilling prophecy effects on each others' behavior. Mothers, fathers, and their adolescent children completed self-report surveys and engaged in videotaped dyadic interaction tasks. The surveys assessed parents' and children's perceptions of their own and the other's typical hostility and warmth. Observers coded the videotaped interactions to assess the actual hostility and warmth exhibited by mothers, fathers, and children. Data from 658 mother-child dyads were consistent with the conclusion that children had a self-fulfilling effect on their mothers' hostile behavior, but that mothers did not have a reciprocal self-fulfilling effect on their children's hostility. The data did not support the existence of self-fulfilling prophecies among the mother-child dyads with respect to warmth, or among the 576 father-child dyads for either the hostility- or warmth-relevant data.. Madon, S., Guyll, M. and Spoth, R. The Self-

fulfilling Prophecy as an Intra-family Dynamic, Journal of Family Psychology 18(3), pp. 459-469, 2004.

The Importance of Family-based Prevention Interventions in Rural Areas

There are several reasons to promote the implementation of evidence-based family-focused interventions in rural, small town or micropolitan communities. One key reason is research demonstrating that youth problem behaviors are especially prevalent in rural areas and that these problems can be effectively reduced though family-focused programs. For example, studies have found that rural youth are involved in tobacco, alcohol, and illegal substance use at rates that often exceed those of youth living in urban and suburban communities (America's Children, 2000-Federal Interagency Forum on Child and Family Statistics, 2000; National Institute on Drug Abuse, 1997; Johnston, O'Malley, & Bachman, 2000, 2002). Further, earlier program evaluation research has demonstrated the effectiveness of several evidence-based family-focused programs among rural youth, including the reduction of substance use; related economic analyses also have shown that these programs are cost-beneficial. These programs focus on the enhancement of competencies related to reducing risk and increasing protective factors among families and youth. Meek, J., Lillehoj, C.J., Welsh, J. and Spoth, R. Rural Community Partnership Recruitment for an Evidence-based Family-focused Prevention Program: The PROSPER Project, Rural Mental Health 29(2), pp. 23-28, 2004.

Early Identifiers of Later Risk for Depression

This study examined childhood behavior problems at ages 10 and 11 years as predictors of young adult depression, social phobia, and violence at age 21 years. Data were collected on 808 elementary school students from high-crime neighborhoods of Seattle. Reports of childhood behavior problems were obtained from parents and children in fall 1985 and from teachers in spring 1986. Follow-up reports of violence and DSM-III-R depression and social phobia were collected from 765 respondents using standard survey items and the Diagnostic Interview Schedule in 1996. The past-year prevalence of depressive episodes and social phobias were 20% and 17%, respectively. Several available measures of childhood behavior problems as reported by parents, teachers, and children predicted violence; the strongest positive predictor of young adult violence was self-reported conduct problems, whereas self-reported shyness inhibited later violence. Relatively few child behavioral problems predicted social phobia. Results showed that children who reported higher, relative to lower, levels of conduct problems were nearly four times more likely to experience a depressive episode in early adulthood. Mason, W.A., Kosterman, R., Hawkins, J.D., Herrenkohl, T. I., Lengua, L.J. and McCauley, E. Predicting Depression, Social Phobia, and Violence in Early Adulthood from Childhood Behavior Problems, Journal of the American Academy of Child Psychiatry 43(3), pp. 307-315, 2004.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

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

Abstinence Relates to Depression Symptoms in Methamphetamine Dependent Gay and Bisexual Men Undergoing Behavioral Substance Abuse Treatment

Dr. Peck and colleagues evaluated the relationship between symptoms of depression and drug abuse treatment among methamphetamine dependent gay and bisexual men undergoing treatment for substance abuse. Participants (N=162) were assigned to sixteen weeks of either standard cognitive behavioral therapy (CBT), contingency management (CM), or combined CBT+CM and a culturally tailored cognitive behavioral therapy (CCBT). Depression was measured using Beck Depression Inventory scores collected weekly. At intake 73.2% of participants endorsed symptoms consistent with mild to moderate depression. Reductions in methamphetamine use and depression generally were sustained for one year after treatment entry regardless of treatment condition. A secondary analysis revealed that urinalysis results positive for methamphetamine predicted depression symptoms. However, depression symptoms were not predictive of methamphetamine use. These post-hoc results suggest that abstinence, regardless of the behavioral intervention used to obtain it, is likely to improve symptoms of depression. Additionally, they suggest depression symptoms may not trigger relapse among gay or bisexual men in treatment as was previously supposed. Peck, J.A., Reback, C.J., Yang, X., Rotheram-Fuller, E., and Shoptaw, S. Journal of Urban Health. Mar 82(1 Suppl 1), i100-i108, 2005.

Drug Abusers and Therapists Perceive Sources of Reinforcement and Punishment in Clinics Differently

Dr. Roll and colleagues at UCLA evaluated provider and patient perceptions of the opportunities for reinforcement and punishment in a drug free clinic, to determine whether existing inexpensive methods might be available for impacting the behavior of drug users in treatment. Despite evidence for the efficacy of contingency management interventions, community based treatment providers often cite the cost of providing reinforcers as a primary reason why they do not adopt these approaches. Cost may be lower if naturalistic sources of reinforcement within a drug treatment environment could be used. Additionally, research suggests that withholding reinforcement in cases of non-compliance (punishment) may be more effective than simply reinforcing abstinence. In this study 93 patients and 18 clinical staff members at a drug free clinic were asked to rate 38 potential punishers and 44 potential reinforcers. Generally both clients and staff agreed about the order and magnitude of reinforcers. However clinic staff's ratings of potential punishers were generally higher than that of clients. Several low cost activities such as ceremonies recognizing treatment completion, attendance certificates, and assistance with finding employment were highly rated. Events rated as punishers included letters to the legal system indicating poor treatment compliance, withdrawal of smoking privileges, increase in the price of treatment, and premature treatment discharge. Future contingency management approaches may reduce costs by using naturally available services and consequences. Roll, J.M., Chudzynski, J.E. and Richardson, G. American Journal of Drug and Alcohol Abuse 31(1), pp. 21-33 2005.

A Meta-Analysis of Smoking Cessation Interventions with Individuals in Substance Abuse Treatment or Recovery

A systematic review was conducted to examine the effectiveness of smoking cessation

interventions for individuals with substance abuse problems. An extensive literature search identified 19 randomized controlled trials of smoking cessation interventions with individuals in current addictions treatment (n=12) or recovery (n=7). Smoking and substance use outcomes at post-treatment and long-term follow up (6- to 12-months) were abstracted. Smoking cessation intervention effects for smokers in addictions treatment and recovery were significant at post-treatment. Effects were no longer significant at 6- to 12-months follow up. For participants in addictions treatment, smoking cessation interventions were associated with a 25% increased likelihood of long-term abstinence from alcohol and illicit drugs. The findings suggest short-term success with treating tobacco dependence among individuals in addictions treatment and recovery and the need for innovative strategies for long-term cessation. Contrary to previous concern, smoking cessation efforts delivered during addictions treatment appeared to enhance rather than compromise long-term sobriety. Prochaska, J.J., Delucchi, K. and Hall, S.M. Journal of Consulting and Clinical Psychology, 72(6), pp. 1144-1156, 2004.

A Pilot Study on Voucher-based Incentives to Promote Abstinence from Cigarette Smoking during Pregnancy and Postpartum

Dr. Higgins and colleagues from the University of Vermont report results from a pilot study examining the use of vouchers redeemable for retail items as incentives for smoking cessation during pregnancy and postpartum. Fifty-eight women who were still smoking upon entering prenatal care were assigned to either contingent or noncontingent voucher conditions. Vouchers were available throughout pregnancy and for 12 weeks postpartum. In the contingent condition, vouchers were earned for biochemically verified smoking abstinence; in the noncontingent condition, vouchers were earned independent of smoking status. Contingent vouchers significantly increased abstinence at the end-of-pregnancy (37% vs. 9%), and 12-week postpartum (33% vs. 0%) assessments. That effect remained significant at the 24-week postpartum assessment (27% vs. 0%), which was 12 weeks after discontinuation of the voucher program. The magnitude of these treatment effects exceeds levels typically observed with pregnant and recently postpartum smokers, and the maintenance of effects through 24 weeks postpartum extends the duration beyond those reported previously. Higgins, S.T., Heil, S.H., Solomon, L.J., Lussier, J.P. and Lynch, M.E. Nicotine and Tobacco Research, 6(6), pp. 1015-1020, 2004.

Perceived Risks and Benefits of Smoking Cessation: Gender-specific Predictors of Motivation and Treatment Outcome

The primary aim of this study was to examine gender differences in perceived risks and benefits of smoking cessation and their relationship to pretreatment motivation and treatment outcome. A self-report instrument was developed for this purpose. Findings are reported from a subsample of 93 participants out of 573 treatment seeking smokers entering a smoking cessation study. Females indicated greater likelihood ratings of perceived risks and benefits than males. For women and men, perceived benefits were positively associated with motivation, and perceived risks were negatively associated with motivation and treatment outcome. Women evidenced stronger associations between perceived risks and pretreatment motivation, and treatment outcome. Knowledge of perceived risks and benefits associated with smoking cessation is critical for public education campaigns and could inform intervention strategies designed to modify sex-specific beliefs associated with lowered behavioral intentions to quit smoking. McKee, S.A., O'Malley, S.S., Salovey, P., Krishnan-Sarin, S. and Mazure, C.M. Addictive Behaviors, 30, pp. 423-435, 2005.

Depressed Smokers and Stage of Change: Implications for Treatment Interventions

Dr. Prochaska and colleagues from the University of California, San Francisco examined depressed smokers' readiness to quit and the applicability of the Stages of Change framework to a psychiatric sample. Currently depressed smokers (N=322) from four outpatient psychiatric clinics participated. The majority (79%) reported intention to quit smoking with 24% ready to take action in the next 30 days. Individuals in the preparation stage reported more prior quit attempts, a greater commitment to abstinence, increased recognition of the cons of smoking, and greater use of the processes of change. Precontemplators were least likely to identify a goal related to their smoking behavior. Depressive symptom severity and history of recurrent depressive episodes were unrelated to readiness to quit. This study is one of the first to examine the smoking behaviors of currently depressed psychiatric outpatients. The level and longevity of their tobacco use underscore the need for cessation interventions. The consistency in hypothesized patterns among theoretical constructs of the Stages of Change model supports the transfer of stage-tailored

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interventions to this clinical population. Prochaska, J.J., Rossi, J.S., Redding, C.A., Rosen, A.B., Tsoh, J.Y., Humfleet, G.L., Eisendrath, S.J., Meisner, M.R., and Hall, S.M. Depressed Smokers and Stage of Change: Implications for Treatment Interventions. Drug Alcohol Depend. 76(2), pp. 143-151, November 11, 2004.

Acceptance-Based Treatment for Smoking Cessation

This pilot study applied a theoretically derived model of acceptance-based treatment process to smoking cessation, and compared it to a pharmacological treatment based on a medical dependence model. Seventy-six nicotine-dependent smokers were randomly assigned to one of two treatments: Nicotine Replacement Treatment (NRT), or a smoking-focused version of Acceptance and Commitment Therapy (ACT). There were no differences between conditions at posttreatment; however, participants in the ACT condition had better long-term smoking outcomes at 1-year follow-up. As predicted by the acceptance process model, ACT outcomes at 1 year were mediated by improvements in acceptance-related skills. Withdrawal symptoms and negative affect neither differed between conditions nor predicted outcomes. Gifford, E.V., Kohlenberg, B.S., Hayes, S.C., Antonuccio, D.O., Piasecki, M.M., Rasmussen-Hall, M.L. and Palm, K.M. Behavior Therapy, 35, pp. 689-705, 2004.

Methadone versus Buprenorphine with Contingency Management or Performance Feedback for Cocaine and Opioid Dependence

In this study Dr. Schottenfeld and colleagues at Yale University compared the effects of buprenorphine and methadone and evaluated the efficacy of combining contingency management with maintenance treatment for patients with co-occurring cocaine and opioid dependence. One hundred and sixty two subjects with cocaine and opioid dependence were provided manual-guided counseling and randomly assigned in a double-blind design to receive daily sublingual buprenorphine (12-16 mg) or methadone (65-85 mg, p.o.) and to contingency management or performance feedback. Contingency management subjects received monetary vouchers for opioid and cocaine negative urine tests, which were conducted three times per week; voucher value escalated during the first 12 weeks for consecutive drug free tests and was reduced to a nominal value in weeks 13-24. Performance feedback subjects received slips of paper indicating the urine test results. The primary outcome measures were the maximum number of consecutive weeks abstinent from illicit opioids and cocaine and the proportion of drug free tests. Analytic models included two-by-two analysis of variance and mixed-model repeated measures analysis of variance. In this study the methadone treated subjects remained in treatment significantly longer and achieved significantly longer periods of sustained abstinence and a greater proportion of drug free urine tests, compared with the subjects who received the buprenorphine. Subjects receiving contingency management achieved significantly longer periods of abstinence and a greater proportion of drug free tests during the period of escalating voucher value, compared with those who received performance feedback, but there were no significant differences between groups in these variables during the entire 24-week study. Contingency management improved outcomes during both buprenorphine and methadone maintenance, supporting the efficacy of combining opioid agonist maintenance with this behavioral treatment. Schottenfeld, R.S., Chawarski, M.C., Pakes, J.R., Pantalon, M.V., Carroll, K.M. and Kosten, TR. American Journal of Psychiatry 162(2), pp. 340-349, February 2005.

A Trial of Three Strategies of Training Clinicians in Cognitive-Behavioral Therapy

Until recently there has been little research on the effectiveness of different training strategies or the impact of exposure to treatment manuals alone on clinicians' ability to effectively implement empirically supported therapies. In this study 78 community-based clinicians were assigned to 1 of 3 training conditions: review of a cognitive-behavioral (CBT) manual only, review of the manual plus access to a CBT training Web site, or review of the manual plus a didactic seminar followed by supervised casework. The primary outcome measure was the clinicians' ability to demonstrate key CBT interventions, as assessed by independent ratings of structured role plays. Statistically significant differences favoring the seminar plus supervision over the manual only condition were found for adherence and skill ratings for 2 of the 3 role plays, with intermediate scores for the Web condition. Sholomskas, D.E., Syracuse-Siewert, G., Rounsaville, B.J., Ball, S.A., Nuro, K.F. and Carroll, K.M. Journal of Consulting and Clinical Psychology 73(1), pp. 106-115, February 2005.

The Effectiveness of Telephone-Based Continuing Care for Alcohol and Cocaine Dependence

Dr. James McKay of the University of Pennsylvania and colleagues tested an intervention delivered mostly by telephone to patients with cocaine or alcohol dependence after initial success in an intensive outpatient group treatment. A total of 359 patients were randomized to receive one of three 12-week interventions: the telephone-based continuing care treatment; once weekly individualized and group therapy based on a relapse prevention model; or standard continuing care involving twice weekly, disease-model group sessions. Results showed overall efficacy of the telephone-based intervention in supporting abstinence from cocaine and alcohol, with different measures of substance use outcomes showing different relative efficacy compared to the other treatment conditions. Of particular interest is the apparent superiority of the telephone-based intervention for participants with lower risk factors for relapse, as compared to standard continuing care which seemed to be superior for participants with higher risk of relapse. These results suggest that creative use of disease-management, telephone-based brief interventions can support continued abstinence after initial treatment. McKay, J.R., Lynch, K.G., Shepard, D.S. and Pettinati, H.M. Archives of General Psychiatry, 62, pp. 199-207, 2005.

Dual and Multiple Diagnosis among Runaway and Homeless Youth

Dr. Natasha Slesnick and Jillian Prestopnik report on the clinical presentations of 226 youth at two homeless shelters participating in a study of family treatment for substance abuse. Regarding substance use disorders, 81% met criteria for marijuana abuse or dependence, 64% met criteria for alcohol abuse or dependence, and about half (44%) met criteria for two substance use disorders. About 60% of youth met criteria for at least one substance use disorder and at least one psychiatric diagnosis. Of these youth, 60% met criteria for Oppositional Defiant Disorder or Conduct Disorder (ODD/CD); 34% met criteria for an Affective Disorder; and 54% met criteria for an Anxiety Disorder. Youth with ODD/CD were significantly more likely to use marijuana than other youth. Young men were significantly more likely than young women to meet criteria for ODD/CD, while young women were significantly more likely to meet criteria for Affective Disorders and Anxiety Disorders, and to have multiple diagnoses. These results highlight the large overlap between substance use disorders and psychiatric disorders found, and the need for appropriate treatment, among runaway youth. Slesnick, N. and Prestopnik, J.L. American Journal of Drug and Alcohol Abuse, 31, pp. 179-201, 2005.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Research on Pharmacotherapies for Drug Abuse

Risperidone May Diminish Cocaine-Induced Craving

Dr. Richard De La Garza II and colleagues at UCLA examined the effects of the D2/5HT2A antagonist risperidone on cocaine-induced craving in a human laboratory study, based on the hypothesis that rispiridone would reduce cocaine-induced craving in individuals who experienced priming. Study participants were 7 non-treatment seeking, cocaine-dependent individuals. Subjects were administered cocaine to induce drug priming, then treated with rispiridone for five days. At the end of the treatment regimen, cocaine was again administered, and subjective responses to the cocaine challenge were assessed through rating craving for cocaine. In this study, risperidone blunted cocaine craving in those subjects who experienced cocaine-induced craving, suggesting that this medication might be effective in reducing relapse. De La Garza II, R., Newton, T.F. and Kalechstein, A.D. Risperidone Diminishes Cocaine-Induced Craving. Psychopharmacology, 178, pp. 347-350, 2005.

Modafinil As a Treatment for Cocaine Dependence

Dr. Charles Dackis and colleagues at the University of Pennsylvania in Philadelphia conducted a double-blind, placebo controlled outpatient study in 62 cocaine-dependent individuals to assess the efficacy of modafinil for cocaine abstinence. Modafinil was tested based on the hypothesis that its glutamate-enhancing action may be effective in treating cocaine dependence, as the repeated administration of cocaine depletes extracellular glutamate levels. This study found that modafinil reduced cocaine use in the outpatient setting. Dackis, C.A., Kampman, K.M., Lynch, K.G., Pettinati, H.M. and O'Brien, C.P. A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence. Neuropsychopharmacology, 30, pp. 205-211, 2005.

Role Played by the Smoking-related Stimuli that are Delivered by Denicotinized Cigarettes

Pharmacologically, pure nicotine suppresses tobacco abstinence symptoms partially, and non-nicotine, smoking-related stimuli suppress these abstinence symptoms fully, at least for 24 hours. The current study was designed to clarify the impact of smoking-related stimuli on tobacco withdrawal, and to explore the duration of their ability to suppress withdrawal in smokers. Three double-blind, within-subjects, Latin square-ordered, 5-day conditions in which participants smoked nicotinized, denicotinized or no cigarettes were conducted in 13 women and 19 men. Subjective, physiological and performance measures were collected daily and compliance with study conditions was verified objectively. The results showed that smoking-related stimuli are sufficient for suppressing some symptoms of tobacco abstinence over a 5-day period [i.e. Questionnaire of Smoking Urges (QSU) factor 1, -Desire for sweets', -Hunger' and -Urges to smoke'], while in this study a combination of nicotine and smoking-related stimuli suppressed other symptoms (i.e. -Difficulty concentrating', -Increased eating', -Restlessness' and -Impatient'). These results indicate that, while some tobacco abstinence symptoms may be suppressed with nicotine, suppressing others may also require strategies that address the absence of smoking-related stimuli. Buchhalter, A.R., Acosta, M.C., Evans, S.E., Breland, A.B. and Eissenberg, T. Tobacco Abstinence Symptom Suppression: The Role Played by the Smoking-related Stimuli that are Delivered by Denicotinized Cigarettes. Addiction, 100, pp. 550—559, 2005.

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Urine Cotinine as an Index of Smoking Status

Biomarkers such as carbon monoxide (CO) and cotinine are used in tobacco cessation studies to assess smoking status. CO is easy to assess, is inexpensive, and provides immediate results. However, the short half-life of CO may limit its ability to identify smokers who have abstained for several hours. Quantitative methods (e.g., gas chromatography/mass spectrometry, or GC/MS) for measuring urine cotinine, which has a longer half-life, are valid and reliable, though costly and time consuming. Recently developed semi-quantitative urine cotinine measurement techniques (i.e., urine immunoassay test strips, or ITS) address these disadvantages, though the value of ITS as a means of identifying abstaining smokers has not been evaluated. The present study examined ITS as a measure of smoking status in temporarily abstaining smokers. A total of 236 breath and urine samples were collected from smokers who participated in two separate studies involving three independent, 96-hr (i.e., Monday-Friday), Latin-square-ordered, abstinence or smoking conditions; a minimum 72-hr washout separated each condition. Each urine sample was analyzed with GC/MS and ITS. Under these study conditions, CO demonstrated moderate sensitivity (83.1%) and strong specificity (100%), whereas ITS assessment showed strong sensitivity (98.5%) and weak specificity (58.5%). In this study of short-term abstinence, ITS classified as non-abstinent nearly half of the samples collected from abstaining smokers. However, it classified nearly all non-abstinent smokers as currently smoking. Acosta, M., Buchhalter, A., Breland, A., Hamilton, D. and Eissenberg, T. Urine Cotinine as an Index of Smoking Status in Smokers During 96-hr Abstinence: Comparison between Gas Chromatography/Mass Spectrometry and Immunoassay Test Strips. Nicotine.Tob.Res. 6(4), pp. 615-620, 2004.

Uptake of Lung Carcinogens by Smokers of Regular, Light, and Ultralight Cigarettes

Cigarette design has changed markedly over the past 60 years and sales-weighed levels of tar and nicotine have decreased. Currently, cigarettes are classified as regular (>14.5 mg tar), light (>6.5-14.5 mg tar), and ultralight (< or =6.5 mg tar), based on a Federal Trade Commission-specified machine-smoking protocol. Epidemiologic studies suggest that there is no difference in lung cancer risk among people who smoke light or ultralight cigarettes compared with regular cigarettes, but the uptake of lung carcinogens in smokers of these types of cigarettes has never been reported. We recruited 175 smokers, who filled out a tobacco use questionnaire in which their current brand was identified as regular, light, or ultralight. Urine samples were collected and analyzed for 1-hydroxypyrene (1-HOP), total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL plus its glucuronides) and total cotinine (cotinine plus its glucuronides). 1-HOP and total NNAL are biomarkers of uptake of polycyclic aromatic hydrocarbons and 4-(methylnitrosamino) -1-(3-pyridyl)-1-butanone, lung carcinogens in cigarette smoke. Total cotinine is a biomarker of nicotine uptake. There were no statistically significant differences in urinary levels of 1-HOP, total NNAL, and total cotinine in smokers of regular, light, and ultralight cigarettes, whether the results were expressed per mg urinary creatinine, per mL of urine, or per mg creatinine divided by cigarettes per day. Levels of machine measured tar were available for the cigarettes smoked by 149 of the subjects. There was no correlation between levels of tar and any of the biomarkers. These results indicate that lung carcinogen and nicotine uptake, as measured by urinary 1-HOP, total NNAL, and total cotinine is the same in smokers of regular, light, and ultralight cigarettes. The results are consistent with epidemiologic studies that show no difference in lung cancer risk in smokers of these cigarettes. Hecht, S.S., Murphy, S.E., Carmella, S.G., Li, S., Jensen, J., Le, C., Joseph, A.M. and Hatsukami, D.K. Similar Uptake of Lung Carcinogens by Smokers of Regular, Light, and Ultralight Cigarettes. Cancer Epidemiol Biomarkers Prev. 14(3), pp. 693-698, 2005.

Transdermal Nicotine Use in Postmenopausal Women and Hormone Replacement Therapy

Ninety-four postmenopausal female smokers were recruited according to HRT and non-HRT use (self-selecting) then randomized within strata to active nicotine or placebo nicotine patch. After 1 baseline week of smoking, participants quit smoking for 2 weeks. Women received cessation counseling and were monitored for abstinence. Dependent measures were collected during five clinic visits. Two-way analysis of covariance (ANCOVA) were run on change scores for dependent variables, with nicotine patch group (active/placebo) and HRT group (HRT/non-HRT) as independent variables and age as a covariate. No interactions were found between HRT and patch condition, but both showed specific effects. During the first abstinent week, women on active nicotine patch (compared with placebo) experienced less

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severe withdrawal, greater reductions in cigarette cravings, and lower (more favorable) Factor 1 scores on the Questionnaire of Smoking Urges. During the second abstinent week, women using HRT (compared with the non-HRT group) exhibited better mood (Profile of Mood States scores) and less depression (Beck Depression Inventory scores). These results suggest the following: First, the efficacy of transdermal nicotine replacement is not adversely modified by women's HRT use; second, ovarian hormones might influence women's responses to smoking cessation, and thus should be considered in developing effective strategies for women to quit smoking. Allen, S.S., Hatsukami, D.K., Bade, T. and Center, B. Transdermal Nicotine Use in Postmenopausal Women: Does the Treatment Efficacy Differ in Women Using and Not Using Hormone Replacement Therapy? Nicotine Tob. Res. 6(5), pp. 777-788, October 2004.

Urinary Biomarkers of Tobacco and Carcinogen Exposure in Smokers

The investigators report the comparison of urinary concentrations of tobacco alkaloid and tobacco carcinogen biomarkers in a subset of smokers during a 7-week period prior to any reduction in cigarette consumption. Urine samples were collected at four time points and analyzed for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and its glucuronide, 1-hydroxypyrene, anatabine, free nicotine, total nicotine (free plus glucuronidated), free cotinine, total cotinine (free plus glucuronidated), and total trans-3'-hydroxycotinine (free plus glucuronidated). Anatabine is a minor alkaloid that may be useful in assessing tobacco exposure in individuals using nicotine replacement therapies. Urinary anatabine levels were well correlated ($P < 0.0001$) with both free and total nicotine ($r = 0.753$ and 0.773, respectively). Anatabine levels were also correlated with free cotinine ($r = 0.465$; $P < 0.001$), total cotinine ($r = 0.514$; $P < 0.001$), and total NNAL ($r = 0.633$; $P < 0.001$). These data support the role of anatabine as a biomarker of tobacco exposure. 1-Hydroxypyrene is a biomarker of polycyclic aromatic hydrocarbon exposure, but unlike NNAL it is not tobacco specific. Whereas urinary concentrations of 1-hydroxypyrene were consistent across the four visits, the levels were not correlated with NNAL, anatabine, nicotine, or any nicotine metabolites. These results provide: (a) demonstration of a strong correlation between anatabine and urinary NNAL, a metabolite of the tobacco-specific carcinogen NNK, confirming the potential usefulness of anatabine as a biomarker of tobacco exposure for smokers using nicotine replacement therapy; (b) support for the use of total cotinine as the most consistent and reliable urinary marker of nicotine exposure; and (c) reiteration of the findings that CPD is not an adequate measure of tobacco toxin exposure. In addition, the data provide additional evidence that the percent glucuronidation of cotinine measured in urine is reproducible and potentially useful as a reflection of UDP-glucuronosyltransferase activity. Murphy, S.E., Link, C.A., Jensen, J., Le, C., Puumala, S.S., Hecht, S.S., Carmella, S.G., Losey, L. and Hatsukami, D.K. A Comparison of Urinary Biomarkers of Tobacco and Carcinogen Exposure in Smokers. Cancer Epidemiol Biomarkers Prev. 13(10), pp. 1617-1623, October 2004.

Re-emergence of Tobacco Smoking Using a Waterpipe

Waterpipes are increasing in popularity, and more must be learned about them so that we can understand their effects on public health, curtail their spread, and help their users quit. Research regarding waterpipe epidemiology and health effects is limited; no published studies address treatment efforts. Waterpipe use is increasing globally, particularly in the Eastern Mediterranean Region, where perceptions regarding health effects and traditional values may facilitate use among women and children. Waterpipe smoke contains harmful constituents and there is preliminary evidence linking waterpipe smoking to a variety of life threatening conditions, including pulmonary disease, coronary heart disease, and pregnancy related complications. More scientific documentation and careful analysis is required before the spread of waterpipe use and its health effects can be understood, and empirically guided treatment and public policy strategies can be implemented. Maziak, W., Ward, K. D., Afifi Soweid, R. A. and Eissenberg, T. Tobacco Smoking Using a Waterpipe: A Re-emerging Strain in a Global Epidemic. Tob. Control, 13(4), pp. 327-333, 2004.

Gender Effects of Reported in Utero Tobacco Exposure on Smoking Initiation, Progression and Nicotine Dependence in Adult Offspring

The investigators studied the relationship between self-reported in utero tobacco exposure and gender on smoking initiation, progression of cigarette use (i.e., telescoping), and current levels of nicotine dependence in adult treatment-seeking smokers. Subjects (N = 298) who reported "yes" (28% of the original sample) or "no" (50% of the original sample) to in utero tobacco exposure were included in the analyses. Telescoping was calculated as the difference between the age respondents smoked their "first full cigarette" and the age when they started smoking daily.

Females who reported being exposed in utero transitioned from initial to daily cigarette use more rapidly than females not exposed. The opposite effect was found for males, which may be related to our finding that in utero exposure lowered the age of cigarette experimentation in exposed compared with unexposed males. Measures of current cigarette use and dependence (i.e., Fagerstrom Test for Nicotine Dependence, prior withdrawal, number of past year quit attempts) were significantly associated with reported in utero exposure, gender, or interactions of exposure and gender. In utero tobacco exposure may accelerate the progression from experimentation to daily use in girls, result in early tobacco experimentation among boys, and produce higher levels of nicotine dependence among adult smokers. Oncken, C., McKee, S., Krishnan-Sarin, S., O'Malley, S. and Mazure, C. Gender Effects of Reported In Utero Tobacco Exposure on Smoking Initiation, Progression and Nicotine Dependence in Adult Offspring. Nicotine Tob. Res. 6(5), pp. 829-833, October 2004.

Naltrexone for the Treatment of Cocaine-alcohol Dependence

This study evaluates whether patients with cocaine-alcohol dependence might benefit from naltrexone (NTX) pharmacotherapy when delivered in conjunction with psychotherapy. Eighty outpatients meeting DSM-IV criteria for alcohol and cocaine dependence were randomly assigned to receive NTX (placebo or 50 mg/d) combined with psychotherapy (Relapse Prevention [RP] or Drug Counseling [DC]) for twelve weeks. It was hypothesized that the skills training focus of RP therapy, in combination with NTX 50 mg/d, would produce greater reductions in cocaine and alcohol use. Outcome measures included self- and objective reports of substance use, treatment retention, medication compliance, and adverse effects. During the first four weeks of treatment, the percentage of cocaine-positive urine screens was significantly lower for those receiving RP therapy (22%) than those receiving DC (47%); however, this difference subsequently diminished. No medication effects were found. All groups reported less alcohol use at the end of treatment. Treatment retention was the same among the groups, with about 33% of the subjects completing all twelve weeks of treatment. The active medication group showed better medication compliance, while the number of adverse events was low overall and not significantly different by group. In conclusion, NTX at 50 mg/d did not reduce cocaine or alcohol use. These findings stand in contrast to previously reported positive findings for NTX and RP in patients with a single diagnosis of cocaine dependence. Schmitz, J.M., Stotts, A.L., Sayre, S.L., DeLaune, K.A. and Grabowski, J. Treatment of Cocaine-alcohol Dependence with Naltrexone and Relapse Prevention Therapy. Am J Addict.13(4), pp. 333-341, July-September 2004.

Relative Efficacy of Daily, Twice and Thrice Weekly Buprenorphine Dosing

This randomized clinical trial evaluated the relative efficacy of three buprenorphine dosing schedules. Opioid-dependent adults were randomly assigned to receive buprenorphine seven, 3 or 2 days per week for 24 weeks. Daily maintenance doses were 4, 8, 10, or 12 mg of the sublingual buprenorphine solution. Participants who attended the clinic daily received a maintenance dose of buprenorphine daily. Participants who attended the clinic thrice weekly received double their maintenance dose on Monday and Wednesday, followed by a triple dose on Friday. Participants who attended the clinic twice weekly received quadruple their maintenance dose of buprenorphine on Monday and triple their maintenance dose on Friday. Results demonstrated that all dosing regimens were of comparable efficacy in promoting treatment retention, opioid and cocaine abstinence, and reductions in HIV risk behavior (especially as related to drug use) and severity of life problems. Predictor analyses identified sub-populations of opioid-dependent individuals that may have a more positive treatment outcome under each buprenorphine dosing condition. Less-than-daily dosing schedules may provide the opportunity for treatment programs to serve a greater number of opioid-dependent patients and reduce the risk of medication diversion, which may, in turn, have a positive impact on community support of science-based treatment for opioid-dependence. Marsch, L.A., Bickel, W.K., Badger, G.J. and Jacobs, E.A. Buprenorphine Treatment for Opioid Dependence: The Relative Efficacy of Daily, Twice and Thrice Weekly Dosing. Drug Alcohol Depend. 77(2), pp. 195-204, February 14, 2005.

Effects of Acute Opiate Withdrawal and Drug Reinforcement Opportunity on Opioid Craving and Seeking Behaviors

The author used a 3 x 2 within-subject randomized crossover design to assess craving and operant behavioral effects of 3 pretreatments (naloxone 0.1 mg/70 kg, fentanyl 0.75 mg/70 kg, or saline iv) and drug or money reinforcement opportunity in 8 methadone-maintained volunteers. Each pretreatment was paired with response-

contingent (15 x fixed-ratio 100) delivery of drug (fentanyl 1.5 mg/70 kg iv) and money (rated equivalent of fentanyl) in different sessions. Naloxone significantly increased opioid craving, withdrawal signs, and symptoms, but not operant behavior, relative to saline and fentanyl pretreatment. However, drug versus money reinforcement opportunity did not significantly increase opioid craving or seeking behavior. Greenwald, M.K. Opioid Craving and Seeking Behavior in Physically Dependent Volunteers: Effects of Acute Withdrawal and Drug Reinforcement Opportunity. Exp Clin Psychopharmacol. 13(1), pp. 3-14, February 2005.

Progesterone Treatment and Cocaine Responses

The investigators examined the interaction between progesterone and cocaine in both male and female cocaine users using subjective, physiological and behavioral outcomes. A total of 10 subjects, 6 male and 4 female cocaine users, had two experimental sessions. Before each session, participants received either two oral doses of 200 mg of progesterone or placebo. Two hours after the second dose of medication treatment, the participants received a 0.3 mg/kg dose of cocaine intravenously and started the self-administration period, in which five optional doses of cocaine were available. Progesterone treatment attenuated the cocaine-induced diastolic blood pressure increases without affecting the systolic blood pressure and heart rate increases. Progesterone treatment also attenuated the subjective ratings of high and feel the effect of last dose in response to cocaine but did not affect cocaine self-administration behavior. These results suggest that progesterone attenuates some of the physiological and subjective effects of cocaine in both male and female participants. Sofuoglu, M., Mitchell, E. and Kosten, T.R. Effects of Progesterone Treatment on Cocaine Responses in Male and Female Cocaine Users. Pharmacol Biochem Behav. 78(4), pp. 699-705, August 2004.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Research on Medical Consequences of Drug Abuse

Integration of Motivational Interviewing and Cognitive Behavioral Therapy to Improve HIV Medication Adherence and Reduce Substance Use Among HIV Positive Men and Women: Results of a Pilot Project

In this pilot study a combined motivational interviewing and cognitive behavioral therapy intervention was used to increase adherence to highly active antiretroviral therapy and reduce substance use in HIV infected adults. The aims of this study were 1) to confirm the ability to recruit HIV+ substance abusers taking antiretroviral medications; 2) to demonstrate the ability to retain participants over the course of the eight-session intervention; and 3) to examine changes in substance use and HAART adherence from pretreatment to posttreatment. Twelve HIV+ adults with a substance use disorder participated in the 8-week intervention, which consisted of weekly individual sessions with a trained therapist. Preliminary results showed that there was a significant reduction in substance use during treatment. Retention for all 8 sessions was 73.3%. No statistically significant differences were found for changes in HIV medication adherence, but the trends suggest the potential for positive results with a larger sample. This pilot study demonstrated the feasibility and acceptability of the treatment. However, additional research is needed to determine if this may be an effective intervention to improve HIV medication adherence in HIV + drug abusers. Parsons, J.T., Rosof, E., Punzalan, J.C. and Di Maria, L. AIDS Patient Care STDS. 19(1), pp. 31-39, January 2005.

Patient-Clinician Relationships and Treatment System Effects on HIV Medication Adherence

The aims of this study were to determine the impact of the patient-clinician relationship on patient adherence to HIV medication, to identify which aspects of the patient-clinician and the treatment system influenced adherence, and to determine which of these variables remained important when the impact of mental distress and substance abuse was considered. This was a cross-sectional study using a sample of 120 HIV+ clinic patients. The Primary Care Assessment Survey (PCAS) assessed the clinician-patient relationship and the treatment system. The Composite International Diagnostic Inventory-Short Form (CIDI-SF) screened for mental disorders, and the Brief Substance Abuse History Form measured recent and remote substance use. Patient adherence was assessed using five markers including 3 interview-elicited self-reports, 1 medical chart review, and 1 summary score. Logistic regression analyses identified independent predictors of each adherence behavior. PCAS scores contributed to all five models, and their effects persisted when mental distress and substance abuse were considered. Adherence behaviors are explained by a variety of factors and should be assessed using multiple methods. Further research is needed to illuminate the mechanisms of action of the clinician-patient relationship on adherence to HIV medication. Ingersoll, K.S. and Heckman, C.J. AIDS and Behavior 9(1), pp. 89-101, March 2005.

Human Immunodeficiency Virus 1 Infection, Cocaine, and Coronary Calcification

Although cocaine use and human immunodeficiency virus (HIV) infection have been linked with clinical cardiovascular disease, the effects of cocaine use and HIV infection, especially the combination of the 2, on subclinical disease have rarely been reported. The objective of this study was to evaluate whether cocaine use alone, HIV infection alone, or a combination of the 2 is associated with coronary calcification, a

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marker of subclinical atherosclerosis. Between May 20, 2000, and March 31, 2003, 224 African-American study participants from Baltimore were enrolled in an observational study of subclinical atherosclerosis as related to HIV and cocaine use. Interviews about sociodemographic characteristics and drug use behaviors, clinical examinations, echocardiographic examinations, lipid profiles, high-sensitivity C-reactive protein tests, and computed tomographic scans for coronary calcium were performed. Although the overall investigation is a cohort study, the data presented herein are cross sectional only. Results indicated that the highest proportion (37.6%) of presence of coronary calcification was in the HIV-positive and cocaine-positive group, followed by 29.8% in the HIV-negative and cocaine-positive group, 28.6% in the HIV-positive and cocaine-negative group, and 18.8% in the HIV-negative and cocaine-negative group. Univariate analysis showed that HIV, cocaine use, and both were associated with a higher number of lesions, calcified area, volume, and calcium score. In multiple regression analysis with adjustment for age, body mass index, low-density lipoprotein cholesterol level, triglyceride level, mean corpuscular volume, and systolic blood pressure, HIV, cocaine use, and both were independently associated with coronary calcification. These results suggest that HIV infection alone, cocaine use alone, or the 2 combined may contribute to early subclinical atherosclerotic cardiovascular disease. Lai, S., Lima, J.A., Lai, H., Vlahov, D., Celentano, D., Tong, W., Bartlett, J.G., Margolick, J. and Fishman, E.K. Human Immunodeficiency Virus 1 Infection, Cocaine, and Coronary Calcification. Arch Intern Med. 165, pp. 690-695, March 28, 2005.

Long-Term Cocaine Use is Related to Cardiac Diastolic Dysfunction in an African-American Population in Baltimore, Maryland

Only limited studies have been done on the effects of long-term cocaine use on the human heart, and the results remain controversial. In this study, the authors examined and compared the diastolic function of non-cocaine users and chronic cocaine users to reveal the impact of long-term cocaine use on the human heart. Two-dimensional echocardiogram and pulsed Doppler transmitral blood flow pattern were obtained from 138 recruited study participants with different cocaine histories. The indices of cardiac structure and function were measured from the echocardiogram of each participant. Student's t-test was used to compare the average echocardiographic measurements of the non-cocaine user group and the cocaine user group. Multivariate regression analysis was deployed to eliminate the effects of age, gender, blood pressure, and HIV infection on the functional measurements of the two groups. Results indicated that the cocaine user group had a significantly longer average deceleration time than did the non-cocaine user group (208.1 38.2 vs. 167.5 39.1 ms, P< 0.001). A linear association existed between the deceleration time and the log-transformed duration of cocaine use (beta=0.00351, S.E.=0.00104, P=0.001). Cocaine users in this study were approximately five times more likely to have an elongated deceleration time (>200 ms) than were non-users (OR, 4.799; 95% CI, 1.000-23.044; P=0.05). No significant differences were observed in the other measured diastolic functional parameters, such as isovolumic ventricular relaxation time, E wave, A wave, and E/A ratio. Authors conclude that Long-term cocaine use is linked to decline in diastolic function. Tong, W., Lima, J.A., Meng, Q., Flynn, E. and Lai, S. Long-term Cocaine Use is Related to Cardiac Diastolic Dysfunction in an African-American Population in Baltimore, Maryland. Int J Cardiol. 97(1), pp. 25-28, October 2004.

Sexual Risk Among Injection Drug Users Recruited from Syringe Exchange Programs in California

The objective of this study was to examine correlates of sexual risk among injection drug users (IDUs). A total of 1445 IDUs were recruited from California syringe exchange programs. Consistent condom use was independently related to being HIV-positive, having multiple sex partners, not having a steady partner, not sharing syringes, and not injecting amphetamines for men; and engaging in sex work, not sharing syringes, and not having a steady partner for women. Having multiple recent sexual partnerships that included a steady partner was related to engaging in sex work, speedball injection, and amphetamine use among men; and younger age, having had a sexually transmitted disease (STD), engaging in sex work, and using alcohol among women. Having heterosexual anal sex was related to having had an STD, having multiple sexual partners, using amphetamines, and syringe-sharing for men; and younger age and amphetamine use for women. Authors conclude that comprehensive prevention interventions addressing multiple sexual and injection risk behaviors are needed for IDUs. Bogart, L.M., Kral, A.H., Scott, A., Anderson, R., Flynn, N., Gilbert, M.L. and Bluthenthal, R.N. Sexual Risk Among Injection Drug Users Recruited from Syringe Exchange Programs in California. Sex Transm Dis. 32(1), pp.

27-34, January 2005.

Injection Risk Behaviors Among Clients of Syringe Exchange Programs With Different Syringe Dispensation Policies

While there have been numerous papers published in the medical, social, and epidemiologic literature about the effectiveness of syringe exchange programs (SEPs), few papers identify operational characteristics of the SEPs they study or assess which of those characteristics are associated with optimal HIV risk reduction among clients. The objective of this study was to examine whether different syringe dispensation policies were associated with client-level injection-related HIV risk. Injection drug users (IDUs) were recruited at 23 SEPs in California in 2001 (n = 531). SEPs were classified by their executive directors as to whether they provided a strict one-for-one syringe exchange, gave a few extra syringes above the one-for-one exchange, or distributed the amount of syringes based upon need as opposed to how many syringes were turned in by the clients. Injection-related risk was compared by SEP program type. In multivariate logistic regression analysis, clients of distribution-based programs had lower odds of reusing syringes (adjusted odds ratio = 0.43; 95% CI = 0.27, 0.71) when adjusting for confounding variables. There were no statistical differences with regards to distributive or receptive syringe sharing by dispensation policy. It is concluded that SEPs that base syringe dispensation policy upon need may facilitate reductions in reuse of syringes. Kral, A.H., Anderson, R., Flynn, N.M. and Bluthenthal, R.N. Injection Risk Behaviors Among Clients of Syringe Exchange Programs With Different Syringe Dispensation Policies. J Acquir Immune Defic Syndr. 37(2) pp. 1307-1312, October 1, 2004.

Injection Drug Use and Crack Cocaine Smoking: Independent and Dual Risk Behaviors for HIV Infection

Previous studies have examined the practices of injecting drugs or smoking crack cocaine as high-risk, but independent, factors for HIV transmission. To explore the independent and dual risks of injection practices and crack smoking, this study examined HIV seroprevalence rates among distinct drug user groups, based on patterns of daily administration. A sample of 3,555 drug users and neighborhood controls in urban Miami, FL and rural Belle Glade and Immokalee, FL were partitioned into four mutually-exclusive groups: 1) injection drug users (IDUs); 2) crack-cocaine smokers; 3) dual users who both smoked crack and injected drugs; and 4) non-drug-user controls. HIV seroprevalence rates were 45.1% for IDUs, 30.5% for dual users, 20.1% for crack smokers and 7.3% for controls. Multivariate logistic regression analysis found that when compared with controls odds ratios for HIV seropositivity were 9.81 for IDUs, 5.27 for dual users, and 2.24 for crack smokers. These findings provide evidence of: 1) behavioral and structural co-factors that influence HIV exposure patterns among drug users; and 2) the substantially higher risk of HIV infection among IDUs compared with other drug users. Intervention strategies must be tailored for the specific drug use subpopulations to optimize efficacy. McCoy, C.B., Lai, S., Metsch, L.R., Messiah, S.E. and Zhao, W. Injection Drug Use and Crack Cocaine Smoking: Independent and Dual Risk Dehaviors for HIV Infection. Ann Epidemiol. 14(8), pp. 535-542, September 2004.

Drug Abuse and Neuropathogenesis of HIV Infection: Role of DC-SIGN and IDO

Dendritic cells are the critical mediators of various immune responses and are the first line of defense against any infection including HIV. They play a major role in harboring HIV and the subsequent infection of T cells and passage of virus through the blood-brain barrier (BBB). The recently discovered DC-specific, CD4-independent HIV attachment receptor, DC-SIGN, and T-cell suppressing factor, indolamine 2,3-dioxygenase (IDO), are known to play a critical role in the immuno-neuropathogenesis of HIV infection. Since brain microvascular cells (BMVEC) express dendritic cell (DC)-specific C type ICAM-3 grabbing nonintegrin (DC-SIGN), it is possible that DC-SIGN may play a critical role in human immunodeficiency virus-type 1 (HIV-1) infection and migration of infected DC across BBB. Matrix metalloproteinases (MMPs) are proteolytic enzymes known to be responsible for maintenance, turnover and integrity of extracellular matrix. Results show that cocaine upregulates IDO and DC-SIGN expression by DC. Further, cocaine upregulates DC-SIGN and MMPs in BMVEC supporting the hypothesis that cocaine causes membrane permeability facilitating endothelial transmigration of infected DC into the CNS. Targeting DC-SIGN and IDO with specific monoclonal antibodies, inexpensive synthetic antagonists, antisense oligonucleotides and siRNA may lead to the development of novel treatment strategies particularly in high-risk populations such as cocaine users. Nair, M.P., Schwartz, S.A., Mahajan, S.D., Tsiao, C., Chawda, R.P.,

Whitney, R., Don Sykes, B.B. and Hewitt, R. Drug Abuse and Neuropathogenesis of HIV Infection: Role of DC-SIGN and IDO. J Neuroimmunol. 57(1-2), pp. 56-60, December 2004.

Association of Drug Abuse with Inhibition of HIV-1 Immune Responses: Studies with Long-term of HIV-1 Non-progressors

Recreational drug use has been proposed to affect the course of human immunodeficiency virus (HIV) infections. To investigate the effects of substance abuse on HIV infections, the authors compared virus-specific cytotoxic T lymphocyte (CTL) responses and the expression of IL-16, TGF-beta1, and CXCR4 in three different cohorts of HIV-infected patients: (1) long-term nonprogressors (LT-NPs) of HIV infection who do not use recreational drugs; (2) nondrug using normal progressors (NPs), and (3) drug using NPs. Results show that LT-NPs manifest increased CTL activity and IL-16 expression and decreased expression of TGF-beta1 and CXCR4 compared to NPs, regardless of recreational drug usage. Furthermore, drugs using NPs showed significantly lower levels of CTL and IL-16 expression and increased TGF-beta1 and CXCR4 expression compared to nondrugs using NPs. Results suggest that recreational drug use may reduce CTL and IL-16 expression and increase the expression of TGF-beta1 and CXCR4, all of which may facilitate progression of HIV infections Nair, M.P., Mahajan, S., Hewitt, R., Whitney, Z.R. and Schwartz, S.A. Association of Drug Abuse with Inhibition of HIV-1 Immune Responses: Studies with Long-term of HIV-1 Nonprogressors. J Neuroimmunol. 147(1-2), pp. 21-25, February 2004.

Body Habitus in a Cohort of HIV-seropositive and HIV-seronegative Injection Drug Users

Authors determined anthropometric measurements (including height, weight, circumferences, and skinfolds) and self-reported symptoms related to body habitus changes in 324 HIV-seropositive and HIV-seronegative inner city injection drug users (IDUs) who participated in a substudy from the ALIVE (AIDS Linked to Intravenous Experiences) cohort. Participants who reported lipoatrophy in body parts had consistently lower anthropometric measurements and those reporting adiposity had correspondingly higher anthropometric measurements than participants who did not report these changes. Peripheral lipoatrophy was more common among all HIV-seropositive than HIV-seronegative participants, however, it was not associated with highly active antiretroviral therapy (HAART) (39% HIV-seronegatives; 58% HIV-seropositive not receiving HIV treatment [No Tx]; 49% HAART, p = 0.04). Central adiposity was more common among HAART (52%) than No Tx (26.6%) and HIV-seronegative (42%) participants (p = 0.001). However, waist circumference, while somewhat higher among HAART than No Tx participants, did not differ significantly from HIV-seronegative participants (85.2 cm HIV-seronegatives; 83.3 cm No Tx; 85.8 cm HAART). A large proportion of those who reported peripheral lipoatrophy also reported central lipoatrophy (76.9% HIV-seronegatives; 69.6% No Tx; 66.2% HAART). A large proportion of those who reported central adiposity also reported adiposity of the peripheral sites (88.1% HIV seronegatives; 66.7% No Tx; 74.3% HAART). The combination of lipoatrophy and adiposity was associated with HAART treatment (6% HIV-seronegatives; 3% No Tx; 16% HAART, p = 0.002), but may be driven by the association with adiposity. These data suggest validity of self-reports for body habitus changes among injection drug users. Smit, E., Semba, R.D., Pilibosian, E., Vlahov, D., Tun, W., Purvis, L. and Tang, A.M. Body Habitus in a Cohort of HIV-seropositive and HIV-seronegative Injection Drug Users. AIDS Patient Care STDS. 19(1), pp. 19-30, January 2005.

The Effect of Drug Abuse on Body Mass Index in Hispanics with and without HIV Infection

There is a widely held view that the lower weight of drug abusers is attributable to diet. However, many studies on the dietary intake of drug abusers have failed to find energy insufficiency, while non-dietary factors have rarely been examined. The purpose of this study was to examine non-dietary factors that could affect the weight of drug abusers with and without HIV infection. Participants were recruited into one of three groups: HIV-positive drug abusers (n=85), HIV-negative drug abusers (n=102) and HIV-positive persons who do not use drugs ('non-drug abusers', n=98). Non-dietary factors influencing weight included infection with HIV and/or hepatitis, malabsorption, resting energy expenditure and physical activity. The baseline data was from a prospective cohort study of the role of drug abuse in HIV/AIDS weight loss conducted in Boston, USA. The first 286 participants to enroll in the study served as subjects. HIV-positive drug abusers had a body mass index (BMI) that was significantly lower than that of HIV-positive non-drug abusers. The differences in

weight were principally differences in fat. In the men, cocaine abuse, either alone or mixed with opiates, was associated with lower BMI, while strict opiate abuse was not. Infection with HIV or hepatitis, intestinal malabsorption, resting energy expenditure and physical activity, as measured in this study, did not explain the observed differences in weight and BMI. Drug abuse, and especially cocaine abuse, was associated with lower weight in men. However, infection with HIV and/or hepatitis, malabsorption and resting energy expenditure do not explain these findings. Forrester, J.E., Tucker, K.L. and Gorbach, S.L. The Effect of Drug Abuse on Body Mass Index in Hispanics with and without HIV Infection. Public Health Nutr. 8(1), pp. 61-68, February 2005.

Dietary Intake and Body Mass Index in HIV-positive and HIV-negative Drug Abusers of Hispanic Ethnicity

Malnutrition in drug abusers has been attributed to poor diet. However, previous studies are conflicting. Many studies have not considered possible concurrent HIV disease. The purpose of this study was to determine the relationship between drug abuse and dietary intake in Hispanic Americans with and without HIV infection. Dietary intake was measured using 3-day food records and 24-hour dietary recalls in three groups: HIV-positive drug abusers, HIV-negative drug abusers and HIV-positive persons who do not use drugs ('non-drug abusers'). The baseline data was from a prospective cohort study of the role of drug abuse in HIV/AIDS weight loss and malnutrition conducted in Boston, Massachusetts. The first 284 participants to enroll in the study served as subjects. HIV-positive drug abusers had a body mass index (BMI) that was significantly lower than that of HIV-positive non-drug abusers. Reported energy, fat and fiber intakes did not differ between groups. All groups had median reported intakes of vitamin A, vitamin B6, vitamin B12, selenium and zinc that were in excess of the dietary reference values (DRI). Intakes of alpha-tocopherol were below the DRI, but did not differ from intakes of the general US population. However, increasing levels of drug abuse were associated with lower reported intakes of vitamin B6, vitamin B12, selenium and zinc. Overall, this study does not support the notion that dietary intake can explain the lower BMI of HIV-positive drug abusers. Further studies examining non-dietary determinants of nutritional status in drug abusers are warranted. Forrester, J.E., Tucker, K.L. and Gorbach, S.L. Dietary Intake and Body Mass Index in HIV-positive and HIV-negative Drug Abusers of Hispanic Ethnicity. Public Health Nutr. 7(7), pp. 863-870, October 2004.

HIV Prevalence and Risk Behaviors Among Men Who Have Sex with Men and Inject Drugs in San Francisco

The dual risks of male-to-male sex and drug injection have put men who have sex with men and inject drugs (MSM-IDU) at the forefront of the HIV epidemic, with the highest rates of infection among any risk group in the United States. This study analyzes data collected from 357 MSM-IDU in San Francisco between 1998 and 2002 to examine how risk behaviors differ by HIV serostatus and self-identified sexual orientation and to assess medical and social service utilization among HIV-positive MSM-IDU. Twenty-eight percent of the sample tested HIV antibody positive. There was little difference in risk behaviors between HIV-negative and HIV-positive MSM-IDU. Thirty percent of HIV-positive MSM-IDU reported distributive syringe sharing, compared to 40% of HIV negatives. Among MSM-IDU who reported anal intercourse in the past 6 months, 70% of positives and 66% of HIV negatives reported unprotected anal intercourse. HIV status varied greatly by self-identified sexual orientation: 46% among gay, 24% among bisexual, and 14% among heterosexual MSM-IDU. Heterosexual MSM-IDU were more likely than other MSM-IDU to be homeless and to trade sex for money or drugs. Gay MSM-IDU were more likely to have anal intercourse. Bisexual MSM-IDU were as likely as heterosexual MSM-IDU to have sex with women and as likely as gay-identified MSM-IDU to have anal intercourse. Among MSM-IDU who were HIV positive, 15% were currently on antiretroviral therapy and 18% were currently in drug treatment, and 87% reported using a syringe exchange program in the past 6 months. These findings have implications for the development of HIV interventions that target the diverse MSM-IDU population. Kral A.H., Lorvick, J., Ciccarone, D., Wenger, L., Gee, L., Martinez, A. and Edlin, B.R. HIV Prevalence and Risk Behaviors Among Men Who Have Sex with Men and Inject Drugs in San Francisco. J Urban Health. 82(1 Suppl 1):i43-i50, March 2005. Epub February 28, 2005.

Early Puberty in Girls: The Case of Premature Adrenarche

In this article authors examine the issue of early puberty in girls. First, a brief overview of normal pubertal development is provided, including the two endocrine components of puberty: gonadarche and adrenarche. Second, authors critically

discuss the controversy regarding whether puberty truly is occurring earlier in girls. Third, they emphasize one type of early puberty, the case of premature adrenarche (PA). PA is used to illustrate the importance of identifying types of early puberty, evaluating the types to determine causality, determining whether follow-up of early puberty is necessary, and showing the potential ramifications of ignoring this variation in pubertal development. Findings from a pilot study comparing PA and on-time puberty children are used to show the importance of determining whether early puberty is normal in all cases. Dorn, L.D. and Rotenstein, D. Early Puberty in Girls: The Case of Premature Adrenarche. Womens Health Issues 14(6), pp. 177-183, November-December 2004.

Vitamin D Deficiency and Seasonal Variation in an Adult South Florida Population

Hypovitaminosis D is associated with impaired neuromuscular function, bone loss, and fractures. If a person is not taking a vitamin supplement, sun exposure is often the greatest source of vitamin D. Thus, vitamin D deficiency is not uncommon in the winter, particularly in northern latitudes. The goal of this study was to establish the prevalence of vitamin D deficiency in south Florida (U.S.), a region of year-round sunny weather. At the end of the winter, 212 men and women attending an internal medicine clinic at a local county hospital were enrolled for measurements of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D, and PTH; 99 participants returned at the end of summer. The mean (sd) winter 25(OH)D concentration was 24.9 8.7 ng/ml (62.3 21.8 nmol/liter) in men and 22.4 8.2 ng/ml (56.0 20.5 nmol/liter) in women. In winter, the prevalence of hypovitaminosis D, defined as 25(OH)D less than 20 ng/ml (50 nmol/liter), was 38% and 40% in men and women, respectively. In the 99 subjects who returned for the end of summer visit, the mean 25(OH)D concentration was 31.0 11.0 ng/ml (77.5 27.5 nmol/liter) in men and 25.0 9.4 ng/ml (62.5 23.5 nmol/liter) in women. Seasonal variation represented a 14% summer increase in 25(OH)D concentrations in men and a 13% increase in women, both of which were statistically significant. The prevalence of hypovitaminosis D is considerable even in southern latitudes and should be taken into account in the evaluation of postmenopausal and male osteoporosis. Levis, S., Gomez, A., Jimenez, C., Veras, L., Ma, F., Lai, S., Hollis, B. and Roos, B.A. Vitamin D Deficiency and Seasonal Variation in an Adult South Florida Population. J Clin Endocrinol Metab. 90(3), pp. 1557-1562, March 2005.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Services Research

Multiple Episodes Of Care Over Several Years Are Norm For Addicts

Interview data were collected at 6, 18, 24, 36, 48, and 60 months post-intake from 1,271 of 1,326 (96%) people recruited from a stratified sequential sample of admissions to publicly funded treatment programs in a large metropolitan area. The most common dependence diagnoses were for cocaine (64%), alcohol (44%), opioids (41%), and/or marijuana (14%). Survival analysis of patient histories was used to estimate the time from first use and first treatment until people reported 12 months of abstinence or died. During the three years after intake, 47% reached at least 12 months of abstinence. The median time from first to last use was 27 years. The median time from first treatment episode to last use was 9 years. Years to recovery were significantly longer for males, people starting use under the age of 21 (particularly those starting under the age of 15), people who had participated in treatment 3 or more times, and for people high in mental distress. These exploratory results suggest that multiple episodes of care over several years are the norm and that rather than thinking of multiple episodes in terms of "cumulative dosage," it might be better thought of as further evidence of chronicity and that we need to develop and evaluate models of longer term recovery management. Dennis, M.L., Scott, C.K, Funk, R.R., and Foss, M.A. The Duration and Correlates of Addiction and Treatment. Journal of Substance Abuse Treatment 28(4), pp. 9-60, 2005.

New Information Increases Understanding Of Addiction Relapse

This study replicates earlier work, by documenting transition patterns during a 3-year period within the relapse cycle, and identifies variables that predict transitions across pathways between one of four states: (1) in the community using, (2) incarcerated, (3) in treatment, or (4) in the community not using. Data are from 1,326 adults recruited from sequential admissions to 12 substance abuse treatment facilities in Chicago, IL, between 1996 and 1998. Participants were predominantly female (60%) and African American (88%) adults. Participants were interviewed at intake, and at 6, 24, and 36 months post-intake and follow-up rates ranged from 94% to 98% per wave. Over 83% of the participants transitioned from one point in the cycle to another during the 3 years (including 36% two times, 14% three times). Results examining follow-up data also showed that the longer a person stayed abstinent the greater the odds that she would remain abstinent. However, the percentage of addicts who maintained abstinence over the 3-year cycle studied was only 10.6%. Factors predicting transition within the cycle varied depending upon in which of the four paths a subject was at each follow-up period. Results help demonstrate the need to adopt a chronic vs. acute care model for addiction. While exploratory and observational, several of the predictors are time-dependent and identify promising targets for interventions designed to shorten the cycle and increase the long-term effectiveness of treatment. Scott, C.K., Foss, M.A., and Dennis, M.L. Pathways to Relapse, Treatment, and Recovery Cycle Over Three Years. Journal of Substance Abuse Treatment 28, pp. 61-70, 2005.

Average Substance Abuse Care Costs Higher For Co-Occurring Alcohol And Drug Disorders Than For Alcohol Or Drug Disorders Alone

The study investigated the relationship of substance use disorders, concurrent psychiatric disorders, and patient demographics to patterns of treatment use and spending in behavioral health and medical treatment sectors. Researchers examined insurance claims (data on costs and use of services) for 1899 individuals who received treatment for substance use disorders in 1997. Medical and pharmacy spending was

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assessed for 590 individuals. The most prevalent services were outpatient, intensive outpatient, residential, and detoxification. Average mental health/substance abuse care spending conditional on use was highest for those with concurrent alcohol and drug disorders ($5235) compared to those with alcohol ($2507) or drugs ($3360) alone; other psychiatric illness ($4463) compared to those without ($1837); and employees' dependents ($4138) compared to employees ($2875) or their spouses ($2744). A significant minority of individuals also sought mental health/substance abuse services in the medical sector. Understanding services use and associated costs can best be achieved by examining services use across treatment sectors. Greenfield, S.F., Azzone, V., Huskamp, H., Cuffel, B., Croghan, T., Goldman, W. and Frank, R.G. Treatment for Substance Use Disorders in a Privately Insured Population Under Managed Care Costs and Services Use. Journal of Substance Abuse Treatment 27(4), pp. 265-275, 2004.

Drug Court Has Positive Net Economic Benefits

This study conducted a cost-benefit analysis of three drug court programs in Kentucky for two groups of drug court participants: program graduates (n=222) and program terminators (n=371). Economic cost data were collected using the Drug Abuse Treatment Cost Analysis Program (DATCAP). Data related to economic benefits of the drug court programs were assessed by calculating the reduction in costs associated with criminal justice system, domestic violence, mental health services, motor vehicle accidents, and by considering increased child support payments and earnings from employment. Economic benefits of the drug court programs were estimated relative to a comparison group of individuals who were assessed for the drug court programs, but did not enter the programs. Cost per treatment episode was estimated to be $3,178 per drug court participant. Findings indicate that, particularly for graduates, drug court involvement was associated with reductions in incarceration, mental health services, and legal costs, as well as increases in earnings and child support payments. There is an economic benefit of $8,624 over 12 months and a net savings of $5,446. Logan, T.K., Hoyt, W.H., McCollister, K.E., French, M.T., Leukefeld, C. and Minton, L. Economic Evaluation of Drug Court: Methodology, Results, and Policy Implications. Evaluation and Program Planning 27(4), pp. 381-396, 2004.

Increased Recidivism Among Offenders Treated Under California's Proposition 36

In November 2000, California voters approved the Substance Abuse and Crime Prevention Act (SACPA), also known as "Proposition 36," which offered adults convicted of non-violent drug possession offenses the option of participating in drug treatment in lieu of incarceration. The investigators compared data collected from a sub-sample of 3,748 offenders in 13 California counties admitted to drug treatment during the first six months of SACPA (July-December, 2001) to 1,178 offenders referred to treatment under criminal justice pressure other than SACPA, and 1,882 patients admitted without legal pressure. Relative to non-SACPA patients, SACPA patients with severe drug problems were significantly less likely to be treated in residential programs. Subsequent analyses further revealed a significant severity by modality interaction, with high-severity/outpatient clients being most likely to be rearrested on a drug-related charge in the 12 months after treatment admission. Although the prevalence of arrests decreased for all three groups after treatment admission, SACPA clients were more likely to be re-arrested for a drug crime even after controlling for the interaction between drug use severity and treatment modality. These findings underscore the role of client-treatment matching (based on addiction severity) and of actively applying legal pressure to increase treatment retention and maximize potential treatment benefits. Farabee, D., Hser, T., Anglin, M.D. and Huang, Y. Recidivism Among an Early Cohort of California's Proposition 36 Offenders. Criminology and Public Policy 3(4), pp. 563-584, 2004.

Psychological Distress Is A Significant Indicator of Drug Abuse Relapse

This study examined the background characteristics and psychological distress of 180 drug abuse patients in relationship to drug use and drinking. Distress was measured by the 24-item Brief Symptoms Inventory Hopkins Checklist. A modified linear scale for drug use and drinking was derived from retrospective self-reports using the Time Line Follow Back (TLFB) and Lifetime Drinking History (LDH). Structural equation modeling found that psychological distress at baseline and follow-up were direct, robust predictors of reuse of alcohol, and to a lesser extent reuse of illicit drugs, 2 years following substance user treatment. Described as negative emotional states or depressive symptomatology --psychological distress'' may constitute a common and costly proximal high-risk situation and a marker of return to substance use among patients with substance use problems. Regardless of causal origin, for practical

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In Memoriam

purposes, assessment of psychological distress during substance user treatment, preferably after a --reasonable'' detoxification period, may provide a marker for further investigation for risk for resumed substance use or relapse. Flynn, H.A., Walton, M.A., Curran, G.M., Blow, F.C. and Knudtzen, S. Psychological Distress and Return to Substance Use Two Years Following Treatment. Substance Use and Misuse 39, pp. 885-910, 2004.

New Analytic Method for Evaluating Causal Effects in Observational Studies

Causal effect modeling with naturalistic rather than experimental data is challenging. In observational studies participants in different treatment conditions may also differ on pre-treatment characteristics that influence outcomes. Propensity score methods can theoretically eliminate these confounds for all observed covariates, but accurate estimation of propensity scores is impeded by large numbers of covariates, uncertain functional forms for their associations with treatment selection, and other problems. This article demonstrates that boosting, a modern statistical technique, can overcome many of these obstacles. The authors illustrate this approach with a study of 449 adolescent probationers in substance abuse treatment programs. Propensity score weights estimated using boosting eliminate most pre-treatment group differences and substantially alter the apparent relative effects of adolescent substance abuse treatment. McCaffrey, D.F., Ridgeway, G. and Morral, A.R. Propensity Score Estimation with Boosted Regression for Evaluating Causal Effects in Observational Studies. Psychological Methods 9(4), pp. 403-425, December 2004.

California Women Benefit More Than Men From Treatment Of Methamphetamine Abuse

A prospective longitudinal study examined treatment outcomes among 1073 methamphetamine-abusing patients (567 women, 506 men) from 32 community-based outpatient and residential programs in 13 California counties. Data were collected at intake and at 3 months and 9 months after admission. With one exception, improvements from baseline to follow-up were observed in all areas measured by the Addiction Severity Index (ASI) for both women and men in either modality. However, compared to men, women demonstrated greater improvement in family relationships and resolution of medical problems, while maintaining the same level of improvement as men in all other areas. These results showed gains for women despite higher unemployment, greater childcare responsibilities, cohabitation with someone who also used alcohol or drugs, relatively more reports of physical or sexual abuse and more psychiatric symptoms. Hser, Y., Evans, E., and Huang, Y. Treatment Outcomes Among Women and Men Methamphetamine Abusers In California. Journal of Substance Abuse Treatment 28(1), pp. 77-85, 2005.

Treatment Retention Increased in Oregon and Washington, 1994-1998

This study examined individual and system characteristics associated with retention in methadone maintenance treatment among Medicaid-eligible adults (aged 18-64 years) in publicly funded treatment for opiate use in Oregon (N=3557) and Washington (N=5308), 1994-1998. Logistic regression was used to examine the contributions of predisposing, need, and enabling characteristics on 365-day retention in methadone maintenance treatment. Older patients, patients with a history of methadone maintenance treatment, and persons with stable Medicaid eligibility had higher rates of retention than did patients with disabilities, polysubstance users, and those with an arrest record. In Oregon, which delivers methadone maintenance treatment through managed care, retention rose sharply from 28% to 51% between 1994 and 1998 and then leveled off. During the same time period, retention in Washington State grew from 28% to 34%. The higher rates of retention in Oregon can be explained in part by differences in service delivery influenced by financing. Faced with long waiting lists, Washington providers were more than twice as likely as their Oregon counterparts to discharge patients for rule violations. Given the importance of retention, policies and practices that influence retention should be carefully considered. Because Medicaid eligibility has a dramatic impact on retention, policies that help extend eligibility or stabilize eligibility among individuals actively engaged in treatment should be carefully considered. Deck, D. and Carlson, M.J. Retention in Publicly Funded Methadone Maintenance Treatment in two Western States. Journal of Behavioral Health Services Research, 32(1), pp. 43-60, 2005.

Relationship Between Drug Treatment Services, Retention and Outcomes

This longitudinal study examined the relationships between treatment processes and outcomes among 1939 patients in 36 outpatient and residential community-based drug treatment programs in 13 California counties who were assessed at intake,

discharge, three months after admission, and nine months after admission. Path analyses related the quantity and quality of services received in the first three months of treatment to retention in treatment and outcomes at the nine-month follow-up. Patients were determined to have a favorable outcome if for at least 30 days before the follow-up assessment they did not use drugs, were not involved in criminal activity, and lived in the community. Analyses controlled for patients' baseline characteristics. Greater service intensity and satisfaction were positively related to either treatment completion or longer treatment retention, which in turn was related to favorable treatment outcomes. Patients with greater problem severity received more services and were more likely to be satisfied with treatment. These patterns were similar for patients regardless of whether they were treated in outpatient drug-free programs or residential programs. Hser, Y., Evans, E., Huang, Y., and Anglin, M.D. Relationship Between Drug Treatment Services, Retention and Outcomes. Psychiatric Services 55(7), pp. 767-774, 2004.

Transitions During Effective Treatment For Cocaine-Abusing Homeless

Seventy-two cocaine dependent homeless persons receiving day treatment, which included abstinence-contingent housing and employment; established abstinence, maintained abstinence for longer durations, and were significantly less likely to relapse than 69 similar patients in a day treatment-only condition. This random controlled study indicated that day treatment with abstinence-contingent housing and employment was more effective in maintaining complete abstinence once it was established, and patients who relapsed returned more quickly to abstinence than those day treatment patients not in abstinence-contingent situations. Milby, J.B., Schumacher, J.E., Vuchinich, R.E. and Wallace, D. Transitions During Effective Treatment for Cocaine-abusing Homeless Persons: Establishing Abstinence, Lapse, and Relapse, and Reestablishing Abstinence. Psychology of Addictive Behaviors 18(3), pp. 250-256, 2004.

Psychiatric Services for Patients with Chemical Dependency Enhance Treatment Outcomes

This study examined the relationship between use of psychiatric services and alcohol and drug treatment outcomes five years after such treatment. It was anticipated that receipt of psychiatric services would predict long-term abstinence. A sample of 604 outpatients from a managed care organization's chemical dependency program was interviewed about substance use and severity of psychiatric symptoms at baseline and at five years. Patients were required to have at least three years of membership in the health plan during the five years after intake. Severity of psychiatric symptoms was categorized as zero, low, middle, or high. Use of psychiatric services was ascertained on the basis of administrative data from the health plan. Logistic regression analysis was used to assess the relationship between receipt of psychiatric services during the five years after intake and abstinence at five years. Results were adjusted for individual, treatment, and extra-treatment characteristics; severity of psychiatric symptoms at baseline; and other contacts with the health system. Results revealed that patients who received a threshold level of psychiatric services (an average of at least 2.1 hours a year) were significantly more likely to be abstinent at five years than patients who received less than 2.1 hours a year. The use of psychiatric services among patients with chemical dependency is associated with enhanced long-term outcomes. Ray, G.T., Mertens, J. and Weisner, C. Relationship Between Use of Psychiatric Services and Five-year Alcohol and Drug Treatment Outcomes. Psychiatric Services 56(2), pp. 164-171, 2005.

New Screener and Assessment Measure For Patients With Chronic Pain

Under a small business innovation research grant a self-administered screening tool (Screener and Opioid Assessment for Patients with Pain (SOAPP) was developed and validated for chronic pain patients considered for long-term opioid therapy. A consensus of 26 pain and addiction experts was obtained on important characteristics of chronic pain patients that predict future medication misuse using concept mapping. A 24-item SOAPP (version 1.0) was developed based on this consensus and was administered to 175 patients who were taking opioids for chronic pain. After 6 months, 95 of these patients were re-evaluated. Validation of the SOAPP was conducted. Of the original 24 items, 14 SOAPP items reliably (alpha = .74) predicted subsequent aberrant behaviors (a positive score on the Prescription Drug Use Questionnaire (PDUQ) interview, positive urine toxicology screen, and/or ratings by staff). Receiver operating characteristics curve analysis yielded an area under the curve of 0.881 ($P<0.001$), suggesting adequate sensitivity and specificity for a screening device. Butler, S.F., Budman, S.H., Fernandez, K. and Jamison, R.N. Validation of a Screener and Opioid Assessment Measure for Patients with Chronic

Pain. Pain 112, pp. 65—75, 2004.

Chronic Severe Pain Plays A Role In Heroin Use Among Methadone Patients

Recent studies indicate that severe chronic pain is common among patients in methadone maintenance treatment (MMT). This study used qualitative methods to explore the experiences of 12 MMT patients with chronic pain as measured on the Brief Pain Inventory. Results suggest that chronic severe pain may be linked to illegal drug use, social isolation, and role failure. A variety of barriers limited access to effective pain treatment due to providers' perceived lack of concern or inability to "listen." These preliminary results suggest that more research is needed to guide the development of effective treatment strategies. Karasz, A., Zallman, L., Berg, K., Gourevitch, M., Selwyn, P., and Arnstein, J. The Experience of Chronic Severe Pain in Patients Undergoing Methadone Maintenance Treatment. Journal of Pain Symptom Management 28, pp. 517—525, 2004.

Brief Family-Based Treatment for Adolescent Substance Abuse Superior to Peer Group Therapy In Clinical Trial

A randomized clinical trial compared a family-based therapy (Multidimensional Family Therapy, MDFT) and a peer group therapy with 80 urban, low-income, and ethnically diverse young adolescents (between the ages of 11 and 15). Both treatments were outpatient, relatively brief, manual-guided, equal in intervention dose, and delivered by community drug treatment therapists. Results indicated that the family-based treatment was significantly more effective than peer group therapy in reducing risk and promoting protective processes in the individual, family, peer, and school domains, as well as in reducing substance use over the course of treatment. These results support the clinical effectiveness of MDFT with young adolescents and also supports the dissemination potential of this family-based, multi-system, developmentally-oriented intervention. Liddle, H.A., Rowe, C.L., Dakof, G.A., Ungaro, R.A. and Henderson, C.E. Early Intervention for Adolescent Sbstance Ause: Petreatment to Post-treatment Outcomes of a Randomized Clinical Trial Comparing Multidimensional Family Therapy and Peer Group Treatment. Journal of Psychoactive Drugs 36(1), pp. 49-63, 2004.

Treatment Fidelity For Multidimensional Family Prevention (MDFP) Demonstrated

Multi-dimensional family prevention (MDFP) is a new family-based prevention counseling model for adolescents at high risk for substance abuse and related behavior problems which emerged from Multi-dimensional family therapy (MDFT). Fidelity was assessed by comparing and contrasting MDFP to both MDFT and a second empirically-based intervention used for adolescent substance abusers, cognitive-behavioral therapy (CBT). Randomly-selected videotapes of 109 MDFP sessions, 57 MDFT sessions, and 31 CBT sessions were observationally-rated along two key dimensions of implementation: intervention parameters and intervention techniques. Overall, MDFP was similar to MDFT and different from CBT in a manner congruent with its theoretical principles of interactional, systemic intervention. Hogue, A., Liddle, H.A., Singer, A., and Leckrone, J. Intervention Fidelity in Family-based Prevention Counseling for Adolescent Problem Behaviors. Journal of Community Psychology 33, pp. 191-211, 2005.

Family Focus Predicts Post-treatment Improvement For Adolescent Substance Abusers

The relationship between specific therapy techniques and treatment outcome was examined for two empirically-supported treatments for adolescent substance abuse: individual cognitive-behavioral therapy and multi-dimensional family therapy. Participants were 51 inner-city, substance abusing adolescents receiving outpatient psychotherapy within a larger randomized trial. One session per case was evaluated using a 17-item observational measure of model-specific techniques and therapeutic foci. Exploratory factor analysis identified two subscales, Adolescent Focus and Family Focus, with strong inter-rater reliability and internal consistency. Process-outcome analyses revealed that family focus, but not adolescent focus, predicted post-treatment improvement in drug use, externalizing, and internalizing symptoms within both study conditions. Hogue, A., Liddle, H.A., Dauber, S., and Samuolis, J. Linking Session Focus to Treatment Outcome in Evidence-based Treatments for Adolescent Substance Abuse. Psychotherapy: Theory, Research, Practice, and Training, 41, pp. 83-96, 2004.

Patients Increasingly Referred Outside Substance Abuse Treatment Program for Psychiatric Care

Face-to-face interviews were conducted with a nationally representative panel of 450 privately-funded centers in 1995-1996, 1997-1998, and 2000-2001. Over the study period, the percentage of centers that referred clients with serious mental illness to external providers increased from 57% to 67%. For-profit centers and hospital-based programs, however, were significantly less likely to refer these dually diagnosed clients to external agencies. These data demonstrate that integrated care for clients with co-occurring drug abuse and mental health disorders has become less available over time, despite the consensus that such care is evidence-based treatment for this population. Knudsen, H.K., Roman, P.M., and Ducharme, L.J. The Availability of Psychiatric Programs in Private Substance Abuse Treatment Centers, 1995-2001. Psychiatric Services, 55, pp. 270-273, 2004.

Managerial Practices Result In More Evidence-Based Innovation In Private Substance Abuse Treatment Organizations

Widespread concern about the slow rate of adoption of evidence-based drug abuse treatment technologies has resulted in an emerging literature on the organizational characteristics that are associated with the adoption of innovations. Most research has considered the adoption of specific innovations rather than aggregate measures of innovation adoption. This paper examines "absorptive capacity," a concept from the management literature that refers to such business practices as hiring professionally-trained staff, scanning the competitive environment, and the collection of satisfaction data from third-party payers and referral sources. This research draws upon data from 322 privately-funded substance abuse treatment centers. The three managerial practices reflecting absorptive capacity: the hiring of professionally-trained staff; scanning the competitive environment; and the collection of satisfaction data were significantly associated with the adoption of evidence-based practices, suggesting that that center leadership can play an important role in closing the research-to-practice gap. Knudsen, H.K. and Roman, P.M. Modeling the Use of Innovations in Private Treatment Organizations: The Role of Absorptive Capacity. Journal of Substance Abuse Treatment 26, pp. 51-59, 2004.

Housing Offers Protective Function For Substance Abuse and Violence in Indigent Women

A study examining retrospective self-reports of stratified random samples of women residing in shelters (N = 460) and low-income housing (N = 438) in Los Angeles County, California found that sheltered women were more likely than housed women to report physical and sexual violence, substance use and disorder, HIV risk behavior, and the co-occurrence of these problems in the past year. Differences remained when propensity weights were used to equate the groups on demographic and background characteristics. Wenzel, S.L., Tucker, J.S., Elliott, M.V., Hambarsoomians, K., Perlman, J., Becker, K., Kollross, C. and Golinelli, D. Prevalence and Co-occurrence of Violence, Substance Use and Disorder, and HIV Risk Behavior: A Comparison of Sheltered and Low-income Housed Women in Los Angeles County. Preventive Medicine 39, pp. 617-624, 2004.

Men and Women Similar In Recovery Rates But Different In Psychosocial Functioning

Gender differences were examined at 36 months following residential or outpatient drug-free treatment among 951 participants in the Chicago Target Cities Project, the majority of whom were female (62%) and African American (93%). There were no differences in the proportion of men and women who reported any alcohol or drug use at the 36-month follow-up, with an overall reduction of 41% from intake. Greater proportions of men were incarcerated or employed, whereas greater proportions of women had returned to treatment, lived with their children, lived with a substance user, or had interpersonal problems. Women, as a group, had greater increases over time in self-help participation, free time spent with family, non-using family/friends, and employment. Although both men and women showed significant improvements following treatment, gender differences persisted in several areas of psychosocial functioning related to recovery. Grella, C.E., Scott, C.K, and Foss, M.A. Gender Differences in Long-term Drug Treatment Outcomes in Chicago PETS. Journal of Substance Abuse Treatment, 28, pp. 3-12, 2005.

Using Client Characteristics to Understand Treatment Process in the Therapeutic Community

Therapeutic communities (TCs) improve post-treatment outcomes for substance abusers, but little is known about the in-treatment experience for clients with different backgrounds, experiences, and needs. This study examined the in-treatment

experience of TC participants and examined the relationships between treatment process and client characteristics. Research participants included 447 adults and 148 adolescents receiving treatment in community-based TC programs in New York, California, and Texas. Data related to treatment process were collected using the Therapeutic Community Treatment Process: Dimensions of Change Instrument. Data on demographic characteristics, substance use and treatment history, and client risk factors were extracted from intake interviews and analyzed separately for adolescent and adult residents. Multivariate general linear models were used to examine the effect of client variables on treatment process, after controlling for treatment duration and program effects. Adult clients in the study were on average 36 years old, over half were male, and 57% were African American. The average age of adolescent clients was 17, with 73% being male, and 43 % Hispanic. Adult program participants who were 25 years or older, female, and had prior drug treatment were more positive about their experiences in the TC as indicated in their higher Community Environment scores. Adolescents with one or more arrests within the past 2 years were more negative about both their experiences in the TC and their self-concept as indicated in lower scores on process dimensions of the Community Environment and Personal Development and Change scales. Results from this study indicate how differences in client characteristics affect important treatment process variables including readiness for change and motivation for treatment. Chan, K.S., Wenzel, S., Orlando, M., Montagnet, C., Mandell, W., Becker, K. and Ebener, P. How Important are Client Characteristics to Understanding Treatment Process in the Therapeutic Community? The American Journal of Drug and Alcohol Abuse, 30(4), pp. 871—891, 2004.

Predictors of Treatment Retention for Drug Court Participants

Factors distinguishing clients who complete drug court treatment from those who do not complete drug court have been documented, but differences between urban and rural drug court participants have not been examined. The present study seeks to determine predictors of treatment retention for drug court participants in urban and rural settings. Mental health, drug use, criminal activity, and education/employment and their association with treatment retention are examined. Research subjects included 250 participants from an urban drug court and 250 participants in a rural drug court, both located in Kentucky. Most subjects were male (69%), average age of 30, white (59%), never married (56%) with 1 child. Data collection methods included interviews and record reviews of drug court participants. Study findings indicate that retention in treatment for urban drug court participants could be predicted by examining marital status, employment, drug use, and criminal activity. For the rural drug court, however, retention was only predicted by age and juvenile incarceration. Findings from this study suggest there are different factors associated with drug court retention between urban and rural drug court settings. These findings may be useful to drug court administrators and community treatment providers seeking to tailor drug abuse treatment and services to match client needs. Mateyoke-Scrivner, A., Webster, J.M., Staton, M. and Leukefeld, C. Treatment Retention Predictors of Drug Court Participants in a Rural State. The American Journal of Drug and Alcohol Abuse 30(3), pp. 605—625, 2004.

Ethical Dilemmas in Longitudinal Studies Can Be Addressed with Planning, Training, and Supervision

Many complex ethical issues arise in the day-to-day conduct of longitudinal studies of addiction treatment. These issues are rooted, in part, in the sustained and potentially ambiguous relationship between research staff and study participants; the frequently changing clinical and legal status of study participants; the assertive methods required to generate high follow-up rates and the numerous systems of care and control in which participants are involved. To identify common ethical issues that arise in such studies, the authors conducted individual and group interviews with seasoned members (case trackers, field trackers, interviewers, and supervisors) of the research team. The ethical dilemmas identified through these interviews fell into seven broad arenas: (1) informed consent for research participation; (2) confidentiality and information disclosure; (3) relationship boundaries between study participants and research staff; (4) duty to warn/report responsibilities; (5) questions of autonomy and privacy; (6) issues related to compensation for research participation and (7) data integrity. Case studies illustrate these common ethical dilemmas can be effectively managed via ethically informed research protocols, staff training in ethical decision-making, monitoring and supervision, and collective debriefing of critical events. Scott, C.K. and White, W.L. Ethical Issues in the Conduct of Longitudinal Studies. Journal of Substance Abuse Treatment, 28, pp. 89-99, 2005.

Women's Perception of Therapeutic Communities

A comprehensive measure of treatment was administered to 447 adults and 148 adolescents receiving treatment at community-based TC programs in New York, California, and Texas. Data on demographic characteristics, substance use and treatment history, and client risk factors were extracted from intake interviews and analyzed separately for adult and adolescent residents. Controlling for treatment duration and program effects, female clients over 25 who had prior drug treatment experience reported more positive perceptions of the therapeutic community environment and expressed more willingness to change in contrast to younger males with no prior treatment experience or with one or more arrests within the past 2 years. Chan, K.S., Wenzel, S., Orlando, M., Montagnet, C., Mandell, W., Becker, K., and Ebener, P. How Important Are Client Characteristics to Understanding Treatment Process in the Therapeutic Community? The American Journal of Drug and Alcohol Abuse 30(4), pp. 871-891, 2004.

Physical Violence Against Impoverished Women: Risk and Protective Factors

Violence represents a significant threat to the health of impoverished women. Few studies have attempted to identify risk and protective factors associated with violence directed at these women, although this information might be useful for violence prevention. In a representative probability sample of impoverished women, this study prospectively examined multiple risk and protective factors to understand their relative importance to physical victimization. Study participants included 810 women in Los Angeles County, 402 living in shelters and 408 living in Section 8 low-income housing, who completed structured interviews at baseline and 6-month follow-up. Significant ($p < .05$) multivariate predictors of physical violence experienced during the 6 months prior to the follow-up interview included physical or sexual violence experienced as a child, physical violence experienced during the 6 months prior to baseline interview, having multiple sexual partners, psychological distress, and poor social support. Results highlight the persistence of physical violence in the lives of impoverished women and prospective risk factors for this violence. Findings also highlight opportunities to reduce women's risk of experiencing violence through enhancing social support and mental health. Wenzel, S.L., Tucker, J.S., Elliott, M.N., Marshall, G.N. and Williamson, S.L. Physical Violence Against Impoverished Women: A Longitudinal Analysis of Risk and Protective Factors. Women's Health Issues 14(5), pp. 144-154, 2004.

Improving Assessments and Service Referrals Utilizing A Software Program

Knowledge of service resources and lower burdens for referral have been shown to be directly associated with an increase in problems identified and with services provided. Non-substance abuse professionals, such as child welfare workers often are the first gatekeepers of mental health and addiction services for young people. A newly developed software, IMPROVE (Intervention for Multisector Health Provider Enhancement-child welfare), enables child welfare workers to assess child and adolescent mental health and substance abuse needs and to then find the best fit for them among over 1200 potential mental health and substance abuse referral resources. These findings are based on focus groups of 46 workers and supervisors and a pilot evaluation of the program involved 19 workers, 8 of whom were given the hand-held computers. The IMPROVE decision support software allows a worker to record a youth's mental health symptoms, behaviors, and addictions by checking items on an assessment screen. A keyword checklist also allows workers to note peer problems, environmental stress, strengths and talents in order to find mental health services, foster care availability, and alternatives to formal treatment options (sports, the arts, and skill building) as well as traditional social welfare programs (housing, clothing and food). The software then matches assessments or keywords indicating client need with resource names, program descriptions, and contact information. Stiffman, A.R., Foster, K., Hamburg, and Dore, P. IMPROVE: A Software Program to Improve Assessments and Multisector Referrals. In C.J. Liberton, K. Kutash and R.M. Friedman (Eds.), Conference Proceedings: A System of Care for Children's Mental Health, Expanding the Research Base. Tampa, FL: Research and Training Center for Children's Mental Health, pp. 449-452, 2005.

Organizational Factors Associated With Provision Of Hepatitis C Care In Drug Treatment

Substance abusers are at high risk for hepatitis C (HCV) infection, are medically underserved, and are hard to reach. Researchers conducted a nationwide survey with 445 randomly selected drug treatment units in the U.S. to determine unit and patient characteristics associated with the provision of on-site medical services for HCV-infected drug users. Eighty-four percent of the 322 units that estimated having at least one HCV-infected patient reported that they provided patients with HCV-related

medical care. Drug treatment units were more likely to provide at least some of this care on site if they were residential, part of a network, or affiliated with a hospital, had medical staff, and required that their patients undergo a medical examination before entering treatment. Vassilev, Z.P., Strauss, S.M., Astone, J.M., Friedmann, P.D. and Des Jarlais, D.C. Provision of On-site Medical Care to Patients with Hepatitis C in Drug Treatment Units. Journal of Health Care for the Poor and Underserved, 15(4), pp. 663-671, Nov. 2004.

Organizational Characteristics Influence Length Of Stay In Detoxification Centers

Admissions to 20 publicly-funded alcohol and drug detoxification centers in Massachusetts were examined to identify program and patient variables that influenced length of stay. The last admission during fiscal year 1996 was abstracted for patients 18 years of age and older seeking alcohol, cocaine, or heroin detoxification (n = 21,311; 29% women). A hierarchical, generalized linear model examined the effects of patient and program characteristics on variation in length of stay and tested case-mix adjustments. Program size had the most influence on mean adjusted length of stay; stays were more than 40% longer in detoxification centers with 35 or more beds (7.69 days) than in centers with less than 35 beds (5.42 days). The study highlights the contribution of program size to treatment processes and suggests the need for more attention to program attributes in studies of patient outcomes and treatment processes. Jonkman, J.N., McCarty, D., Harwood, H.J., Normand, S.L. and Caspi, Y. Practice Variation and Length of Stay in Alcohol and Drug Detoxification Centers. Journal of Substance Abuse Treatment, 28, pp. 11-18, 2005.

Lifelong Addiction Leads To Health Problems In Elder Years

This study examined health conditions among an aging cohort of male narcotics addicts for the period 1964 to 1998. Data included interviews and medical testing for 108 surviving subjects who had been admitted to the California Civil Addict Program during the years 1962 through 1964. The study empirically demonstrated poor health conditions and high morbidity among surviving narcotics addicts. Medical results indicated that: 51.9% had high blood pressure; 22.4% showed hyperlipidemia; 13.3% had elevated levels of blood glucose and 33.6% had abnormal pulmonary function. Half of the sample had abnormal liver function; 94.2% tested positive for hepatitis C; 85.6% for hepatitis B; 3.8% for syphilis and 27.3% for TB. Hser, Y., Gelberg, L., Hoffman, V., Grella, C.E., McCarthy, W. and Anglin, M.D. Health Conditions Among Aging Narcotics Addicts: Medical Examination Results. Journal of Behavioral Medicine 27(6), pp. 607-622, 2004.

Rural Drinkers More Problematic than Urban Drinkers

A study to examine predictors of changes in drinking and drinking consequences in untreated at-risk drinkers in a community sample used telephone interviews at 6-month intervals over a 2-year period. A probability sample of at-risk drinkers in both rural and urban South localities was used (initial N = 733). Individuals reporting receiving services for drinking (n = 69) were excluded from the analyses. Illegal drug use and social consequences of drinking were associated with worse outcomes. Rural residents maintained higher drinking quantity and were less likely to be safe drinkers than urban residents. Participants scoring high on religiosity experienced better living outcomes. Psychiatric comorbidity was significantly associated only with drinking quantity. Results suggest that targeted interventions to encourage problem drinkers to enter treatment might improve their health and well-being. Booth, B.M., Curran, G.M., and Han, X. Predictors of Short-term Course of Drinking Among Untreated At-risk Drinkers. Journal of Studies on Alcohol 65, pp. 63-73, 2004.

Parents' Perceptions of Mediation vs. Pretrial Conferences in Juvenile Drug Court

Two hundred parents were randomly assigned to mediation (facilitated by master's-level social workers) or to pretrial conferences (guided by judges) to examine the effects of the dispute resolution methods on the attitudes of parents in child dependency disputes. No differences in dispute method were observed for either mediation or pretrial conferences. However, parents assigned to mediation perceived a higher degree of settlement in the case. Justice variables were more salient than trust variables in predicting parents' perceptions of the unfairness of the third parties and the degree of settlement achieved, but not in predicting dissatisfaction with the juvenile court system. Ashford, J. and Faith, R. Testing Models of Justice and Trust: A Study of Mediation in Child Dependency Disputes. Social Work Research 28(1), pp. 18-27, 2004.

TCs Offer Less Personal Freedom Yet Tolerate More Annoying Behaviors Compared to Self-Governed, Communal Living Residences

The rules and regulations from 55 self-governed, communal-living sites, managed and operated by residents called Oxford Houses in three states were compared to 14 traditional, staff-managed, therapeutic communities (TCs). Results indicated that both types of facilities prohibited self-injurious behaviors (such as physical self-harm or over medication of drugs). However, the Oxford Houses were more likely to establish policies restricting setting-destructive behaviors (e.g., disturbing, attacking, threatening, or harming others and playing loud music that annoys others), permitting residents to engage in personal liberties (e.g., staying out late or overnight and having guests stay at the sight), and to having personal possessions (e.g., own TV, stereo, and furniture) within the dwelling. Implications related to establishing social regularities that permit persons in recovery to have personal freedoms within communal-living, safe and sober settings are discussed. Ferrari, J.R., Jason, L.A., Davis, M.I., Olson, B.D. and Alvarez, J. Assessing Similarities and Differences in Governance Among Residential Recovery Programs: Self vs. Staff Rules and Regulations in Therapeutic Communities. The International Journal for Therapeutic and Supportive Organizations, 25, pp. 185-198, 2004.

Communal-Living Residents (Oxford Houses) More Confident in Ability to Remain

Abstinent from Drugs than Individuals Participating in 12-Step Self-Help Groups A study comparing 42 Oxford House communal-living members to 42 individuals participating in 12-Step self-help groups but who were not in communal living arrangements. All had less than 180 days of abstinence. Results showed that Oxford House residents reported higher levels of optimism and belief they could remain abstinent than those in the self-help groups. Findings were compelling as Oxford House members were more likely to have served time in jail (83%) compared to the 12-Step members (55%). The 12-Step members with convictions reported lower optimism and were less confident about their abstinence potential than 12-Step members without convictions; yet, for the Oxford House members there was no difference in levels of optimism and beliefs they could remain abstinent. Majer, J.M., Jason, L.A., and Olson, B.D. Optimism, Abstinence Self-efficacy and Self-mastery Among Oxford House Residents: A Comparative Analysis of Personal Resources. Assessment, 11, pp. 57-63, 2004.

Gender Differences Found in Comprehensive Services in Substance Abuse Treatment

Utilizing data from the National Treatment Improvement Evaluation Study (NTIES), collected from 1992 to 1997, researchers report noteworthy gender differences. The analytic sample consisted of 3,142 clients (1,123 women and 2,019 men) from 59 treatment facilities. Findings show that greater proportions of women receive services; and when individual, service, and treatment organizational characteristics are controlled for, women show greater reductions in post-treatment substance use. Further, women and men differ in their responsiveness to organizational characteristics. The availability of on-site services and the frequency of counseling significantly predict reduced post-treatment substance use for men, but not for women. Marsh, J.C., Cao, D. and D'Aunno, T.D. Gender Differences in the Impact of Comprehensive Services in Substance Abuse Treatment. Journal of Substance Abuse Treatment 27, pp. 289-300, 2004.

Prevalence Of HIV and Hep C Virus Among Injection Drug Users In Miami, Florida

Prevalence of HIV-1 and HCV co-infection in hard-to-reach intravenous drug users was estimated in 199 subjects from high risk inner-city locales, the so called "shooting galleries" in Miami, Florida. Positive HIV status was based on repeated reactive enzyme-linked immunosorbent assay (ELISA) and confirmatory Western Blot. Positive HCV status was based on reactive ELISA and confirmatory polymerase chain reaction techniques. Overall, 50 (25%) of participants were not infected with either virus; 61 (31%) were HIV-1/HCV co-infected; 17 (8%) were infected by HIV-1 only and 71 (36%) were infected by HCV only. The results of the multivariable analyses showed that the number of years using heroin was the only significant risk factor for HCV only infection (OR=1.15; 95% CI=1.07, 1.24) and for HIV-1/HCV (OR=1.17; 95% CI=1.09, 1.26). This study demonstrates that HIV-1/HCV co-infection is highly prevalent among so called "shooting galleries." McCoy, C.B., Metsch, L.R., Collado-Mesa, F., Arheart, K.L., Messiah, S.E., Katz, D. and Shapshak, P. The Prevalence of Human Immunodeficiency Virus Type 1 and Hepatitis C Virus among Iinjection Drug

Users who use High Risk Inner-city locales in Miami, Florida. Mem Inst Oswaldo Cruz, Rio de Janeiro 99(8), pp. 789-793, 2004.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Truncated N-Terminal Mutants of SV40 Large T Antigen as Minimal Immortalizing Agents for CNS Cells Immortalized CNS cell lines are useful as in vitro models for innumerable purposes such as elucidating biochemical pathways, studies of effects of drugs, and ultimately, such cells may also be useful for neural transplantation. The SV40 LT oncoprotein, commonly used for immortalization, interacts with several cell cycle regulatory factors, including binding and inactivating p53 and retinoblastoma family cell-cycle regulators. In an attempt to define the minimal requirements of SV40 T antigen for immortalizing cells of CNS origin, authors constructed T155c, encoding the N-terminal 155 amino acids of LT. The p53 binding region is known to reside in the C-terminal region of LT. In a p53 temperature sensitive cell line model, T64-7B, expression of T155c and all constructs having mutations outside of the first 82 amino acids were capable of overriding cell-cycle block at the non-permissive growth temperature. Several cell lines were produced from fetal rat mesencephalic and cerebral cortical cultures using the T155c construct. The E107K construct contained a mutation in the Rb binding region, but was nonetheless capable of overcoming cell cycle block in T64-7B cell and immortalizing primary cultured cells. Cells immortalized with T155c were often highly dependent on the presence of bFGF for growth. Telomerase activity, telomere length, growth rates, and integrity of the p53 gene in cells immortalized with T155c did not change over 100 population doublings in culture, indicating that cells immortalized with T155c were generally stable during long periods of continuous culture. Freed, W.J., Zhang, P., Sanchez, J.F., Dillon-Carter, O., Coggiano, M., Errico, S.L., Lewis, B.D. and Truckenmiller, M.E. Experimental Neurology, 191, pp. S45-S59, 2005.

Electrophysiology Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Independent Presynaptic and Postsynaptic Mechanisms Regulate Endocannabinoid Signaling at Multiple Synapses in the Ventral Tegmental Area Dopamine (DA) neurons in the ventral tegmental area have been implicated in psychiatric disorders and drug abuse. Understanding the mechanisms through which their activity is regulated via the modulation of afferent input is imperative to understanding their roles in these conditions. Here, IRP researchers demonstrate that endocannabinoids liberated from DA neurons activate cannabinoid CB1 receptors located on glutamatergic axons and on GABAergic terminals targeting GABA(B) receptors located on these cells. Endocannabinoid release was initiated by inhibiting either presynaptic type-III metabotropic glutamate receptors or postsynaptic calcium-activated potassium channels, two conditions that also promote enhanced DA neuron excitability and bursting. Thus, activity-dependent release of endocannabinoids may act as a regulatory feedback mechanism to inhibit synaptic inputs in response to DA neuron bursting, thereby regulating firing patterns that may fine-tune DA release from afferent terminals. Riegel, A.C. and Lupica, C.R. Journal of Neuroscience 24, pp. 11070-11078, 2004.

Effects of Saturated Long-Chain N-Acylethanolamines on Voltage-Dependent Ca2+ Fluxes in Rabbit T-Tubule Membranes The effects of saturated long-chain (C: 16-22) N-acylethanolamines and a series of saturated fatty acids with the same length of carbon chains were investigated on depolarization-induced (45)Ca(2+) fluxes mediated by voltage-dependent Ca(2+) channels in transverse tubule membrane vesicles from rabbit skeletal muscle. Vesicles were loaded with (45)Ca(2+) and membrane potentials were generated by establishing potassium gradients across

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the vesicle using the ionophore valinomycin. Arachidonoylethanolamide and docosaenoylethanolamide but not palmitoylethanolamide and stearoylethanolamide (all 10 microM) caused a significant inhibition of depolarization-induced (45)Ca(2+) fluxes and specific binding of [(3)H]Isradipine to transverse tubule membranes. On the other hand, saturated fatty acids including palmitic, stearic, arachidic, and docosanoic acids (all 10 microM) were ineffective in functional and radioligand binding experiments. Additional experiments using endocannabinoid metabolites suggested that whereas ethanolamine and arachidic acids were ineffective, arachidonoylethanolamide inhibited Ca(2+) effluxes and specific binding of [(3)H]Isradipine. Further studies indicated that only those fatty acids containing ethanolamine as a head group and having a chain length of more than 18 carbons were effective in inhibiting depolarization-induced Ca(2+) effluxes and specific binding of [(3)H]Isradipine. In conclusion, results indicate that depending on the chain length and the head group of fatty acid, N-acylethanolamines have differential effects on the function of voltage-dependent Ca(2+) channels and on the specific binding of [(3)H]Isradipine in skeletal muscle membranes. Oz, M., Alptekin, A., Tchugunova, Y. and Dinc, M. Archives of Biochemistry and Biophysics 434, pp. 344-351, 2005.

Proteomics Unit, Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Direct Tissue Analysis of Phospholipids in Rat Brain using MALDI-TOFMS and MALDI-Ion Mobility-TOFMS After water, lipids are the most common biomolecules found in the brain (12%). A brief perusal of the physiology, anatomy, and pathophysiology of the brain illustrates the importance of lipids. Recent advances in mass spectrometry have allowed the direct probing of tissues. However, most studies have focused on proteins. In the present work, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) and MALDI-ion mobility (IM)-TOFMS were employed for direct analysis of phospholipids in rat brain tissue. Molecular ions (MH(+)) corresponding to phosphatidylcholines, phosphatidylethanolamines, and sphingomyelin, were recorded. When studying pharmacology, it has been learned that many therapeutic compounds are stored in the body's adipose tissue. MALDI-TOFMS and MALDI- IM-TOFMS were thus used to analyze rat brain tissue with chlorisondamine added directly onto the tissue slice. With both techniques, noncovalent complexes between the tissue phospholipids and chlorisondamine were detected. In addition, MALDI-IM-TOFMS of noncovalent complexes between phospholipids and chlorisondamine displayed a mobility between that of an isobaric lipid and peptide. Jackson, S.N., Wang, H.Y., Woods, A.S., Ugarov, M., Egan, T. and Schultz, J.A. Journal of American Society of Mass Spectrometry 16, pp. 133-138, 2005.

Clinical Psychopharmacology Section, Medications Discovery Research Branch

Development of a Rationally-designed, Low-abuse Potential, Biogenic Amine Releaser that Suppresses Cocaine Self-administration Convergent lines of evidence support a dual deficit model of stimulant withdrawal, where reductions in synaptic dopamine (DA) and serotonin (5-HT) contribute to dysphoria, drug craving, and relapse. Thus, IRP scientists predicted that a non-amphetamine compound with substrate activity at DA and 5-HT transporters (i.e., a dual DA/5-HT releaser) would be an effective medication for treating stimulant addictions. Ideally, this type of medication would alleviate withdrawal symptoms, suppress cocaine self-administration, and lack side effects commonly associated with CNS stimulants. In the present work, over 350 compounds were screened in vitro for activity as substrate-type releasing agents at DA, 5-HT and norepinephrine (NE) transporters. These efforts identified PAL-287 (1-napthyl-2-aminopropane) as a non-amphetamine compound with potent substrate activity at biogenic amine transporters. In vivo microdialysis in rats demonstrated that PAL-287 (1-3 mg/kg, i.v.) increased extracellular DA and 5-HT in frontal cortex, but effects on 5-HT were somewhat greater. PAL-287 induced substantially less locomotor stimulation than (+)-amphetamine, a drug which increases only extracellular DA. Administration of high-dose (+)-methamphetamine or (±)-MDMA to rats produced long-lasting depletion of cortical 5-HT, whereas PAL-287 (18 mg/kg, i.p. X 3) did not. PAL-287 displayed little or no reinforcing properties in rhesus monkeys trained to self-administer cocaine, yet PAL-287 produced a dose-dependent decrease in responding for cocaine when infused at a dose of 1.0 mg/kg/hr. Collectively, the findings reported here demonstrate that non-amphetamine monoamine releasing agents like PAL-287 might be promising candidate medications for the treatment of stimulant dependence. Rothman, R.B., Blough, B.E., Woolverton, W.L., Anderson, K.G., Negus, S.S., Mello, N.K., Roth, B.L. and Baumann, MH. Development of a Rationally-designed, Low-abuse potential,

Biogenic Amine Releaser that Suppresses Cocaine Self-administration. Journal of Pharmacology and Experimental Therapeutics Fast Forward. Published on March 10, 2005 as DOI: 10.1124/jpet.104.082503.

N-substituted Piperazines Abused by Humans Mimic the Molecular Mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or 'Ecstasy') 3,4-Methylenedioxy-methamphetamine (MDMA, or "Ecstasy") is an illicit drug that stimulates the release of serotonin (5-HT) and dopamine (DA) from neurons. Recent evidence reveals that drug users are ingesting piperazine analogs, like 1-benzylpiperazine (BZP, or "A2") and 1-(m-trifluoromethylphenyl)piperazine (TFMPP, or "Molly"), to mimic psychoactive effects of MDMA. In the present study, IRP scientists compared the neurochemistry of MDMA, BZP, and TFMPP in rats. The effects of MDMA, BZP, and TFMPP on transporter-mediated efflux of [3H]5-HT and [3H]MPP+ (DA transporter substrate) were determined in synaptosomes. The effects of drugs on extracellular levels of 5-HT and DA were examined using in vivo microdialysis in conscious rats. MDMA evoked transporter-mediated release of [3H]5-HT and [3H]MPP+. BZP released [3H]MPP+, whereas TFMPP was a selective releaser of [3H]5-HT. MDMA (1-3 mg/kg, i.v.) increased dialysate 5-HT and DA in a dose-related fashion, with actions on 5-HT being predominant. BZP (3-10 mg/kg, i.v.) elevated dialysate DA and 5-HT, while TFMPP (3-10 mg/kg, i.v.) elevated 5-HT. Administration of BZP plus TFMPP at a 1:1 ratio (BZP/TFMPP) produced parallel increases in dialysate 5-HT and DA; a 3 mg/kg dose of BZP/TFMPP mirrored the effects of MDMA. At a 10 mg/kg dose, BZP/TFMPP increased dialysate DA more than the summed effects of each drug alone, and some rats developed seizures. Results show that BZP/TFMPP and MDMA share the ability to evoke monoamine release, but dangerous drug-drug synergism may occur when piperazines are co-administered at high doses. Baumann, M.H., Clark, R.D., Budzynski, A.G., Partilla, J.S., Blough B.E. and Rothman, RB. N-substituted Piperazines Abused by Humans Mimic the Molecular Mechanism of 3,4-methylenedioxy-methamphetamine (MDMA, or 'Ecstasy'). Neuropsychopharmacology 30, pp. 550-560, 2005.

Evidence for Alterations in alpha2-adrenergic Receptor Sensitivity in Rats Exposed to Repeated Cocaine Administration It is well established that cocaine stimulates monoamine transmission by blocking reuptake of norepinephrine (NE), dopamine and serotonin into nerve cells, yet few investigations have addressed the effects of chronic cocaine on NE function. In the present study, IRP investigators examined the effects of repeated cocaine injections on neuroendocrine responses evoked by the alpha2-adrenergic receptor agonist, clonidine. Previous findings show that clonidine increases pituitary growth hormone (GH) secretion by a central mechanism involving postsynaptic alpha2-adrenergic receptors. Male rats previously fitted with indwelling jugular catheters received two daily injections of cocaine (15 mg/kg, i.p.) or saline for 7 days. At 42 h and 8 days after treatment, rats were challenged with clonidine (25 microg/kg, i.v.) or saline, and serial blood samples were withdrawn. Plasma GH and corticosterone levels were measured by radioimmunoassay. Prior cocaine exposure did not affect basal levels of either hormone. However, cocaine-pretreated rats displayed a significant reduction in clonidine-evoked GH secretion at 42 h, and this blunted response was still apparent 8 days later. Corticosterone responses produced by clonidine were similar regardless of pretreatment. The present data suggest that withdrawal from repeated cocaine injections may be accompanied by desensitization of postsynaptic alpha2-adrenoreceptors coupled to GH secretion. Since human patients with depression often exhibit blunted GH responses to clonidine, these findings provide evidence that cocaine withdrawal might produce depressive-like symptoms via dysregulation of NE mechanisms. Baumann, M.H., Milchanowski, A.B. and Rothman, R.B. Evidence for Alterations in alpha2-adrenergic Receptor Sensitivity in Rats Exposed to Repeated Cocaine Administration. Neuroscience, 125, pp. 683-690, 2004.

Opioid Peptide Receptor Studies. 17. Attenuation of Chronic Morphine Effects after Antisense Oligodeoxynucleotide Knock-down of RGS9 Protein in Cells Expressing the Cloned Mu Opioid Receptor RGS proteins are a recently described class of regulators that influence G-protein-mediated signaling pathways. IRP scientists have shown previously that chronic morphine results in functional uncoupling of the mu opioid receptor from its G protein in CHO cells expressing cloned human mu opioid receptors. In the present study, the authors examined the effects of morphine treatment (1 microM, 20 h) on DAMGO-stimulated high-affinity [35S]GTP-gamma-S binding and DAMGO-mediated inhibition of forskolin-stimulated cAMP accumulation in HN9.10 cells stably expressing the cloned rat mu opioid receptor, in the absence and presence of the RGS9 protein knock-down condition (confirmed by Western blot analysis). RGS9 protein expression was reduced by blocking its mRNA with an antisense oligodeoxynucleotide (AS-114). Binding surface analysis resolved

two [35S]GTP-gamma-S binding sites (high affinity and low affinity sites). In sense-treated control cells, DAMGO-stimulated [35S]GTP-gamma-S binding by increasing the B(max) of the high-affinity site. In sense-treated morphine-treated cells, DAMGO-stimulated [35S]GTP-gamma-S binding by decreasing the high-affinity Kd without changing the B(max). AS-114 significantly inhibited chronic morphine-induced upregulation of adenylate cyclase activity and partially reversed chronic morphine effects as measured by DAMGO-stimulated [35S]GTP-gamma-S binding. Morphine treatment increased the EC50 (6.2-fold) for DAMGO-mediated inhibition of forskolin-stimulated cAMP activity in control cells but not in cells treated with AS-114 to knock-down RGS9. These results provide additional evidence for involvement of RGS9 protein in modulating opioid signaling, which may contribute to the development of morphine tolerance and dependence. Xu, H., Wang, X., Wang, J. and Rothman R.B. Opioid Peptide Receptor Studies. 17. Attenuation of Chronic Morphine Effects after Antisense Oligodeoxynucleotide Knock-down of RGS9 Protein in Cells Expressing the Cloned Mu Opioid Receptor. Synapse 52, pp. 209-217, 2004.

MRI Physics Unit, Neuroimaging Research Branch

Simultaneous MRI Acquisition of Blood Volume, Blood Flow and Blood Oxygenation Information during Brain Activation IRP investigators have developed a new functional MRI technique that is able to achieve concurrent acquisition of three hemodynamic images based primarily on the changes of cerebral blood volume, blood flow and blood oxygenation, respectively, associated with brain activation. The feasibility and efficacy of the new technique were assessed by brain activation experiments with visual stimulation paradigms. Experiments on healthy volunteers showed that this technique provided efficient image acquisition and thus higher contrast-to-noise ratio (CNR) per unit time, compared with conventional techniques collecting these functional images separately. In addition, it was demonstrated that the proposed technique was able to be utilized in event-related functional MRI experiments, with potential advantages of obtaining accurate transient information of the activation-induced hemodynamic responses. This new technique allows for efficient measurement of three complementary functional signals associated with brain activation, and provides a valuable tool to assist with data interpretation and functional transduction mechanisms. Yang, Y., Gu, H. and Stein, E.A. Magnetic Resonance Medicine, 52, pp. 1407-1417, 2004.

Mapping the Orientation of Intravoxel Crossing Fibers Based on the Phase Information of Diffusion Circular Spectrum IRP scientists have developed a new method to map the orientation of intravoxel crossing fibers by using the phase of the diffusion circular spectrum harmonics. In a previous paper, we demonstrated that the magnitude of the 4th order harmonic of the diffusion circular spectrum can be used to identify the existence of fiber crossings. However, the orientation of the intravoxel crossing fibers remained unknown. This study extends the previous approach so that it is able to identify the orientation of the intravoxel crossing fibers by utilizing the phase information of the circular spectrum. In general, the phase of the circular harmonic determines the rotation of the apparent diffusion coefficient (ADC) profile on the sampling circle that is spanned by the major and medium eigenvector of the diffusion tensor and thus can be used to determine the orientation of the crossing fibers. Results of simulations and in vivo experiments indicated that the estimated intravoxel crossing fibers are consistent with the orientations of the single fibers in surrounding tissues, significantly reducing the discontinuity of the fiber orientation field given by the conventional major eigenvector method. The proposed method provides important information on the white matter tracts in the fiber crossing area, and would be useful for improving accuracy in tractography. Zhan, W., Stein, E.A. and Yang, Y. NeuroImage, 23, pp. 1358-1369, 2004.

Medicinal Chemistry Section, Medications Discovery Research Branch

Novel Heterocyclic Trans Olefin Analogues of N-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}arylcarboxamides as Selective Probes with High Affinity for the Dopamine D3 Receptor Dopamine D3 receptor subtypes have been hypothesized to play a pivotal role in modulating the reinforcing and drug-seeking effects induced by cocaine. However, definitive pharmacological investigations have been hampered by the lack of highly D3 receptor selective compounds that can be used in vivo. To address this problem, the potent and D3 receptor selective antagonist NGB 2904 (9H-fluorene-2-carboxylic acid {4-[(2,3-dichlorophenyl)-piperazin-1-yl]-butyl}-amide, Ki (hD3)=2.0 nM; Ki (hD2L)=112 nM; D2/D3 selectivity ratio of 56) was chosen as a lead structure for chemical modification in an attempt to reduce its high lipophilicity (cLogD = 6.94) while optimizing D3 receptor binding affinity and D2/D3 selectivity. A series of >30 novel analogues were

synthesized and their binding affinities were evaluated in competition binding assays in HEK 293 cells transfected with either D2L, D3 or D4 human dopamine receptors using the high affinity, selective D2-like receptor antagonist 125I-IABN. Structural diversity in the aryl amide end of the molecule was found to have a major influence on (sub)nanomolar D3 receptor affinity and D2/D3 selectivity, which was optimized using a more rigid trans-butenyl linker between the aryl amide and the piperazine. Several analogues demonstrated superior D3 receptor binding affinities and selectivities, as compared to the parent ligand. One compound, N-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]-trans-but-2-enyl}-4-pyridine-2-yl-benzamide, displayed the most promising pharmacological profile (Ki (hD3)=0.7 nM; Ki (hD2L)=93.3 nM; D2/D3 selectivity ratio of 133). In addition, this ligand inhibited quinpirole stimulation of mitogenesis at human dopamine D3 receptors transfected into Chinese hamster ovary (CHO) cells, with an EC50 of 3.0 nM. This compound was a nearly 5-times more potent antagonist at the D3 receptor than NGB 2904 (EC50=14.4 nM). Moreover, a decrease in cLogD value of ~2-orders of magnitude was determined for this novel D3 receptor preferring ligand, compared to NGB 2904. In summary, chemical modification of NGB 2904 has resulted in compounds with high affinity and selectivity for D3 receptors. The most promising candidate is currently being evaluated in animal models of cocaine abuse and will provide an important tool with which to elucidate the role of D3 receptors in drug reinforcement in vivo. Grundt, P., Carlson, E.E., Cao, J., Bennett, C.J., McElveen, E., Taylor, M., Luedtke, R.R. and Newman, A.H. Journal of Medicinal Chemistry 48, pp. 839-848, 2005.

Psychobiology Section, Medications Discovery Research Branch

Identification of a Dopamine Transporter Ligand that Blocks the Stimulant Effects of Cocaine Studies have indicated that the dopamine transporter (DAT) is the primary biological target of cocaine. Most drugs that have affinity for the DAT have behavioral effects like those of cocaine, suggesting that drugs targeting the DAT will all have abuse liability like cocaine. However, analogs of benztropine have high affinity for the DAT, and behavioral effects with varying degrees of similarity to cocaine. Among these compounds is the benztropine analog, JHW 007, which has high affinity for the DAT, but substantially reduced cocaine-like behavioral effects. The present study reports that JHW 007 antagonized the effects of cocaine in two animal models, locomotor stimulation and cocaine discrimination. JHW 007 occupied the DAT in vivo more slowly than did cocaine, and had not reached an apparent plateau up to 270 min after injection. The in vivo binding of cocaine to the DAT suggested rate of DAT occupancy as an important contributor to its behavioral effects, and the slow association with the DAT may provide an explanation for why JHW 007 is relatively devoid of cocaine-like behavioral effects. The antagonism of cocaine suggests that DAT ligands with reduced cocaine-like activity can function as cocaine antagonists and suggests JHW 007 as a lead for discovery of cocaine-abuse pharmacotherapeutics. Possibly more important, these findings indicate that the DAT is a suitable target for drug discovery efforts to identify treatments for cocaine abuse. Desai, R.I., Kopajtic, T.A., Koffarnus, K., Newman, A.H. and Katz, J.L. Identification of a Dopamine Transporter Ligand that Blocks the Stimulant Effects of Cocaine. The Journal of Neuroscience, 25, pp. 1889-1893, 2005.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

Central Amygdala ERK Signaling Pathway is Critical to Incubation of Cocaine Craving Using a rat model of craving and relapse, IRP scientists previously found time-dependent increases in cocaine seeking induced by exposure to drug-associated cues over the first months of withdrawal from cocaine, suggesting that drug craving incubates over time. Here, we explored the role of amygdala extracellular signal-regulated kinases (ERK) signaling pathway in this incubation. Cocaine seeking induced by exposure to cocaine cues was substantially higher after 30 withdrawal days than after 1 day. Exposure to these cues increased ERK phosphorylation in the central, but not basolateral, amygdala after 30 days, but not 1 day, of withdrawal. After 30 days of withdrawal from cocaine, inhibition of central, but not basolateral, amygdala ERK phosphorylation decreased cocaine seeking. After 1 day of withdrawal, stimulation of central amygdala ERK phosphorylation increased cocaine seeking. Results suggest that time-dependent increases in the responsiveness of central amygdala ERK pathway to cocaine cues mediate the incubation of cocaine craving. Lu, L., Hope, B.T., Dempsey, J., Liu, S.Y., Bossert, J.M. and Shaham, Y. Nature Neuroscience 8, pp. 212-219, 2005.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Nicotine Induces Conditioned Place Preferences over a Large Range of Doses in Rats Conditioned place preference (CPP) procedures provide one measure of

potential rewarding effects of abused drugs. Many attempts to induce CPP with nicotine have been unsuccessful. To assess the influence of nicotine dose and stimulus-assignment procedure on the development of nicotine-induced CPP. Initial preferences for one side of a two-compartment apparatus were first determined in Sprague-Dawley rats. In subsequent conditioning trials, the compartment paired with nicotine was the initially preferred side for half of the rats, and the initially non-preferred side for the other half. Rats received either an injection of nicotine (0.01-2 mg/kg SC) before being placed in one compartment (three trials) or saline before being placed in the other compartment (three trials). Control rats had saline injections associated with both compartments. A final test trial with no injection assessed final place preference. Significant CPP were induced by 0.1-1.4 mg/kg doses of nicotine. Nicotine-induced CPP were only apparent when nicotine was paired with the initially non-preferred side. Moreover, a very high dose of nicotine (2 mg/kg) induced conditioned place aversion when paired with the initially preferred side of the apparatus. Nicotine induced significant CPP across a wide range of doses, in accordance with its role as the primary addictive component of tobacco. Small preferences for one side of the apparatus played a major role in the development of nicotine-induced CPP. LeFoll, B. and Goldberg, S.R. Psychopharmacology (Berl), 178, pp. 481-492, 2005.

Human Cocaine-seeking Behavior and its Control by Drug-associated Stimuli in the Laboratory Second-order schedules of drug self-administration were developed to incorporate the effects of drug-related environmental stimuli into an animal model of drug abuse, making it more similar to human situations. Ironically, little is known about how human subjects behave under these schedules. In this study, human volunteers with a history of cocaine use worked on a second-order schedule in which every 100th lever response produced an auditory-visual brief stimulus (2 seconds). The first stimulus produced after 1 hour was extended to 10 seconds and paired with an intravenous injection of cocaine (25 mg). Up to three injections were allowed per session. In different phases of the experiment, presentation of the brief stimulus was discontinued and/or saline solution (placebo) was injected instead of cocaine. Injections of cocaine were found to maintain responding even when the brief stimulus was not presented. Placebo injections alone did not maintain responding. In contrast, the brief stimulus maintained high levels of responding under placebo conditions, even though self-reports indicated that subjects could clearly discriminate that they were not receiving cocaine. These results demonstrate that drug-related environmental stimuli can maintain persistent drug seeking during periods of drug unavailability. As this procedure directly measures the effects of stimuli on drug seeking, it may provide a valuable complement to indirect measures, such as self-reports of craving, that are often used with human subjects. The similarity of the response patterns in humans and animals also supports the use of second-order schedules in animals as a valid model of human drug seeking. Panlilio, L.V., Yasar, S., Nemeth-Coslett, R., Katz, J.L., Henningfield, J.E., Heishman, S. and Goldberg, S.R. Neuropsychopharmacology, 30, pp. 433-443, 2005.

Involvement of Adenosine A1 Receptors in the Discriminative-stimulus Effects of Caffeine in Rats Caffeine is a non-selective adenosine receptor antagonist in vitro, but involvement of different adenosine receptor subtypes, particularly adenosine A1 and A2A receptors, in the central effects of caffeine remains a matter of debate. The purpose of this study was to investigate the role of adenosine A1 and A2A receptors in the discriminative-stimulus effects of caffeine. Rats were trained to discriminate an injection of 30 mg/kg (i.p.) caffeine from saline. The selective A1 receptor antagonist CPT, the selective A2A receptor antagonist MSX-3 and the non-selective adenosine receptor antagonist DMPX were assessed for their ability to produce caffeine-like discriminative effects. The ability of CPT, MSX-3, the A1 receptor agonist CPA and the A2A receptor agonist CGS21680 to reduce the discriminative effects of caffeine was also tested. Radioligand binding experiments with membrane preparations from rat striatum and transfected mammalian cell lines were also performed to characterize binding affinity profiles of the different adenosine antagonists (caffeine, DMPX, CPT and MSX-3) in relation to all known adenosine receptors (A1, A2A, A2B, A3). DMPX and CPT, but not MSX-3, produced significant caffeine-like discriminative effects. MSX-3, but not CPT, markedly reduced the discriminative effects of caffeine and the caffeine-like discriminative effects of CPT. Furthermore, the A1 receptor agonist CPA, but not the A2A agonist CGS21680, reduced the discriminative effects of caffeine. Adenosine A1 receptor blockade is involved in the discriminative-stimulus effects of behaviorally relevant doses of caffeine; adenosine A2A receptor blockade does not play a central role in caffeine's discriminative effects and counteracts the A1 receptor-mediated discriminative-stimulus effects of caffeine. Solinas, M., Ferre, S., Antoniou, K., Quarta, D., Justinova, Z., Hockmeyer, J., Pappas, L., Segal, P. and Goldberg, S.R. Psychopharmacology

(Berl), Feb 5, 2005. Epubmed ahead of print, PMID 15696333.

Role of Central and Peripheral Adenosine Receptors in the Cardiovascular Responses to Intraperitoneal Injections of Adenosine A1 and A2A Subtype Receptor Agonists The cardiovascular effects of the adenosine A1 receptor agonist N(6)-cyclopentyladenosine (CPA) and the adenosine A2A receptor agonist 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS 21680) were investigated in rats implanted with telemetry transmitters for the measurement of blood pressure and heart rate. Intraperitoneal (i.p.) injections of the adenosine A1 receptor agonist CPA led to dose-dependent decreases in both blood pressure and heart rate. These effects of CPA were antagonized by i.p. injections of the adenosine A1 receptor antagonist 8-cyclopentyl-1,3-dimethyl-xanthine (CPT), but not by i.p. injections of the adenosine A2A receptor antagonist 3-(3-hydroxypropyl)-8-(m-methoxystyryl)-7-methyl-1-propargylxanthine phosphate disodium salt (MSX-3). Injections (i.p.) of the peripherally acting nonselective adenosine antagonist 8-sulfophenyltheophylline (8-SPT) and the purported nonselective adenosine antagonist caffeine also antagonized the cardiovascular effects of CPA. The adenosine A2A agonist CGS 21680 given i.p. produced a dose-dependent decrease in blood pressure and an increase in heart rate. These effects of CGS 21680 were antagonized by i.p. injections of the adenosine A(2A) receptor antagonist MSX-3, but not by i.p. injections of the antagonists CPT, 8-SPT or caffeine. Central administration (intracerebral ventricular) of CGS 21680 produced an increase in heart rate, but no change in blood pressure. MSX-3 given i.p. antagonized the effects of the central injection of CGS 21680.These results suggest that adenosine A1 receptor agonists produce decreases in blood pressure and heart rate that are mediated by A1 receptors in the periphery, with little or no contribution of central adenosine A1 receptors to those effects. The heart-rate increasing effect of adenosine A2A agonists appears to be mediated by adenosine A2A receptors in the central nervous system. The blood pressure decreasing effect of adenosine A2A agonists is most probably mediated in the periphery. Schindler, C.W, Karcz-Kubicha, M., Thorndike, E.B., Muller, C.E., Tella, S.R., Ferre, S. and Goldberg, S.R. British Journal of Pharmacology, Jan 24, 2005. Epubmed ahead of print, PMID 15678095.

Cannabinoid CB1 Antagonists as Promising New Medications for Drug Dependence This review examines the development of cannabinoid CB1 receptor antagonists as a new class of therapeutic agents for drug addiction. Abused drugs [alcohol, opiates, Delta(9)-tetrahydrocannabinol (THC), and psychostimulants, including nicotine] elicit a variety of chronically relapsing disorders by interacting with endogenous neural pathways in the brain. In particular, they share the common property of activating mesolimbic dopamine brain reward systems, and virtually all abused drugs elevate dopamine levels in the nucleus accumbens. Cannabinoid CB1 receptors are expressed in this brain reward circuit and modulate the dopamine-releasing effects of THC and nicotine. Rimonabant (SR141716), a CB1 receptor antagonist, blocks both the dopamine-releasing and the discriminative and rewarding effects of THC in animals. Blockade of CB1 receptor activity by genetic invalidation also decreases rewarding effects of opiates and alcohol in animals. Although CB1 receptor blockade is generally ineffective in reducing the self-administration of cocaine in rodents and primates, it reduces the reinstatement of extinguished cocaine-seeking behavior produced by cocaine-associated conditioned stimuli and cocaine-priming injections. Likewise, CB1 receptor blockade is effective in reducing nicotine-seeking behavior induced by re-exposure to nicotine-associated stimuli. Some of these findings have been recently validated in humans. In clinical trials, Rimonabant blocks the subjective effects of THC in humans and prevents relapse to smoking in ex-smokers. Findings from both clinical and preclinical studies suggest that ligands blocking CB1 receptors offer a novel approach for patients suffering from drug dependence that may be efficacious across different classes of abused drugs. LeFoll, B. and Goldberg, S.R. Journal of Pharmacology and Experimental Therapeutics, 312, pp. 875-883, 2005.

Involvement of Mu-, Delta- and Kappa-opioid Receptor Subtypes in the Discriminative-stimulus Effects of Delta-9-tetrahydrocannabinol (THC) in Rats Many behavioral effects of delta-9-tetrahydrocannabinol (THC), including its discriminative-stimulus effects, are modulated by endogenous opioid systems. To investigate opioid receptor subtypes involved in the discriminative effects of THC. Rats trained to discriminate 3 mg/kg i.p. of THC from vehicle using a two-lever, operant, drug-discrimination procedure, were tested with compounds that bind preferentially or selectively to either mu-, delta- or kappa-opioid receptors. The preferential mu-opioid receptor agonist heroin (0.3-1.0 mg/kg, i.p.), the selective delta-opioid receptor agonist SNC-80 (1-10 mg/kg, i.p.) and the selective kappa-opioid receptor agonist U50488 (1-10 mg/kg, i.p.) did not produce generalization to

the discriminative effects of THC when given alone. However, heroin, but not SNC-80 or U50488, significantly shifted the dose-response curve for THC discrimination to the left. Also, the preferential mu-opioid receptor antagonist naltrexone (0.1-1 mg/kg, i.p.), the selective delta-opioid receptor antagonist, naltrindole (1-10 mg/kg, i.p.) and the kappa-opioid receptor antagonist nor-binaltorphimine (n-BNI, 5 mg/kg, s.c.), did not significantly reduce the discriminative effects of the training dose of THC. However, naltrexone, but not naltrindole or n-BNI, significantly shifted the dose-response curve for THC discrimination to the right. Finally, naltrexone, but not naltrindole or n-BNI, blocked the leftward shift in the dose-response curve for THC discrimination produced by heroin. mu- but not delta- or kappa-opioid receptors are involved in the discriminative effects of THC. Given the role that mu-opioid receptors play in THC's rewarding effects, the present findings suggest that discriminative-stimulus effects and rewarding effects of THC involve similar neural mechanisms. Solinas, M. and Goldberg, S.R. Psychopharmacology, Dec 24, 2004, Epubmed ahead of print, PMID 15619107.

Dopamine D3 Receptor Ligands Block Nicotine-induced Conditioned Place Preferences through a Mechanism that Does Not Involve Discriminative Stimulus or Antidepressant-like Effects Environmental stimuli previously paired with drug taking appear to play a critical role in nicotine dependence. Converging anatomical, pharmacological, and behavioral evidence implicates dopamine D3 receptors in the mechanisms underlying stimulus-controlled drug-seeking behavior. This study assessed the effects of BP 897, a dopamine D3 receptor partial agonist and ST 198, a dopamine D3 receptor antagonist, on nicotine-induced conditioned place preferences (CPPs), used as a measure of drug-seeking behavior, on discrimination performance under a two-lever-choice nicotine discrimination procedure and on food-maintained responding. BP 897 and ST 198 both blocked the expression of nicotine-induced CPP at doses selective for dopamine D3 receptors. They had no effect on locomotor activity in the CPP apparatus and no significant effect on nicotine discrimination performance or food-maintained responding under the discrimination procedure. Involvement of antidepressant actions in the effects of BP 897 and ST 198 on CPP is unlikely, since the authors found no effect of dopamine D3 receptor blockade with BP 897 or genetic depletion of dopamine D3 receptors in a forced-swimming test, used as a behavioral test for antidepressant activity. This suggests that dopamine D3 receptor ligands reduce the motivational effects of nicotine by a mechanism distinct from those of nicotine replacement therapy and bupropion, the two currently used aids for smoking cessation in humans. These findings support the use of dopamine D3 receptor ligands as aids for smoking cessation and indicate that their effects would be selective for those rewarding or reinforcing effects of nicotine that contribute to the maintenance of tobacco-smoking behavior, without affecting subjective responses to nicotine or producing any antidepressant-like effects. LeFoll, B., Sokoloff, P., Stark, H. and Goldberg, S.R. Neuropsychopharmacology 30, pp. 720-730, 2005.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

A Role of Ventral Tegmental Area Glutamate in Contextual Cue-induced Relapse to Heroin Seeking The environmental context previously associated with opiate use plays an important role in human relapse, but the neuronal mechanisms involved in context-induced drug relapse are not known. Using a rat relapse model, IRP researchers determined the effect of a group II metabotropic glutamate receptor agonist, LY379268, on contextual cue-induced reinstatement of heroin seeking. LY379268, which acts centrally to reduce evoked glutamate release, was injected systemically or directly into the ventral tegmental area (VTA), a brain area involved in opiate reward and conditioned drug effects. Rats were trained to self-administer intravenous heroin for 12 days; drug infusions were paired with a discrete tone-light cue. Subsequently, lever pressing was extinguished in the presence of the discrete cue in a context that differed from the drug self-administration context in terms of visual, auditory, tactile, and circadian cues. After extinction of lever responding, LY379268 was injected systemically or into the VTA, and non-reinforced responding was determined in the extinction context or the drug context. Exposure to the heroin-associated context induced robust reinstatement of drug seeking, and this effect was attenuated by systemic or intra-VTA injections of LY379268. Results indicate that glutamate transmission in the VTA plays an important role in contextual cue-induced relapse to heroin seeking. Bossert, J.M., Liu, S., Lu, L. and Shaham, Y. The Journal of Neuroscience, 24, pp. 10726-10730, 2004.

Clinical Pharmacology Section, Clinical Pharmacology and Therapeutics Research Branch

Strategies for Quitting among Non-treatment-seeking Marijuana Smokers

Although marijuana is the most widely used illegal drug in the U.S., relatively few patients each year enter formal treatment for marijuana abuse. This study examined the self-reported quitting strategies used by 65 adult, non-treatment-seeking marijuana smokers who had made at least one (mean [SD] 4.9 [14.1]) serious quit attempt. Subjects rated their use and effectiveness of 13 strategies on the Marijuana Quit Questionnaire. The strategies clustered into three categories/factors, whether grouped by principal components analysis, mean helpfulness ratings, or frequency of endorsement: Change Environment, Seeking Organized/Professional Help, and Social Support. The most commonly used strategies were getting rid of all marijuana (28% of subjects), avoiding places where marijuana is used (26%), and avoiding association with marijuana users (25%). Changing one's environment was rated as most helpful, while seeking help from professionals was the least helpful. These strategies are similar to those reported by individuals trying to quit use of alcohol or tobacco. Clinicians who see marijuana users in their practice should consider incorporating these strategies into treatment plans for their marijuana-using patients. Boyd, S.J., Tashkin, D.P., Huestis, M.A., Heishman, S.J., Dermand, J.C., Simmons, M.S., and Gorelick, D.A. American Journal on Addictions, 14, pp. 35-42, 2005.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Program Activities

New NIDA PAs and RFAs

On March 10, 2005, NIDA issued a Program Announcement (PA) entitled **Collaborative Multisite Research in Addiction (COMRAD) (PA-05-067)**. The purpose of this PA is to increase the collaboration of investigators at two or more sites in order to address critical issues in the epidemiology, services and prevention of substance abuse and related disorders that require sample sizes greater than a single site can reasonably attain.

On March 15, 2005, NIDA issued a Program Announcement entitled **Minority Institutions' Drug Abuse Research Development Program (MIDARP) (PAR-05-069)**. The purpose of this PA is to increase research capacity of minority institutions to conduct research in drug abuse and addiction. Through this announcement, grants will be provided to foster research career development of racial/ethnic minority faculty, student and staff who are underrepresented in drug abuse research, and to enhance research infrastructure at minority institutions. This is a reissue of PAR-02-016, released October 22, 2001.

On April 1, 2005, NIDA issued a Program Announcement entitled **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services and Women and Sex/Gender Differences (PAR-05-083)**. The purpose of this PA is to invite applications for support of drug abuse doctoral dissertation research in epidemiology, prevention, treatment, services and women and sex/gender differences. This PA provides funding support of dissertation research through the NIH Dissertation Award (R36) mechanism. This is a reissue of PA-02-055, released February 5, 2002.

On May 3, 2005, NIDA issued a Program Announcement entitled **Inhalant Abuse: Supporting Broad-Based research Approaches (PA-05-099)**. The goal of this PA is to encourage research on all aspects of inhalant abuse (i.e., epidemiology; prevention, treatment and service delivery; antecedents, consequences and neurobiological mechanisms).

On February 9, 2005, NIDA issued an RFA entitled **Strategic Program for Innovative Research on Drug Addiction Pharmacotherapy (SPIRDAP) (RFA-DA-05-009)**. Through this RFA, NIDA invites applications to support innovative, integrated preclinical and clinical research to validate novel pharmacotherapeutic approaches and to identify potential compounds that are safe and effective, short-term (to reduce and stop drug use) and long-term (to prolong abstinence) pharmacotherapies for cocaine, methamphetamine and cannabinoid addiction. Letter of Intent Receipt Date for this RFA: March 18, 2005;Application Receipt Date: April 18, 2005.

PAs and RFAs Issued With Other NIH Components/Agencies

On February 9, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Research on Sleep and Sleep Disorders (PA-05-046)**. Through this PA co-sponsoring ICs invite grant applications proposing research to advance biomedical knowledge related to sleep disorders, improve understanding of the neurobiology or functions of sleep over the lifespan, enhance timely diagnosis and effective treatment for individuals affected by sleep-related disorders or implement and evaluate innovative community-based public health education and intervention programs. This is a reissue of PA-95-014, released December 23, 1994.

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Grantee Honors

In Memoriam

On February 14, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Functional Links Between the Immune System, Brain Function and Behavior (PA-05-054)**. Through this PA co-sponsoring ICs invite grant applications proposing research to study neuroimmune molecules and mechanisms involved in regulating normal and pathological central nervous system (CNS) function. This is a reissue of PA-02-045, released January 16, 2002.

On February 18, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Jointly Sponsored Ruth L. Kirschstein National Research Service Award Institutional Predoctoral Training Program in the Neurosciences (PAR-05-055)**. Through this PA co-sponsoring ICs support broad and fundamental, early-stage graduate research training in the neurosciences via institutional training grants. This is a reissue of PAR-02-017, released November 6, 2001.

On February 25, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Continued Development and Maintenance of Software (PAR-05-057)**. The goal of this PA is to support the continued development, maintenance, testing and evaluation of existing software. This is a reissue of PA-02-141.

On March 4, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Collaborations with National Centers for Biomedical Computing (PAR-05-063)**. Through this PA co-sponsoring ICs invite grant applications for projects from individual investigators or small groups to collaborate with the recently-formed NIH Roadmap for Medical Research National Centers for Biomedical Computing (NCBCs).

On March 18, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement entitled **International Research Collaboration-Basic Biomedical (FIRCA-BB) (PAR-05-072)**. This PA is intended to facilitate collaborative basic biomedical research between scientists supported by the NIH and investigators in developing countries. This is a modification of PA-02-057, released February 6, 2002.

On March 22, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement entitled **International Research Collaboration-Behavioral, Social Sciences (FIRCA-BSS) (PAR-05-073)**. This PA is intended to facilitate collaborative behavioral and social science research between scientists supported by the NIH and investigators in developing countries. This is a modification of PA-02-057, released February 6, 2002.

On March 25, 2005, NIDA, in conjunction with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH), issued a Program Announcement (PA) entitled **Non-Human Lentiviral Models of the Neurological Complications of AIDS (PAS-05-078)**. Through this PA co-sponsoring ICs invite grant applications aimed at developing non-human lentiviral in vivo model systems for study of the neurologic complications of AIDS, with or without a history of drug use.

On March 30, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Tools for Zebrafish Research (PAR-05-080)**. The goal of this PA is to support investigator-initiated applications designed to exploit the power of the zebrafish as a vertebrate model for biomedical and behavioral research. This is a reissue of PAR-02-142 released August 2, 2002.

On March 31, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Global Research Initiative Program, Social Science (PAR-05-082)**. The goal of this PA is to provide funding opportunities for the increasing pool of foreign biomedical and behavioral scientists, clinical investigators, nurses and other health professionals with state-of-the-art knowledge of research methods to advance critical issues in global health upon their return to their home countries through behavioral and social science research. This is a modification of PAR-03-118 released May 16, 2003.

On April 21, 2005, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Interactions between Stem and Progenitor Cells and the Microenvironment In Vivo (PAS-05-092)**. The goal of this PA is to support studies on the cellular and molecular signaling between the local environment within organisms and stem and progenitor cells that are either

introduced as transplants or are normally resident within host tissues and organs. The objective of this initiative is to promote a thorough exploration and characterization of the bi-directional communication between multipotent cells and the three-dimensional local milieu or niche that they encounter in vivo under normal and compromised states, such as with aging or following injury, disease, or drug exposure. This is a reissue of PAS-03-172.

On April 26, 2005, NIDA, in conjunction with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), issued a Program Announcement (PA) entitled **Complementary and Alternative Medicine for Substance and Alcohol Related Disorders (PA-05-097)**. The goal of this PA 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 3, 2005, NIDA, in conjunction with numerous other NIH components and the Canadian Institutes of Health Research (CIHR), issued a Program Announcement (PA) entitled **Brain Disorders in the Developing World: Research Across the Lifespan (PAR-05-100)**. This PA solicits applications for collaborative research projects involving investigators in developed and developing countries, focusing on brain disorders throughout life relevant to developing nations. This PA is a modification of RFA-TW-03-007, released November 7, 2002.

On February 2, 2005, NIDA, in conjunction with the NIAAA, issued an RFA entitled **Consequences of Drug Abuse and Alcohol Exposure on Brain and Behavioral Development (RFA-DA-05-007)**. The goal of this RFA is to support research on the consequences of drug and alcohol use, abuse, and addiction on human brain and behavioral development. Letter of Intent Receipt Date for this RFA: March 18, 2005; Application receipt Date: April 18, 2005.

On February 10, 2005, NIDA, in conjunction with numerous other NIH components, issued an RFA entitled **Units for HIV/AIDS Clinical Trials Networks (RFA-AI-05-002)**. The objective of this RFA is to solicit applications for Clinical Trials Units (CTUs) to implement the clinical research plans of one or more of the HIV/AIDS Clinical Trials Networks. Letter of Intent Receipt Date for this RFA: June 10, 2005; Application Receipt Date: July 11, 2005.

On February 18, 2005, NIDA, in conjunction with NIMH, issued an RFA **entitled HIV and Psychiatric Comorbidity Research Project (RFA-MH-05-010)**. The goal of this RFA is to support research addressing the cellular, molecular, and genetic factors underlying the high comorbidity between HIV-1 infection and psychiatric disorders. Letter of Intent Receipt Date for this RFA: March 29, 2005; Application Receipt Date: April 26, 2005.

On March 23, 2005, NIDA, in conjunction with numerous other NIH components, issued an RFA entitled **Course Development in the Neurobiology of Disease (RFA-MH-05-011)**. The goal of this RFA, an initiative of the NIH Blueprint for Neuroscience Research, is to support the development and initiation of the significant expansion of courses on the neurobiology of disease for graduate students receiving basic neuroscience training. Letter of Intent Receipt Date for this RFA: April 25, 2005; Application Receipt Date: May 25, 2005.

NIH Roadmap Administrative Supplements to Support Interdisciplinary Research in the Behavioral/Social and Biological Sciences--NOT-RM-05-007. Several NIDA Divisions, including DCNDBT contributed to this announcement. Applications are due June 15, 2005.

Administrative Supplements for Research on the Intersection of Drug Use and Criminal Justice Consequences in the African American Population
The purpose of this administrative supplement solicitation is to give NIDA-funded researchers the opportunity to pursue research that will help clarify the relationship between drug use and addiction and criminalization/criminal justice involvement in the African American population. It is expected that recruitment of additional participants and/or the secondary analysis of existing data sets will lead to better understanding of the drug abuse and criminalization nexus in African Americans and lead to the development of effective prevention and intervention strategies.

NIDA has reissued its **Science Education Drug Abuse Partnership Award** program announcement. This R25 grant mechanism funds 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, teachers, 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.

Response to NIDA RFAs

Neurobiology of Behavioral Treatment: Recovery of Brain Structure and Function —RFA-DA-05-006 — 22 grant applications were received in response to this RFA. http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-05-006.html.

HIV and Drug Abuse Interventions among Pregnant Women in Drug Abuse Treatment--RFA-DA-05-008 — 16 applications were received in response to this RFA. http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-05-008.html.

Other Program Activities

CTN Update

The proposals for the Request for Applications (RFA) DA-05-001 for the fourth solicitation for the CTN were reviewed April 11-12, 2005. This RFA includes both new applications (new Nodes) and competing continuations. The anticipated award date is September 2005.

Two new Requests for Proposal (RFPs) were issued: DA-5-2207 for the Data and Statistics Center for the CTN, and DA-5-2208 for the Clinical Coordinating Center for the CTN. Both contracts are to be awarded in May 2005.

- A total of eleven protocols that started since 2001 have completed enrollment. These studies enrolled 2,670 patients who were randomized in 53 community treatment programs located in 16 states.
- Ten additional protocols are currently recruiting & enrolling patients. These protocols plan to enroll over 4,000 patients across 88 Community Treatment Programs when completed. Highlights of the active protocols include:
    - Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules) began enrollment June 30, 2003. Participation has reached 86% of the targeted enrollment.
    - Protocol CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment in July 2003. This is the first protocol in the CTN that targets adolescent substance abusers. Enrollment is at 40% of the projected target.
    - Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome In Pregnant Substance Abusers) began enrollment in November 2003 and has enrolled 50% of the projected target.
    - Protocol CTN 0014, Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT), has been implemented at 4 sites. The remaining 4 sites have finished the provider training and overall site preparation and will start patient enrollment in April/May 2005. This intervention is the first CTN study to target adolescents and their families.
    - Protocol CTN 0015 (Women's Treatment for Trauma and Substance Use Disorder: A Randomized Clinical Trial) began in March 2004. The study has reached nearly 61% of the targeted patient enrollment.
    - Protocol CTN 0017 (HIV and HCV Intervention in Drug Treatment Settings). The study began enrollment in November 2004 and enrollment has reached 25% of the target.
    - CTN 0018 (Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment) began enrolling in April 2004 and has reached 57% of the target.
    - CTN 0019 (Reducing HIV/STD Risk Behaviors: A Research

Study for Women in Drug Abuse Treatment) began enrollment in April 2004 and has reached 60% of the target.

- CTN 0020 (Job Seekers Training for Substance Abusers). The protocol began enrollment in October 2004 and has reached nearly 30% of the goal.
- 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. This is the first Spanish-only protocol in the CTN. The study has reached nearly 2/3 of the target.

- Two protocols have recently completed all data collection phases and are pending data lock (April/May 2005). Those include:
  - Protocol CTN-0004 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse).
  - Protocol CTN 0008 (Assessment of the National Drug Abuse Clinical Trials Network: A Baseline for Investigating Diffusion of Innovation) has completed all data collection phases.
- Two protocols have recently locked their data sets and are at the analysis stage. Those include:
  - Protocol CTN 0012 (Characteristics of Screening, Evaluation, and Treatment of HIV/AIDS, Hepatitis C Viral Infections, and Sexually Transmitted Infections in Substance Abuse Treatment Programs).
  - Protocol CTN 0016 (Patient Feedback: A Performance Improvement Study in Outpatient Addiction Treatment Settings).
- Four additional Protocols are currently being developed for the Network. Highlights of those protocols include:
  - Protocol CTN 0023: Twelve Step Facilitation: Evaluation of Two Interventions to Increase 12-Step Involvement and Improve Outcomes among Substance Dependent Individuals.
  - Protocol CTN 0028: Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS MPH) for Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD). Protocol is under review by the DSMB/PRB.
  - Protocol CTN-0029: A Pilot Study of Osmotic-Release Methylphenidate (OROS MPH) in Initiating and Maintaining Abstinence in Smokers with Attention Deficit Hyperactivity Disorder (ADHD). The protocol has been reviewed and approved to start implementation planning.
  - Protocol CTN 0030: Prescription Opioid Addiction Treatment Study (POATS) is a randomized 2-phases, open-label, multi-center study in outpatient treatment settings. Protocol is submitted for DSMB/PRB review.
- In addition to the primary CTN trials, there are 12 studies supported by independent grants or as supplements that use CTN studies as a platform.
- New Collaborative Study: Starting Treatment with Agonist Replacement Therapies (START) Study: The CTN will participate with the Division of Pharmacotherapies & Medical Consequences of Drug Abuse on a multi-centered trial to compare the effect of buprenorphine/naloxone (Bup/Nx) and methadone (MET) on liver function. This is a randomized, open-label, multi-center, Phase 4 study in participants entering opioid agonist treatment programs at community centers (methadone centers) throughout the country. It is anticipated that 1,000 patients will be entered into the trial starting January 2006 across 8 CTN nodes.

Review Activities:

- Data and Safety Monitoring Boards (DSMB) met March 11, 2005, March 29, 2005, and April 11, 2005, in Bethesda, Maryland. The DSMB group reviewed developing and ongoing protocols.

NIDA's New and Competing Continuation Grants Awarded Since February 2005

Ahijevych, Karen L. -- Ohio State University
Menthol, Ethnicity and Nicotine Dependence

Aldrich, Jane V. -- University of Kansas Lawrence
Peptidic Ligands for Kappa Opioid Receptors

Aldridge, J. Wayne -- University of Michigan at Ann Arbor
Neural Coding of Reward in Ventral Forebrain

Ananthan, Subramaniam C. -- Southern Research Institute
Novel Nonpeptide Ligands for the Opioid Receptors

Aston-Jones, Gary -- University of Pennsylvania
Alterations In Reward Processing During Drug Abstinence

Bank, Lewis L. -- Oregon Social Learning Center, Inc.
Motivational Parent Training In Community Corrections

Ben-Shahar, Osnat M. -- University of California Santa Barbara
Neuroadaptations Underlying the Transition to Addiction

Bevins, Rick A. -- University of Nebraska Lincoln
Reference-Dose Method and Cocaine-Conditioned Choice

Biederer, Thomas -- Yale University
Mechanisms of Syncam-Induced Synapse Formation

Bisaga, Adam M. -- New York State Psychiatric Institute
Memantine Naltrexone Treatment for Opioid Dependence

Blakely, Randy D. -- Vanderbilt University
Regulation of Serotonin Transporters

Bolanos, Carlos A. -- Florida State University
Adolescent Antidepressant Treatment and Drug Reward

Booth, Brenda M. -- University of Arkansas Medical Sciences Little Rock
Cost-Effectiveness of Reducing Drug Treatment Barriers

Brook, Judith S. -- New York University School of Medicine
Childhood Determinants of Adolescent /Adult Drug Use

Butelman, Eduardo R. -- Rockefeller University
Kappa-Agonist Effects of The Hallucinogen Salvinorin A

Callaway, Edward M. -- Salk Institute for Biological Studies
Fugu Promoters for Mammalian Cortical Neurons

Carroll, Kathleen M. -- Yale University
Maximizing CBT's Efficacy With Medication & CM

Clark, Ann S. -- Dartmouth College
AAS and yhe Neurobiology of Social Behaviors

Clatts, Michael C. -- National Development & Research Institutes
Ethno-Epidemiology In An Emergent MSM Risk Environment

Day, Nancy L. -- University of Pittsburgh at Pittsburgh
Prenatal Marijuana Exposure: Long-Term Outcomes

De Leon, George -- National Development & Research Institutes
Generalization of the Client Matching Protocol

De Wit, Harriet -- University of Chicago
Drug Abuse and Impulsivity: Human Laboratory Models

Donny, Eric C. -- University of Pittsburgh at Pittsburgh

Mechanisms of Smoking Reinforcement

Dykstra, Linda A. -- University of North Carolina Chapel Hill
Opioid Analgesics: Pharmacological & Behavioral Factors

Filizola, Marta -- Weill Medical College of Cornell University
Informatics of Gpcr Dimers In Drug Abuse Mechanisms

Finn, Peter R. -- Indiana University Bloomington
Attention-Biases and Hot Cognition In Drug Dependence

French, Michael T. -- University of Miami Coral Gables
Economic Evaluation Methods: Development and Application

Friedman, Jeffrey M . -- Rockefeller University
Mapping Neural Circuits Using Pseudorabie Virus Vectors

Fuchs Lokensgard, Rita A. -- Medical University of South Carolina
Neural Bases of Drug Context-Induced Cocaine Seeking

Gahring, Lorise C. -- University of Utah
Nicotine Modulation of Caspases In Non-Neuronal Cells

Galea, Sandro -- New York Academy of Medicine
The HIV Risk Behavior and the Urban Environment

Gerak, Lisa R. -- Louisiana State University Health Science Center New Orleans
Behavioral Effects of Neuroactive Steroids

Geyer, Mark A. -- University of California San Diego
Monoamine and Hallucinogen Effects on Rodent Behavior

Gottdiener, William H. -- John Jay College of Criminal Justice
Therapy of Comorbid Substance Use Disorders and PTSD

Gulley, Joshua M. -- University of Illinois Urbana-Champaign
Amphetamine Sensitization and Prefrontal Cortex Function

Hao, Shuanglin -- University of Michigan at Ann Arbor
Transgene for Morphine Tolerance and Withdrawal

Howlett, Allyn C. -- North Carolina Central University
Cannabinoid Receptors In Neuronal Cells and Brain

Johnson, Bankole A. -- University of Virginia Charlottesville
Medication Development for Cocaine Dependence

Kaiyala, Karl J. -- University of Washington
Neuroadaptive Substrates for Nitrous Oxide Tolerance

Kalivas, Peter W. -- Medical University of South Carolina
Glutamate and Craving for Cocaine

Kalman, David W. -- Boston University Medical Campus
Double-Blind Placebo Controlled Study: Bupropion Treatment Smokers In Recovery

Kendler, Kenneth S. -- Virginia Commonwealth University
A Twin-Family Study of Drug Use, Abuse and Dependence

Kish, Stephen J. -- Centre for Addiction and Mental Health
Brain Serotonin Transporter In Ecstasy and MDA Users

Kollins, Scott H. -- Duke University
Methylphenidate Abuse Potential In ADHD Adults

Kuhn, Donald M. -- Wayne State University
Methamphetamine Neurotoxicity and Microglial Activation

Kurtz, Steven P. -- University of Delaware
Prevention For At-Risk Men: A Mixed Serostatus Approach

Lee, Juliet P. -- Pacific Institute for Research and Evaluation
Social Meanings of Drugs for Asian American Youth

Lipton, Jack W. -- University of Cincinnati
Neurochemical Sequelae of Prenatal MDMA

Liu, Xiu -- University of Pittsburgh at Pittsburgh
Neuropharmacology of Cue-Induced Nicotine Relapse

Mahata, Sushil K. -- University of California San Diego
Chromaffin Cell Physiology: Novel Molecular Approaches

Malenka, Robert C. -- Stanford University
Drugs of Abuse and Synaptic Processes In Dopamine Systems

Markou, Athina -- Scripps Research Institute
Neurobiology of Nicotine Reward and Withdrawal

Marsh, Jeanne C. -- University of Chicago
Gender Differences In Treatment Services Effectiveness

Martinez, Charles R. -- Oregon Social Learning Center, Inc.
Linking Acculturation To Latino Adolescent Substance Use

Matsumoto, Rae R. -- University of Mississippi
Cocaine, Sigma Receptors and Fra-2

Mccabe, Sean E. -- University of Michigan at Ann Arbor
Nonmedical Prescription Drug Use Among College Students

McMahon, James M. -- National Development & Research Institutes
Hepatitis C Virus Intranasal Transmission: Pilot Study

Michelhaugh, Sharon K. -- Wayne State University
Analysis of Nurr1 Isoforms In Rat Ventral Midbrain

Mitchell, Suzanne H. -- Oregon Health and Science University
Reinforcer Efficacy: Measures and Neural Mechanisms

Murphy, Sheigla B. -- Scientific Analysis Corporation
A Qualitative Study Of Women In Drug Markets

Nielsen, Darci M. -- Brown University
Nicotine Addiction and Gating Deficits In Schizophrenia

Pavlopoulos, Spiro -- University of Connecticut Storrs
Receptor Structural Features Determining Drug Tolerance

Petry, Nancy M. -- University of Connecticut School of Medicine and Dentistry
Vouchers Vs. Prizes: Cocaine-Dependent Methadone Patients

Pierce, Robert Christopher -- Boston University Medical Campus
Ephrins and Repeated Cocaine

Piomelli, Daniele -- University of California Irvine
Characterization of a Novel Cannabinoid Ligand

Pope, Harrison G. -- Mc Lean Hospital, Belmont, MA
Risk Factors for Anabolic-Androgenic Steroid Abuse

Rebec, George V. -- Indiana University Bloomington
Neuropharmacology of Drugs of Abuse: Amphetamine

Reynolds, James D. -- Duke University
Maternal MDMA (Ecstasy) Exposure and Fetal Physiology

Schoenwald, Sonja K. -- Medical University of South Carolina
Testing Context Effects on Treatment of Drug-Using Youth

Self, David W. -- University of Texas Southwest Medical Center, Dallas, TX
VTA Ionotropic Glutamate Receptors In Cocaine Addiction

Sharp, Burt M. -- University of Tennessee Health Science Center
Interaction Between Nicotine and Stress

Shepard, Paul D. -- University of Maryland Baltimore Professional School
Dopamine Cell Impulse Flow, Reward and Schizophrenia

Silverman, Kenneth -- Johns Hopkins University
Employment-Based Addiction Pharmacotherapy

Simone, Donald A. -- University of Minnesota Twin Cities

Cannabinoid Modulation of Hyperalgesia

Stanwood, Gregg -- Vanderbilt University
Dopaminergic Influences on Brain Formation and Function

Steiner, Heinz -- Rosalind Franklin University of Medicine & Science
Basal Ganglia Output and Psychostimulant Abuse

Stout, Julie C. -- Indiana University Bloomington
Cognitive Modeling of Risky Decisions In Drug Abusers

Taffe, Michael A. -- Scripps Research Institute
Behavioral Toxicity of MDMA In Rhesus Monkeys

Terwilliger, Ernest F. -- Beth Israel Deaconess Medical Center
SiRNA Suppression of Genes Mediating Addictive Behaviors

Thomas, Janet L. -- University of Kansas Medical Center
Supportive Behaviors To Assist In Smoking Cessation

Tietz, Elizabeth I. -- Medical College of Ohio At Toledo
Benzodiazepine-Induced Glutamate Receptor Plasticity

Tildesley, Elizabeth A. -- Oregon Research Institute
Modeling the Sequence of Depression and Substance Use

Unterwald, Ellen M. -- Temple University
Regulation of Delta Opioid Receptor Function By Cocaine

Venanzi, Carol A. -- New Jersey Institute of Technology
Multivariate, Cluster, and Comfa Analysis of GBR Analogs

Vorhees, Charles V. -- Children's Hospital Med Center, Cincinnati, OH
Developmental Effects of Methamphetamine-Like Stimulants

Walker, J. Michael -- Indiana University Bloomington
Role of Endogenous Vanilloids and Cannabinoids In Pain

Wang, Zuoxin -- Florida State University
Dopamine Regulates Drug and Social Reward Interactions

Watkins, Linda R. -- University of Colorado at Boulder
Pain Facilitation Via Neuron-To-Glia Signaling

Weed, Michael R. -- Johns Hopkins University
Pupillometry and Gaze-Tracking In Unrestrained Monkeys

Weinstein, Harel -- Weill Medical College of Cornell University
Structure and Function of Neurotransmitter Transporters

Wellman, Paul J. -- Texas A&M University System
Psychostimulants and Alpha-1 Adrenoceptor Subtypes

Whiteaker, Paul -- University of Colorado at Boulder
Immunochemical Protocols for Nicotinic Receptors

Willging, Cathleen E. -- Behavioral Health Research Center-Southwest
Drug Use, Ethnicity and Help Seeking Among Rural Youth

Williams, John T. -- Oregon Health & Science University
Cocaine Effects on Single Neurons

Williams, Mark -- University of Texas Health Science Center, Houston TX
Tanzania Injection Drug Use/HIV Prevention Project

Wu, Ping -- New York State Psychiatric Institute
Adolescent Use of Substance Use Treatment Services

Yaksh, Tony L. -- University of California San Diego
The Pharmacology of Spinal Analgesics

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1266 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 825 applications.

OEA arranged and managed 18 grant review meetings in which 309 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 11 contract proposal reviews, 2 concept reviews, and reviews of 143 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 14 Special Emphasis Panels for a variety of reasons:

Conflicts with the chartered committees
Center Grant Applications
Program Project Grant applications
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)
2 Special Emphasis Panels that reviewed RFA submissions.

OEA managed the following RFA reviews:

- DA05-001: The National Drug Abuse Treatment Clinical Trials Network
- DA05-003: Developmental Centers for Translational Research on the Clinical Neurobiology of Drug Addiction

Completed Reviews from the Contracts Review Branch since the last Council are as follows:

Non-R&D Contract Reviews

- N01DA-5-9909: Residential Research Support Services

R&D Contract Reviews

- N01DA-5-8855: Statistical Analysis in Support of NIDA's DPMC Clinical Trials

SBIR Phase I and Phase II

- N43DA-5-5529: Topic 060 Develop New Technologies for Screening and Assessing Drug Abuse and Matching Patients with Appropriate Treatment Services
- N43DA-5-5530: Topic 073 Internet-based Application of Existing/Proven Therapies
- N43DA-5-1120: Topic 070 Develop Research Training Modules for International Application

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- N43DA-5-1121: Topic 029 Development of Science Education Materials or Programs
- N43DA-5-5531: Topic 028 Prevention Training
- N43DA-5-7751: Topic 075 Real-time Data Collection Paired with Ecological Momentary Assessment
- N43DA-5-8858: Topic 071 Microarray Data Warehouse for Addiction Research
- N44DA-5-5527: Topic 061 Multi-Problem Youth Screening and Assessment Package
- N44DA-5-7744: Topic 068 Human Factors Analysis in Virtual Reality (VR) for Burn Treatment

R&D Concept Reviews

- N01DA-5-9909C: Residential Research Support Services
- N01DA-5-8856C: Medical Writing, Report Preparation and Project Management

Extramural Outreach

Dr. Mark Swieter, OEA, gave a talk on Friday, March 18, 2005 to the NIDA Humphrey and INVEST fellows titled, "The NIH Grants Enterprise: Referral and Review.

Dr. Khursheed Asghar, OEA, delivered a seminar on March 3, 2005, at the Morgan State University in Baltimore entitled Research Grant Opportunities for New Investigators at NIDA.

Dr. Asghar gave an invited talk on April 26, 2005, at a Special Populations Research Development Seminar Series Workshop sponsored by NIDA's Office of Special Populations; the title was, "Research Grant Opportunities for New Investigators and the Review Process at NIDA".

Dr. Rita Liu, OEA, continues to work with NIMH and NINDS to co-organize a monthly seminar series in 2005 on Neuroimaging. The topics will encompass structural MRI, computational tools, DTI (diffuse tensor imaging) and tract tracing, image guided surgery, imaging developing brain, and ethics in neuroimaging. The series is meant to educate NIH staffers to this rapidly growing field.

Dr. Teri Levitin, Directorm, OEA, continues her work as the NIDA Research Integrity Officer and representative to the NIH on these matters.

Dr. Levitin organized and chaired a discussion hour on the NIH grant review process at the meeting of the Society for Research on Child Development, April 7-10, 2005. Representatives from several ICs participated in providing information about extramural grant review policies and procedures.

Dr. Levitin continues to participate in a number of trans-NIH committees, including the NIH Director's Pioneer Award Committee, the NIH Director's Pioneer Award Evaluation Advisory Committee, a working group of the DEAS advisory committee, the EPMC work group to implement the Office of Human Subjects Research Guidelines, the EPMC workgroup on NIH Advisory Councils as well as the EPMC.

Dr. Levitin is also serving on the Society for Research on Adolescent's Committee on Research, Policy and Public Information.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the winter and spring. Topics addressed have included: Implementation of NIH Guidance on OHRP Guidance on Human Research involving coded private information and biological specimens; Policy on Enhancing Public Access to Archived Publications Resulting from NIH-funded Research Resources for new Investigators; Revised PHS 398, including more on revisions to Human Subjects section; Revised Policy for applications that include consortium/contractual F&A costs; Activities to promote research collaborations; Requests for information in the NIH Guide; and "Working smarter not harder: eRA Commons Program Official's Module and other tips."

Grantee Honors

In Memoriam

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Congressional Affairs (Prepared May 6, 2005)

BUDGET FY 2006

The FY 2006 budget request for NIH is $28.845 billion, an increase of $251 million or 0.7 percent over the FY2005 funding level. The FY 2006 President's request for NIDA $1,010,130,000, 0.4 percent above the FY 2005 level.

NIH Appropriations Hearings for FY 2006

March 9, 2005 - The House Appropriations Subcommittee on Labor, HHS, and Education (Representative Ralph Regula [R-OH], Chairman) held its NIH Overview hearing on the FY2006 Budget, with Dr. Elias Zerhouni, Director, NIH, testifying. Representative Ralph Regula (R-OH), Chairman, presided over a positive hearing that offered the opportunity for NIH to discuss the progress of initiatives begun in FY2004 (The NIH Roadmap), FY 2005 (the NIH Strategic Plan for Obesity Research), and for FY 2006, the NIH Neuroscience Blueprint; and the new Office of Portfolio Analysis and Strategic Initiatives (OPASI), which will include an improved process for collecting data on various diseases, conditions, and research fields, and improvements in data about burden of disease. There was considerable interest in how NIH sets priorities and in what will be the goal of OPASI and the role that the President's new health information system will play in support of decision-making and translational activities at NIH.

April 6., 2005 - The Senate Appropriations Subcommittee on Labor, HHS, and Education (Senator Arlen Specter [R-PA], Chairman) held a hearing on the Fiscal Year 2006 NIH budget. Dr. Elias Zerhouni, Director, NIH, provided the NIH Overview. He was accompanied by Drs. Andrew von Eschenbach, Director, NCI; Anthony S. Fauci, Director, NIAID; James Battey, Director, NIDCD; and Allen Spiegel, Director, NIDDK. The hearing provided Dr. Zerhouni with an opportunity to discuss the progress of initiatives as mentioned above. It also provided committee members, most notably Chairman Specter and Ranking Member Harkin, an opportunity to voice their concerns about the recently implemented NIH Conflict of Interest policy.

April 27, 2005 - The House Appropriations Subcommittee on Labor, HHS, and Education (Representative Ralph Regula [R-OH], Chairman) held a "theme" hearing on Substance Abuse and Mental Health Research and Services -- the FY 2006 budget proposals of SAMHSA, NIDA, NIAAA and NIMH. Testifying were Charles Curie, Administrator, SAMHSA; Dr. Nora Volkow, Director, NIDA; Dr. Faye Calhoun, Deputy Director, NIAAA; and Dr. Thomas Insel, Director, NIMH. To read Dr. Volkow's testimony, go to /Testimony/4-27-05Testimony.html.

Other Hearings and Briefings of Interest

March 16, 2005 — At the request of the Friends of NIDA, Dr. Nora Volkow, Director, NIDA, briefed congressional staff on research focusing on the intersection of drug abuse and criminal justice issues. The briefing was extremely well attended. Dr. Volkow's presentation can be found at http://www2.apa.org/ppo/volkow31505.ppt.

Also speaking at the event were Dexter Manley, Dr. Dwayne Simpson, and Representative Patrick Kennedy.

> *Dexter Manley, Director of Community Outreach, Second Genesis, Inc. and a former NFL football player with the Washington Redskins:* Mr. Manley outlined his cocaine addiction and contact with the criminal justice system. Despite his own experience with relapse, Mr. Manley

Grantee Honors

In Memoriam

returned to follow a regimen that has kept him sober, out of the criminal justice system, and a valuable member of the community. He now works as Director of Outreach at Second Genesis in Silver Spring, Maryland.

Dwayne Simpson, PhD, Director of the Institute of Behavioral Research, Texas Christian University: Dr. Simpson provided an overview of NIDA-funded research in the area of criminal justice. He focused on his work through the Criminal Justice/Drug Abuse Treatment Studies (CJ-DATS) project — a multi-site set of research studies designed to improve outcomes for offenders with substance use disorders by improving the integration of drug abuse treatment with other public health and public safety systems. His presentation is available at http://www2.apa.org/ppo/simpson31505.ppt.

Rep. Patrick Kennedy (D-RI), Co-Chair, House Addiction Treatment and Recovery Caucus and member of the House Appropriations Subcommittee on Labor, Health and Human Services, Education: Rep. Kennedy thanked members of the audience for attending and applauded the event's speakers for their leadership. Rep. Kennedy noted that he enjoyed recent visits with Dr. Volkow, and with scientists at NIDA's intramural program — and shared with briefing attendees the fact that he keeps a large NIDA-generated poster of the brain in his Capitol Hill office to help educate people regarding "addiction as a brain disease." He noted his own experience with addiction and bi-polar disorder — and called on more Americans to step out of the shadow of anonymity in order to chip away at the stigma surrounding addiction.

Pictures of the event can be found at http://www.apa.org/ppo/issues/fonbriefpics305.html.

March 17, 2005 - The House Energy and Commerce Subcommittee on Health and the Environment (Representative Nathan Deal [R-GA], Chairman) held a hearing entitled, "Setting the Path for Reauthorization: Improving Portfolio Management at the NIH." Dr. Elias Zerhouni, Director, NIH, testified.

March 17, 2005 -- The House Committee on Government Reform (Representative Tom Davis [R-VA], Chairman) held a hearing on Steroids and Major League Baseball. Dr. Nora D. Volkow, Director, NIDA, testified. Dr. Volkow testified on the health effects of steroids and what we can do to prevent their abuse. To read Dr. Volkow's testimony, go to /Testimony/3-17-05Testimony.html.

April 21, 2005 - The Senate Appropriations Subcommittee on Labor, HHS, and Education (Senator Arlen Specter [R-PA], Chairman) held a hearing on the escalating problem of methamphetamine abuse. Senator Tom Harkin (D-IA) chaired the hearing in Mr. Specter's absence. Dr. Nora Volkow, Director, NIDA, testified. Dr. Volkow's testimony focused on the health effects of methamphetamine abuse, what we have learned via brain imaging about that abuse and the potential for recovery, and successful treatment approaches. To read Dr. Volkow's testimony, go to /Testimony/4-21-05Testimony.html.

April 26, 2005 — The House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources (Representative Mark Souder [R-IN], Chairman), held a hearing on "Drug Prevention Programs and the Fiscal Year 2006 Drug Control Budget: Is the Federal Government Neglecting Illegal Drug Use Prevention?" Mr. Souder and Ranking Member Elijah Cummings (D-MD) are very concerned about cuts in prevention programs in the President's FY 2006 budget proposal, and made remarks specifically supporting the importance of prevention programs in the fight against drug use and demand. Included in the programs Mr. Souder highlighted were Safe and Drug Free Schools and Communities (SDFSC) State Grants program of the Department of Education, the national media campaign and Drug Free Communities programs of the Office of National Drug Control Policy (ONDCP) and the Center for Substance Abuse Prevention (CSAP) of SAMHSA.

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. 45 — Senator Carl Levin (D-MI), introduced on January 24, 2005 a bill 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. The bill would impact practices that prescribe buprenorphine products for

treatment of opiate addiction. Committees: Health, Education, Labor and Pensions; Judiciary. Related Bills: See H.R. 869. Status: The bill was discharged on February 1, 2005 by the Health, Education, Labor and Pensions Committee, and is currently pending in the Judiciary Committee.

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. Committee: Judiciary. Related Bills: See S.102, H.R. 314.

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. 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. 518 — Senator Sessions (R-OH) introduced on March 5, 2005 the "National All Schedules Prescription Electronic Reporting Act of 2005," which would provide for the establishment of a controlled substance monitoring program in each State. Committee: Health, Education, Labor and Pensions. Related Bills: See H.R. 1132.

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.

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.

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.

S. 927 — 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.

BILLS OF INTEREST - HOUSE

H.R. 3 - Representative Young (R-AK) introduced on February 9, 2005 the "Transportation Equity Act: A Legacy for Users," a bill to authorize funds for federal aid for highways, highway safety programs, and transit programs. Under Section 2013 of HR 3, the "Drug Impaired Driving Research and Prevention Act," the legislation 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. Status: This bill has been passed by the House. A similar bill, which does not contain the drugged driving language, awaits final Senate action.

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 full committee.

H.R. 313 - Representative Blunt (R-MO) introduced on January 25, 2005 the "Exile Meth Act," a bill to provide grants to states to combat methamphetamine abuse. In part the bill would require the Attorney General to establish a program that provides grants to qualified States for combating the problem with a specific focus on the prosecution of repeat offenders. Committee: Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security. Related Bills: See S.102.

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. In part the bill would authorize funds to provide training to State and local prosecutors and law enforcement agents for the investigation and prosecution of methamphetamine offenses. Committees: Judiciary, Subcommittee on Crime, Terrorism, and Homeland Security; Energy and Commerce, Subcommittee on Health. Related Bills: See S. 103.

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: voted out of full committee on 4/13/05, see House Report 109-42.

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.

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. 869 — Representative Souder (R-IN) introduced on February 17, 2005 a bill 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. This would impact group practices where buprenorphine products are prescribed for treatment of opiate addiction. Related Bills: See S. 45. Status: The bill was reported favorably from the Committee to the House on May 4, 2005.

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.

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.

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. 1132 — Representative Whitfield (R-KY) introduced on March 3, 2005 the "National All Schedules Prescription Electronic Reporting Act of 2005," which would provide for the establishment of a controlled substance monitoring program in each State. Committee: Energy and Commerce, Subcommittee on Health. Related Bills: See S. 518.

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.

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.

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.

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.

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.

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. 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 reasearch 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.Res. 246 — Representative Kennedy (D-RI) submitted on April 27, 2005 a resolution expressing the sense of the House of Representatives that there should be established a National Drug Court Month, and for other purposes. Committee: Government Reform.

109TH CONGRESS — KEY COMMITTEE ROSTERS

Senate Committee on Appropriations
Subcommittee on Labor, Health and Human Services, and Education (includes jurisdiction over NIH); Members: Republicans (8) Arlen Specter, PA — chairman; Thad Cochran, MS; Judd Gregg, NH; Larry E. Craig, ID; Kay Bailey Hutchison, TX; Ted Stevens, AK; Mike DeWine, OH; Richard C. Shelby, AL. Democrats (7) Tom Harkin, IA - ranking member; Daniel K. Inouye, HI; Harry Reid, NV; Herb Kohl, WI; Patty Murray, WA; Mary L. Landrieu, LA; Richard J. Durbin, IL.

Senate Committee on Health, Education, Labor and Pensions
(No longer includes a Subcommittee on Substance Abuse and Mental Health Services). Full Committee Members: Republicans (11) : Michael B. Enzi, WY — chairman; Judd Gregg, NH; Bill Frist, TN; Lamar Alexander, TN; Richard M. Burr, NC; Johnny Isakson, GA; Mike DeWine, OH; John Ensign, NV; Orrin G. Hatch, UT; Jeff Sessions, AL; Pat Roberts, KS. Democrats (9) Edward M. Kennedy, MA - ranking member; Christopher J. Dodd, CT; Tom Harkin, IA; Barbara A. Mikulski, MD; James M. Jeffords, VT (I); Jeff Bingaman, NM; Patty Murray, WA; Jack Reed, RI; Hillary Rodham Clinton, NY.

Senate Committee on the Judiciary
Subcommittee on Crime, and Drugs - Members: Republicans (6) Lindsey Graham, SC — chairman; Charles E. Grassley, IA; Jon Kyl, AZ; Mike DeWine, OH; Jeff Sessions, AL; Tom Coburn, OK. Democrats (5) Joseph R. Biden Jr., DE - ranking member; Herb Kohl, WI; Dianne Feinstein, CA; Russell D. Feingold, WI; Charles E. Schumer, NY.

Senate Caucus on International Narcotics Control
Members: Senator Charles E. Grassley (R-IA) Chairman; Senator Joseph R. Biden, Jr. (D-DE) Co-Chairman; Senator Jeff Sessions (R-AL); Senator Mike DeWine (R-OH); Senator Dianne Feinstein (D-CA); Senator Norm Coleman (R-MN).

House Committee on Appropriations
Subcommittee on Labor, Health and Human Services, Education, and Related Agencies. Members: Republicans (10) Ralph Regula, OH — chairman; Ernest Istook, OK; Roger Wicker, MS.; Anne M. Northup, KY - vice chairwoman; Randy "Duke" Cunningham, CA; Kay Granger, TX; John E. Peterson, PA; Don Sherwood, PA; Dave Weldon, FL; James T. Walsh, NY. Democrats (7): David R. Obey, WI - ranking member; Steny H. Hoyer, MD; Nita M. Lowey, NY; Rosa DeLauro, CT; Jesse L. Jackson Jr., IL; Patrick J. Kennedy, RI; Lucille Roybal-Allard, CA.

House Committee on Energy and Commerce
Subcommittee on Health - Members: Republicans (17) Nathan Deal, GA - chairman Ralph M. Hall, TX; Michael Bilirakis, FL; Fred Upton, MI; Paul E. Gillmor, OH; Charlie Norwood, GA; Barbara Cubin, WY; John Shimkus, IL; John Shadegg, AZ; Charles W. "Chip" Pickering Jr., MS; Steve Buyer, IN; Joe Pitts, PA; Mary Bono, CA; Mike Ferguson, NJ - vice chairman; Mike Rogers, MI; Sue Myrick, NC; Michael C. Burgess, TX. Democrats (14) Sherrod Brown, OH - ranking member; Henry A. Waxman, CA; Edolphus Towns, NY; Frank Pallone Jr., NJ; Bart Gordon, TN; Bobby L. Rush, IL; Anna G. Eshoo, CA; Gene Green, TX; Ted Strickland, OH; Diana DeGette, CO; Lois Capps, CA; Tom Allen, ME; Jim Davis, FL; Tammy Baldwin, WI.

House Committee on Government Reform
Subcommittee on Criminal Justice, Drug Policy, and Human Resources — Members: Republicans (10) Mark Souder, IN. — chairman; Patrick T. McHenry, NC - vice chairman; Dan Burton, IN; John L. Mica, FL; Gil Gutknecht, MN; Steven C. LaTourette, OH; Chris Cannon, UT; Candice S. Miller, MI; Ginny Brown-Waite, FL; Virginia Foxx, NC. Democrats (8) Elijah E. Cummings, MD - ranking member; Bernard Sanders, VT (I); Danny K. Davis, IL; Diane Watson, CA; Linda T. Sanchez, CA; C.A. Dutch Ruppersberger, MD; Major R. Owens, NY.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

International Activities

DISCA-Supported Research Supports Fluoxetine as Pharmacotherapy for Methamphetamine; DISCA Team Awarded Additional Binational Funding

Preliminary results from research conducted under the NIDA Distinguished International Scientist Collaboration Awards (DISCA) suggest that fluoxetine has therapeutic effects on methamphetamine self-administration. The researchers, NIDA 2004 Distinguished International Scientist Dr. Kazutaka Ikeda, Tokyo Institute of Psychiatry, Japan, and Dr. Athina Markou, The Scripps Research Institute, have received a 3-year grant from the U.S. - Japan Brain Research Cooperation Program as well as additional support from the Tokyo Institute of Psychiatry and the Japanese Society of Pharmacopoeia. Dr. Ikeda's DISCA award supported his research exchange visit with Dr. Markou to learn research techniques and conduct experiments on intravenous self-administration of methamphetamine in mice. The preliminary results of their experiments suggest that fluoxetine significantly reduced methamphetamine self-administration, and led to their joint application to the U.S. - Japan Brain Research Cooperation Program. The U.S. National Institute of Neurological Disorders and Stroke (NINDS) and the Japanese National Institute for Physiological Sciences organized the joint brain research program; the NIDA International Program has contributed support. In addition to the binational funding, The Tokyo Institute of Psychiatry granted Dr. Ikeda a 4 million yen budget to purchase equipment and the Japanese Society of Pharmacopoeia supported research exchange visits with Dr. Markou for two of Dr. Ikeda's colleagues, Drs. Yukio Takamatsu and Shinya Kasai.

NIDA Helps Fund First fMRI in Africa

NIDA and the University of Stellenbosch, Tygerberg, South Africa, have installed the continent's first functional magnetic resonance imaging (fMRI) system. The installation was part of an ongoing collaboration between Dr. Deborah A. Yurgelun-Todd, Harvard Medical School, and the South African Medical Research Council (MRC) Unit on Anxiety and Stress Disorders at the University of Stellenbosch, which is directed by Dr. Daniel Stein. The binational research team will use fMRI to examine neurobiological correlates of cognitive dysfunctions observed in cannabis and cannabis/methaqualone abusers, their discordant siblings, and normal controls. NIDA's Southern Africa Initiative funded the project with an administrative supplement to Dr. Yurgelun-Todd's parent grant: "Residual Cognitive Effects of Cannabis: An fMRI Study." In addition to the fMRI equipment, the researchers installed fMRI paradigm presentation software that runs simultaneously with the MR scanner protocol designed to measure fMRI blood oxygen dependent level (BOLD) signal during presentation of cognitive tasks, such as spatial working memory and response inhibition paradigms. The system includes a triggering device that interfaces with a computer workstation and an LCD projector. Staff from the MRC group was trained to use the fMRI presentation software, deliver instructions to subjects in both Afrikaans and English, score patient responses, and analyze the behavioral data. To meet the NIDA Southern Africa Initiative goal of establishing collaborative projects that allow mutual use of a shared database, the researchers collected complete fMRI data sets during the visit to verify system functioning, data transfer, and processing.

Two Scientists Named 2005 WHO/NIDA/CPDD International Traveling Fellows

Former NIDA INVEST Fellow Dr. Raka Jain, India, and Dr. Paulo Cunha, Brazil, have been selected as the 2005 WHO/NIDA/CPDD International Traveling Fellows. The fellowships are co-sponsored by NIDA, the World Health Organization, and the College on Problems of Drug Dependence (CPDD) to support the participation of international researchers in the NIDA International Forum and the CPDD Annual Scientific Meeting.

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The Fellowship also supports brief research visits by the Fellows with NIDA grantees in the United States. Dr. Jain, a professor at the All India Institute of Medical Sciences, New Delhi, will work with Dr. Mike Baumann, IRP, on in vivo microdialysis techniques to correlate behavioral changes with neurotransmitter release rates. Dr. Cunha, an associate investigator in neuropsychology at the University of S‹o Paulo, will visit NIDA's functional Magnetic Resonance Imaging and Positron Emission Tomography facilities, working with Dr. Jean Lud Cadet, IRP, to assess the long-term effects of drugs of abuse on neurocognition. He will also visit Dr. Karen I. Bolla, Johns Hopkins University, to learn about Dr. Bolla's research on sleep disturbance in marijuana withdrawal.

NIDA Hosts INVEST and Humphrey Drug Abuse Research Fellows

NIDA hosted a March 17-18 orientation program for the 2005 INVEST Research Fellows, Dr. Marco Bortolato, University of Cagliari, Monserrato, Italy, and Dr. Liliana Cancela, University of Cordoba, Argentina. During their visit to the IRP, the INVEST Fellows toured the imaging facilities, Residential Treatment Unit, Archway Clinic, and Teen Tobacco Clinic. They also met with the following IRP scientists: Dr. Kenzie Preston, Clinical Pharmacology and Therapeutics Research Branch; Dr. David Gorelick, Clinical Pharmacology Section and Residential Unit; Dr. David Epstein, treatment of heroin and cocaine dependence with contingency management; Dr. Eric Moolchan, introduction to adolescent tobacco addiction and its treatment; Dr. Constance Murphy, applications of LC-MS to clinical research at NIDA; and Dr. Alane Kimes, PET Center. At NIDA headquarters, Dr. Bortolato, who is working with Dr. Daniele Piomelli, University of California, Irvine, to evaluate the role of endocannabinoids in the effects of psychostimulants, also met with Dr. Pushpa V. Thadani and Paul Hillery, DBNBR. Dr. Cancela, who is working with Dr. Peter Kalivas, Medical University of South Carolina, to investigate stress- and drug-induced neuroadaptations, met with Dr. Nancy S. Pilotte, Functional Neuroscience Research Branch, DBNBR. The current Hubert H. Humphrey Drug Abuse Research Fellows joined the INVEST Fellows for a March 18 grant-writing symposium that featured presentations by: Dale Weiss, IP; Dr. Mark Swieter, Office of Extramural Affairs; Dr. David Thomas, DBNBR; Ms. Natalie Tomitch, Fogarty International Center; and Dr. Yuan Liu, National Institute of Neurological Disorders and Stroke.

Travel Support

- NIDA supported the participation of three researchers at the Global Tobacco preconference satellite to the Society for Research on Nicotine and Tobacco annual meeting in Prague, Czech Republic, March 20-23, 2005. The NIDA travel awards supported Shahadat Hossain and Monsurul Haque of Bangladesh and Maisara Abdelrazig of Sudan. The satellite meeting featured a poster session and presentations on networking, capacity building, and advocacy supporting the Framework Convention on Tobacco Control. Presenters included former NIDA INVEST Fellow Dr. Neo Morojele, South Africa.
- NIDA supported a symposium, "Agonist Medications for the Treatment of Cocaine Abuse" at the Seventh Annual Neurochemistry Winter Conference in Innsbruck, Austria, on April 8, 2005. Travel support was awarded to three presenters, Dr. Steve Negus, McLean Hospital-Harvard Medical School; Dr. Leonard Howell, Emory University; and Dr. John Grabowski, University of Texas Health Science Center.
- NIDA supported preconference satellites, a plenary session, and symposia at the 2005 International Society of Addiction Medicine meeting. Preconference satellites were held in Buenos Aires, Argentina, April 19-20, 2005; the full conference convened in Mar del Plata, Argentina, April 21-24, 2005. Presenters at the NIDA sessions included Dr. Carlos Rios-Bedoya, Ponce School of Medicine, Puerto Rico; Dr. Edith Serfaty, Center of Epidemiological Research, Argentine National Academy of Sciences; and the following NIDA scientists: Drs. Frank Vocci, Ahmed M. Elkashef, Ivan Montoya, and Jag Khalsa (all of DPMCDA).
- NIDA supported the participation of 3 researchers in the Society of Neuroscientists of Africa Conference, in Cape Town, South Africa, April 20-22, 2005. Travel support was awarded to three presenters, Dr. Peter Kalivas, Medical University of South Carolina; Dr. Linda Porrino, Wake Forest University School of Medicine; and Dr. Anto Bonci, University of California, San Francisco.

IP Redesigns International Web Site

Grantee Honors

In Memoriam

The NIDA International Program has introduced a new web page that streamlines access to announcements about the Institute's activities in the international drug abuse research community. Sections focus on announcements, research training and exchange opportunities, research funding, and information and resources for researchers. Past issues of the new IP E-News Letter are archived on the site. Access the redesigned NIDA International Program web page at www.international.drugabuse.gov.

International Visitors

Professor Dr. Pavel Abraham, President of the Romanian Anti-Drug Agency visited NIDA on February 3, 2005. Accompanying Dr. Abraham was Raluca Golumbeanu, Political Officer at the Embassy of Romania in Washington, DC and Mr. Dan Gheorghita. Meeting with this group from NIDA were Dr. Steve Gust and Ms. Dale Weiss, IP. Dr. Abraham updated NIDA on the current work being done by the Romanian Anti-Drug Agency.

A group of visitors from several Asia-Pacific countries visited NIDA on February 17, 2005. The visitors included Dr. Syahrizal Syarif, Indonesia, Mr. Mohd Yunus Pathi, Malaysia, Mr. Dato' Zainuddin Bahari, Malaysia, Mr. Fadilan Kayong, Singapore and Mr. Tay Bian How, Sri Lanka. Meeting with the group from NIDA was Dr. Ahmed Elkashef, DPMCDA and Dr. Steven W. Gust, IP. The visitors discussed the accomplishments and goals of the Colombo Plan, an organization involved in drug abuse prevention in the Asian-Pacific area.

On February 24, 2005 a group of the visitors from the National Peace Foundation (NPF) came to NIDA to talk about the mission of the NPF and the drug treatment work that is being done by the organization in the Ural mountain region of Russia. Representing the NPF were Jeanne Smith, Sarah Harder, Marjorie Lightman and Corinne Gerwe.

Emran Razzaghi, M.D., M.P.H., Assistant Professor of Psychiatry at the Tehran University of Medical Sciences, Iran, visited NIDA on February 23, 2005. Dr. Razzaghi is a current 2004-5 World Fellow at Yale University. Dr. Razzaghi gave an interesting talk about the history and current state of drug addiction in Iran.

The Chairman of the Australian National Council on Drugs (ANCD), Major Brian Watters, visited NIDA on March 1, 2005. Accompanying Major Watters was Gino Vumbaco, Executive Officer of the ANCD. Major Watters and Mr. Vumbaco met with Drs. Steven Gust, IP, Frank Vocci, DPMCDA and Wilson Compton, DESPR during their visit.

The Honorable Marion Caspers-Merk, Drug Commissioner of the German Federal Government visited NIDA on March 29, 2005. Mrs. Ines Meyer, Mr. Werner Sipp, Mrs. Susanne Wackers, and Mr. Michael Mersmann of the Embassy of the Federal Republic of Germany accompanied Mrs. Caspers-Merk. Meeting with the visitors from Germany were Steve Gust and Dale Weiss, IP, Eve Reider, DESPR, and David McCann, DPMCDA. Also attending the meeting was Ms. Peggy Quinn, SAMSHA.

A group of demand reduction specialists from Haiti visited NIDA on April 5, 2005. Representing NIDA at this meeting were Liz Ginexi, Aria Crump and Dionne Jones, DESPR and Dale Weiss, IP.

On April 5, 2005 Dale Weiss, IP represented NIDA at a meeting that was held at the National Clearinghouse for Alcohol and Drug Addiction. The meeting was sponsored by the U.S. Department of State as part of the Voluntary Visitor Program for nine officers from the National Council Against Drug Addiction (CONADIC) of Mexico.

Participants in a U.S. Department of State sponsored International Visitor Leadership Program visited NIDA on April 8, 2005. All participants in the Program were from Western Hemisphere countries. Meeting with the group were Ana Anders, SPO, Jan Lipkin, PILB and Dale Weiss, IP. Countries represented included Bolivia, Chile, Colombia, Honduras, Mexico, Nicaragua, Peru and Venezuela.

Other International Activities

Dr. Wilson Compton, Director, DESPR, participated in a joint meeting of Dutch and U.S. demand reduction policy and research experts January 15-28, 2005 in The Netherlands.

Dr. Elizabeth Robertson, DESPR, participated in The Annual Campbell Collaboration Colloquium titled Supply and Demand for Evidence, from February 23 -25, 2005 in Lisbon, Portugal. The meeting included representatives from over 20 countries and

was hosted by the University of Lisbon.

Dr. David McCann, DPMCDA, served as a member of the U.S. delegation to the U.N. Commission on Narcotic Drugs (CND) meeting in Vienna, Austria from March 7 to 11, 2005. An ongoing discussion related to the possible rescheduling of buprenorphine at the international level (toward increased regulatory control) was the major reason for NIDA's participation. While the rescheduling of buprenorphine was not addressed at this year's meeting, the issue will be addressed at the 2006 CND meeting if the WHO Expert Committee on Drug Dependence (ECDD) recommends a change. The next WHO ECDD meeting has been tentatively scheduled for mid-October, 2005. Dr. McCann is serving as NIDA's point person to the HHS OD related to international drug scheduling issues and, along with representatives from FDA and SAMHSA, is providing input for HHS planning related to future ECDD and CND meetings.

A March 23, 2005 symposium entitled "New Medications for Smoking Cessation: Beyond NRT and Bupropion" was organized and chaired by Dr. David McCann. The symposium was part of the SRNT meeting in Prague. Four new medications under clinical evaluation for smoking cessation were reviewed and the latest available clinical data were presented. Dr. Tony George presented on selegiline (and MAO-B inhibitor), Dr. Bernard LeFoll presented on BP 897 (a D3 partial agonist), Dr. Steven Sands presented on varenicline (an alpha-4-beta-2 nicotine receptor partial agonist), and Dr. Raymond Niaura presented on rimonabant (a CB-1 receptor blocker). Dr. John Cryan (Novartis) served as the discussant, covering other biological targets (other receptors, enzymes and ion channels) that hold promise for future medications discovery and development efforts related to smoking cessation.

Dr. Ivan Montoya, DPMCDA, was invited to participate as a keynote speaker of the XXXII Annual Meeting of the Spanish Society of Drug and Alcohol (Sociodrogalcohol), in Ciudad Real, Spain.

Director's Report to the National Advisory Council on Drug Abuse - May, 2005

Meetings/Conferences

NIDA/OSPC organized a special research track held at the **PRIDE2005 World Drug & Violence Prevention Conference**, April 6-9, 2005 at the Cinergy Center, Cincinnati, Ohio. NIDA workshops include sessions on "Cigarette Smoking: What Every Community Can Do to Save Lives"; "Truth and Consequences of Marijuana Abuse"; and "Sniffing and Huffing: The Impact of Inhalant Abuse on Youth." Each year this conference provides a forum for some 5,000 attendees, hundreds of organizations - large and small, local, national, and international - that are fighting against drugs.

On March 15-16, 2005, the **Motivational Incentives for Enhanced Drug Abuse Recovery (MIEDAR) Blending Team** met in Chicago, Illinois. The MIEDAR Blending Team is part of the NIDA/SAMHSA-ATTC Blending Initiative, an interagency agreement encouraging the use of evidence-based treatment interventions by professionals in the drug abuse treatment field. "Blending Teams" are comprised of staff from CSAT's Addiction Technology Transfer Center (ATTC) Network and NIDA/CTN researchers. They work together to develop a strategic dissemination plan to introduce research findings for effective adoption within communities, such as trainings, self-study programs, workshops, and distance learning opportunities. The MIEDAR Blending Team is lead by Lonnetta Albright (Great Lakes ATTC) and is being coordinated by Denise Pintello (NIDA) and Karl White (SAMHSA). Team members include: NIDA/CTN: Scott Kellogg, John Hamilton, Therese Killeen and Nancy Petry; ATTC: Anne-Helene Skinstad, Amy Shanahan and Joseph Rosenfeld. The Blending Team discussed the MIEDAR protocol research results. Future efforts will initially focus on developing training and dissemination materials to promote awareness of the use of Motivational Incentives throughout the drug abuse field.

The **Native American and Alaska Native Workgroup** met January 24-25, 2005 at the Hyatt Regency in Bethesda, Maryland. Workgroup members provided updates on their current research and activities. In addition, workgroup members received updates from NIDA Divisions. Dr. Aria Crump provided an update from the Division of Epidemiology, Services and Prevention Research (DESPR), Dr. Paul Schnur provided an update from the Division of Basic Neuroscience and Behavioral Research (DBNBR), Dr. Joseph Frascella provided an update from the Division of Clinical Neuroscience, Development and Behavioral Treatment (DCNDBT) and Dr. Richard Hawks provided an update from the Division of Pharmacotherapy and Medical Consequences of Drug Abuse (DPMCDA). Following an update from Dr. Lula Beatty in the Special Populations Office, workgroup members reviewed and discussed the "Conducting Research with American Indians" Manuscript prepared by Drs. Bernard Segal and Jerry Stubben and organized by Dr. Sally Stevens who are all members of the workgroup. Dale Walker, M.D. gave an update on the One Sky Center and the group discussed additional workgroup activities.

On April 12-13, 2005, members of the **Asian American and Pacific Islander Workgroup** convened for a meeting at the Wyndham Grand Bay Coconut Grove in Miami, Florida. Members were provided with an update on the Special Populations Office from Lula Beatty, Ph.D. and an overview of the National Hispanic Science Network from Jose Szapocznik, Ph.D. and Yolanda Mancilla, Ph.D. Workgroup members, Tooru Nemoto, Ph.D., Rumi Price, Ph.D., and Frank Wong, Ph.D. presented the group with updates on their AAPI research.

On April 16, 2005 a day long Symposium **Prescription Drug Abuse: Science to Practice** was held at the American Society of Addiction Medicine's 36th Annual Medical-Scientific Conference, at the Hyatt Regency Hotel in Dallas, Texas. This

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Grantee Honors

In Memoriam

Symposium was co-sponsored by the National Institute on Drug Abuse/NIH, the Center for Substance Abuse Treatment/ SAMHSA, and the American Society of Addiction Medicine.

The 57th meeting of the **Community Epidemiology Work Group (CEWG)**, chaired by Moira O'Brien, DESPR, was held in Los Angeles, California, on January 26-28, 2005. The January 2005 CEWG meeting, in addition to CEWG area reports, included a panel session on natural history, long-term consequences, and treatment approaches for methamphetamine abuse; and a panel session which explored the potential of using the Internet as a tool for identifying and monitoring new drug abuse trends.

On April 28, 2005, Dr. Timothy P. Condon and Beverly Jackson represented NIDA at the **9th Annual PRISM Award Celebration** in Los Angeles. The PRISM Awards are sponsored by the Entertainment Industries Council (EIC), NIDA, and the Robert Wood Johnson Foundation. The PRISM's recognize the efforts of the entertainment industry to accurately depict drug, alcohol and tobacco addiction. PRISM's were awarded to Jamie Fox for *Performance in a Theatrical Feature Film, "Ray,"* with the movie also receiving a separate award; Katey Sagal for *Performance in a Comedy Series, "8 Simple Rules*; Ray Liotta for *Performance in a Drama Series Episode, "E.R.,"* with the series also receiving an award; Christine Lahti for *Performance In a Drama Storyline, "Jack and Bobby;"* and Justine Waddell for *Performance in a TV Movie or Miniseries, The Mystery of Natalie Wood*. The hit TV show *Desperate Housewives* was honored in the *TV Comedy Multi-Episode Storyline* category; *Lost* and *Queer As Folk* tied for *TV Drama Multi-Episode Storyline;* and *Dr. Phil* for *TV Talk Show Episode*. The 9th *Annual PRISM Awards* will air as a one-hour television special on the FX Network, Sunday, September 4, 2005 at 5:00 p.m.

NIDA co-sponsored a meeting on **Developing a Research Agenda to Improve the Impact of Tobacco Use Quitlines**. The meeting-a collaborative effort among NIDA, CDC, NCI, Health Canada, and the Canadian Tobacco Control Research Initiative-was organized by Drs. Beverly Pringle and Dionne Jones, of the Services Research Branch, DESPR. It was held on February 23-24, 2005, at the Rockville Doubletree Hotel and Conference Center.

NIDA participated in SAMHSA's Center for Substance Abuse Treatment's 2005 Joint Meeting on Adolescent Treatment, March 21-23, 2005, at the Omni Shoreham Hotel in Washington, DC. Dr. Nora Volkow, NIDA Director, gave a plenary talk entitled **Transdisciplinary Perspectives on Adolescent Drug Abuse**. Dr. Jack Stein, DESPR gave a presentation as part of a workshop on **Moving Adolescent Treatment to Evidenced-Based Practice**. Mr. Noble Jones, SRB/DESPR chaired a workshop on **Contingency Management for Adolescent Substance Abusers**. Dr. Melissa Racioppo, BITB/DCNBT, chaired a workshop on **Nicotine Addiction Interventions for Adolescents**. Dr. Jerry Flanzer, SRB/DESPR gave a presentation as part of a workshop on **Strength-Based Treatment: From Case Management to Family Therapy**. Drs. Racioppo and Pringle and Mr. Jones conducted a workshop on preparing research applications for submission to NIDA.

NIDA staff members participated in multiple activities at the **Biennial Meeting of the Society for Research in Child Development (SRCD)** meeting in Atlanta, April 7-10, 2005. Activities included two sessions on translational research, a session on issues and implications of real time data capture methodology for developmental research, a session on research priorities and the grant review process, and a session providing an NIH update on human subjects issues. Several of the sessions were collaborative efforts with other components of NIH. NIDA staff also presented a poster on child and adolescent research opportunities at NIDA, and met with conference attendees at the NIDA exhibit booth. Drs. Nicolette Borek, Jessica Campbell, Aria Crump, Kathy Etz, Teri Levitin, and Vince Smeriglio represented NIDA in these activities.

Drs. Jack Stein, Beverly Pringle, and Jerry Flanzer, DESPR, served on the planning team of the CASA Conference entitled, **Missed Opportunity: Substance Abuse in Primary Care**. The conference was headed by The National Center on Addiction and Substance Abuse (CASA) and was cosponsored by NIDA, the National Center on Primary Care (NCPC) at the Morehouse School of Medicine, and the Henry J. Kaiser Family Foundation. It was held at the Kaiser Foundation's Barbara Jordan Conference Center in Washington, DC, on April 21, 2005.

The **Steering Committee of the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS)** met at NIDA on April 4-6, 2005.

Recent CTN-Related Meetings

CTN National Steering Committee Meetings were held February 7-12, 2005, in San Francisco, CA. Dr. Nora Volkow attended via Video Teleconference. She outlined her goals for the CTN over the next five years, identified steps the CTN might take to meet increasing resource challenges, and identified additional opportunities for the CTN. In addition, the Steering Committee discussed new studies for initiation in 2005 and the status of ongoing efforts.

The CTN CTP Caucus and the PI Caucus met on February 7, 2005. Representatives from community treatment providers from all 17 Nodes attended.

The CTN Executive Committee met on February 8-9, 2005. The committee reviewed plans for prioritization of trials and protocols under development.

The CTN Portfolio Coordinating Committee (PCC) met on February 9, 2005, at the San Francisco meeting. During this meeting, they reviewed the progress of the CTN's Special Interest groups and reviewed the CTN's Common Assessment Battery.

The CTN Operations Coordinating Committee (OCC) met on February 9, 2005, to review the progress of all ongoing protocols and to discuss methods to improve retention and follow-up rates.

The CTN External Affairs Coordinating Committee (EACC) met on February 9, 2005, at the San Francisco meeting. During this meeting, they discussed Internal Dissemination as well as opportunities to promoting the CTN more actively as a research platform through possible studies on dissemination, health care linkages, and genetics.

The CTN Quality Assurance Subcommittee (QAS) met on February 10, 2005, to discuss priorities for the upcoming year and to reorganize to meet adjusted objectives, which include an increased emphasis on monitoring of training opportunities.

The following CTN Special Interest Groups (SIG) met during the San Francisco Steering Committee Meeting: Adolescent, Behavior Therapy, Buprenorphine, Co-Occurring Disorders, Nicotine, Pharmacotherapy, and Treatment Matching.

In collaboration with CSAT, a Buprenorphine Detox Training Session was held in San Francisco, CA on February 7, 2005. The session discussed the rationale for providing detoxification to opioid dependent patients, characterization of opiate withdrawal, goals of detoxification, results of the CTN studies, technical protocol implementation training, patient and treatment program staff perspectives, and overdose risk following detoxification.

A three-day CIDI (Composite International Diagnostic Interview) Train the Trainer program was held February 10-12, 2005, in San Francisco, CA.

The CTN Executive Committee met on April 5, 2005, in Cary, NC. The committee reviewed plans for CTN reorganization and ways of integrating the new coordination centers into CTN operation.

An Advanced QA Monitoring Meeting was held April 6-7, 2005, in Cary, North Carolina to establish a uniform quality monitoring standard and a common approach to monitoring across the CTN trial sites.

On March 21 — 23, 2005, Melissa W. Racioppo and Debra Grossman, DCNDBT, participated in a meeting of CSAT grantees and others involved in adolescent substance abuse treatment entitled, "2005 Joint Meeting on Adolescent Treatment Effectiveness". The meeting was held at the Omni Shoreham Hotel in Washington, D.C., and was co-sponsored by SAMHSA, NIDA, NIAAA, and SASATE (the Society for Adolescent Substance Abuse Treatment Effectiveness). Together with NIDA's Division of Epidemiology, Services, and Prevention Research, DCNDBT organized 2 symposia (addressing the treatment of adolescent substance abuse using contingency management, and addressing the treatment of adolescent smoking cessation), and a grant-writing workshop (along with Program Officials from NIAAA).

Dr. Timothy P. Condon, Deputy Director, NIDA, presented "National Institute on Drug Abuse: Progress, Priorities & Plans for the Future" at the American Psychiatric Association's Academic Consortium, April 12, 2005, in Washington, D.C.

Dr. Timothy P. Condon provided opening remarks at the SAMHSA/NIDA co-sponsored "Buprenorphine Summit 2005," on April 11-12, 2005, at SAMHSA Headquarters in Rockville, Maryland.

Dr. Timothy P. Condon presented "Methamphetamine: The Science of Addiction" to the Iowa State Legislature, March 29, 2005, in Des Moines, Iowa.

Dr. Timothy P. Condon presented "Methamphetamine: The Science of Addiction" to the New Hampshire State Legislature, March 24, 2005, in Manchester, New Hampshire.

Dr. Timothy P. Condon planned and participated in the "Medications Development Scientific Workgroup Meeting," on March 21-22, 2005, in Bethesda, Maryland. The creation of the Medications Development Workgroup is in response to recent recommendations of a subcommittee of the National Advisory Council on Drug Abuse.

Dr. Timothy P. Condon co-chaired the "Methamphetamine Research Workgroup Meeting," sponsored by NIDA and the University of California, Los Angeles, on March 9-10, 2005, in Los Angeles, California.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Science & Sentencing," to the Judicial Focus Group, Criminal Division, Cook County Circuit Court, February 28, 2005, in Chicago, Illinois.

Dr. Timothy P. Condon presented " The Science to Services Initiative: A NIDA Update" at the 41st National Advisory Council meeting of the Center for Substance Abuse Treatment (CSAT) on January 26, 2005, in Rockville, Maryland.

Dr. Timothy P. Condon presented "Research Priorities for the Study of Substance Abuse in the Elderly" at the 43rd Annual Meeting of the American College of Neuropsychopharmacology (ACNP), December 13, 2004, in San Juan, Puerto Rico.

Dr. Cindy Miner, Deputy Director, OSPC, chaired a workshop entitled "Sniffing and Huffing: The Impact of Inhalant Abuse on Youth" at the World Drug & Violence Prevention Conference April 8, 2005, in Cincinnati, Ohio.

Dr. Cindy Miner presented a talk on "Prescription Drug Abuse" at the American Insurance Association Conference on January 28, 2005 in Washington, D.C.

Dr. Gayathri Dowling, Deputy Branch Chief, Science Policy Branch, OSPC, participated in an Expert Panel Meeting of the Older Americans Substance Abuse and Mental Health Technical Assistance Center, sponsored by the Substance Abuse and Mental Health Services Administration, on March 29, 2005, in Rockville, Maryland. Through partnerships with state and federal agencies and community health care providers, the Center will serve as a national repository to disseminate information, training, and direct assistance in the prevention and early intervention of substance abuse and mental health problems.

Dr. Lula Beatty, SPO, participated in a faculty development seminar for the Office of Sponsored Research, Morgan State University, on March 3, 2005 in Baltimore, Maryland.

Dr. Lula Beatty presented a session on funding opportunities at a conference at Florida International University on February 24, 2005 in Miami, Florida.

Dr. Lula Beatty presented a session on drug abuse research at a faculty development seminar at Spelman College on February 25, 2005 in Atlanta, Georgia.

Drs. Lula Beatty and Kathy Etz made a presentation on Native American research and research development at the Department of the Interior on March 24, 2005 in Washington, DC.

Dr. Lula Beatty participated in the Lonnie E. Mitchell HBCU Substance conference on April 20-22, 2005.

Dr. Lula Beatty presented a session on funding opportunities at the NAADPC meeting on April 22, 2005 in Washington, DC.

Ana Anders, SPO, co-chaired the Asian American and Pacific Islander Researchers and Scholars Workgroup meeting on April 12 and 13, 2005 in Miami, FL.

Flair Lindsey, SPO, made a presentation on NIDA's research training opportunities at the Science, Technology and Research Training Conference on April 22, 2005 at the PG Community College in Largo, Maryland.

Dr. Betty Tai, Director, CCTN, presented "CTN as a research platform" at the UCLA Integrated Substance Abuse Program in Los Angeles on March 11, 2005.

Dr. Wilson Compton, Director, DESPR, chaired a symposium on Drug Abuse and Suicide at the American Academy of Addiction Psychiatry Meeting, December 12, 2004, San Juan, Puerto Rico.

Dr. Wilson Compton presented "Methamphetamine in the United States: Epidemiology and Neuroscience" at the Second Annual Methamphetamine Conference in Casper, Wyoming, January 5, 2005.

Dr. Wilson Compton presented "Opioid Prescription Abuse: National Institute on Drug Abuse Perspective" at the Opioid Risk Management Conference, March 29, 2005, Boston, Massachusetts.

Dr. Wilson Compton presented "The Impact of Research on the Care of Addicted Patients" and "Epidemiology of Prescription Drug Abuse" at the American Society of Addiction Medicine Meeting, April 14-17, 2005.

Drs. Jack Stein, Elizabeth Robertson, Beverly Pringle, and Tom Hilton, DESPR, hosted a meeting on May 4, 2005, in Bethesda, MD. The purpose of the meeting was to develop an action plan for stimulating community participation in NIDA-supported research.

Dr. Jessica Campbell, DESPR, presented "Translational Research at NIDA" and participated in a discussion hour "Priorities and Opportunities for Mental Health and Drug Abuse Translational Research," chaired by Drs. Vincent Smeriglio and Susan Swedo at the biennial Society for Research on Child Development meeting, Atlanta, GA on April 8, 2005.

Moira O'Brien, DESPR, organized a panel on Current and Emerging Drug Abuse Trends and gave a presentation titled, "Understanding Current and Emerging Drug Abuse Trends: The Role of the Community Epidemiology Work Group" for the CADCA National Leadership Form XV, January 13, 2005.

Drs. Naimah Weinberg, Kevin Conway, and Yonette Thomas, of the Epidemiology Research Branch, DESPR, convened a panel of outside experts to review NIDA's portfolio of grants on the genetic epidemiology of drug abuse on February 22, 2005. The panel reviewed progress in this area of research since a prior review in 1999 and the issuance of a program announcement in 2002. Key findings and developments as well as continued gaps and challenges were discussed, which will inform future programs and initiatives.

Dr. Kathy Etz, DESPR, chaired a session entitled Real Time Data Capture: Implications for Developmental Research at the biennial meeting of the Society for Research on Child Development, April 7, 2005, Atlanta, Georgia.

Drs. Elizabeth Robertson and Eve Reider hosted a two-day meeting on January 25 and 26, 2005 titled "Youth with Multiple Problem Behaviors: A Translational Perspective." The meeting was held at the Bethesda Marriott, Bethesda, Maryland.

On April 7, 2005 Dr. Aria Crump, DESPR, participated in a NIMH-organized panel held as a part of the Society for Research on Child Development's annual meeting. The panel was designed to inform investigators about current NIH research policy.

Dr. Aria Crump, DESPR, chaired a symposium entitled "Translating the Science of Human Development Into Preventive Interventions: Case Studies From the Field" at the Society for Research on Child Development Meeting on April 10, 2005 in Atlanta, GA.

Dr. William S. Cartwright conducted a seminar, Cost-effectiveness and Financing of Drug Abuse Treatment, March 11, 2005 at the Medical University of South Carolina.

On April 1, 2005, Melissa W. Racioppo presented a talk entitled, "Identifying - Effective' Treatments for Substance Abuse" at the annual meeting of the NIMH Outreach Partnership Program in Omaha, Nebraska.

Drs. Joseph Frascella and Laurence Stanford, DCNDBT, conducted a grant-writing workshop at the University of Hawaii-Manoa and also participated in the dedication of the University's new 3 Tesla imaging facility on February 23-25, 2005 in Honolulu, HI.

Dr. Joseph Frascella participated in the National Hispanic Science Network Steering Committee and Program Committee meeting held in Miami, Florida on March 3-5, 2005.

Dr. Joseph Frascella participated in a small meeting on the state-of-the field on methamphetamine research held in Los Angeles, California on March 9-11, 2005.

Dr. Joseph Frascella participated in the Asian American Pacific Islander Research Scholars Workgroup meeting held in Coconut Grove, Florida on March 11-14, 2005.

Dr. Harold Gordon, DCNDBT, participated by invitation to a Quality of Life Workshop sponsored by Self-Care & Health Program of the International Life Sciences Institute (ILSI) North America on February 16-17, 2005, in Washington, D.C. The purpose of the conference was to explore new approaches to understanding the role of sleep and sleep disorders in a person's well being.

Dr. Steven Grant, DNDBT, presented a talk on "Imaging the Addicted Brain: Treatment Implications " as part of the FDA CDER Seminar Series on March 16, 2005 in Rockville, MD.

Dr. Steven Grant represented NIDA at the annual meeting of the Cognitive Neuroscience Society held in New York City, held in Bethesda, MD on April 9-12, 2005.

Dr. Steven Grant represented NIDA at the biannual Motivational Neural Network Conference. The topic of the conference was "Regulation and Development of the Prefrontal Cortex: Basic and Clinical Perspectives". The conference was held in Clearwater, Florida on May 1-4, 2005.

Dr. Nicolette Borek, DCNDBT, participated as a scientific staff collaborator in the Network Meeting of the Adolescent Trials Network for HIV/AIDS Interventions in Arlington, VA, April 13-16, 2005. The ATN is a collaborative network cosponsored by NICHD, NIDA, NIMH, and NIAAA.

Dr. Nicolette Borek presented a talk on NIDA's research priorities at the Biennial meeting of the Society for Research in Child Development, Atlanta, April 7-10, 2005.

Debbie Grossman, DCNDBT, hosted a roundtable to discuss the Behavioral Therapies Development Program at the Society of Behavioral Medicine on April 14, 2005. The Behavioral Therapies Development Program is an ongoing program of research in the Behavioral and Integrative Treatment Branch to develop and test behavioral therapies for drug abuse and dependence.

On March 24-25 2005, Dr. Lisa Onken, DCNDBT, participated in an NIMH meeting on translational research in neurobiology and interpersonal processes.

Dr. Susan Volman, DBNBR, and Dr. Geoffrey Schoenbaum, University of Maryland School of Medicine, co-chaired a symposium on "Drug Addiction" at the Winter Conference on the Neurobiology of Learning and Memory, January 8, 2005, Park City, UT.

Drs. Cora Lee Wetherington, DBNBR and NIDA's Women & Gender Research Coordinator, and Lisa S. Onken, Chief, Behavioral and Integrative Treatment Branch, DCNDBT, gave an invited presentation, "Drug Abuse Treatment in Women," at the Center for Substance Abuse Treatment, March 17, 2005, Gaithersburg, MD.

Dr. Cora Lee Wetherington was co-author with Drs. Gary Swan and Taline Khroyan on a presentation, "Women, Tobacco, and Cancer: Recommendations for Research on Addiction," given by Dr. Swan at annual meeting of the Society for Research on Nicotine and Tobacco, March 23-25, 2005, Prague.

Dr. Minda Lynch, DBNBR, attended the Winter Conference on Brain Research in Breckenridge, CO during January 2005. She participated in a Federal Funding session with NINDS, NIMH and NIA, and also represented NIDA at an institutional exhibit in the exhibit/poster area of the conference.

Dr. Jonathan D. Pollock, DBNBR, in collaboration with Dr. Jane Peterson, Dr. Mark Moore, and John Hodges organized the NIH Planning Meeting for the Knockout Mouse Project that was held March 24-25, 2005.

Dr. David Shurtleff, Director, DBNBR, participated in the National Inhalants Awareness week press conference with ONDCP, SAMHSA and the National Inhalants Prevention Coalition (NIPC) held on March 17, 2005 at the National Press Club, Washington DC.

Dr. David Shurtleff held a workshop on "NIDA Programs and Funding Opportunities" at the Society for Neuroimmune Pharmacology (SNIP), in Clearwater FL on April 9,2005.

Dr. Paul Schnur, Deputy Director, DBNBR, attended a conference on "Extinction: The

Neural Mechanisms of Behavior Change" in Ponce, Puerto Rico, on February 2-6, 2005. The conference was supported partially by NIDA and NIMH.

Dr. Jerry Frankenheim (DBNBR) hosted an illustrated talk entitled Inhalant Abuse at the Rockville Jewish Community Center on April 13, 2005.

Dr. David Gorelick, IRP, organized and chaired a symposium on "Update on Treatment of Stimulant Abuse" at the 156th annual meeting of the American Psychiatric Association in New York, NY, May 6, 2004. Stories about this symposium, with quotes from Dr. Gorelick and other speakers, appeared in JAMA, 292, pp. 1807-1809, Oct. 20, 2004, and in ASAM [American Society of Addiction Medicine] News, 19, pp. 6-7, Winter 2005-2005.

On March 9, 2005, Dr. Frank Vocci, Director, DPMCDA, presented on medications for methamphetamine at the NIDA-UCLA Methamphetamine workshop in Los Angeles, CA.

Dr. Frank Vocci made several presentations to the International Society for Addiction Medicine meetings in Argentina. Dr. Vocci's talks were as follows: April 19: Buenos Aires: ISAM Satellite Symposium: Neurobiology of Addiction April 20: Buenos Aires: ISAM Satellite Symposium: Pharmacology of cannabinoids April 21: ISAM main Meeting in Mar Del Plata: Addiction is a Brain Disease April 21: ISAM in MDP: Pharmacology of cannabinoids.

Dr. Jag Khalsa, DPMCDA, presented a mini-symposium on Management of Hepatitis C Infection in Drug Abusers at the Annual Meeting of the American Society of Addiction Medicine, Dallas, TX, April 14-16, 2005. Drs. Diana Sylvestre of UCSF, Dr. Richard Garfien of UCSD, and Dr. Ramesh Ganju of Harvard covered epidemiological, basic and clinical issues including disease progression and neuropsychological complications and interventions. A brief summary of the symposium will be placed on NIDA's website.

Dr. Jag Khalsa co-chaired with Dr. Robert Donahoe a mini-symposium on Role of Drugs of Abuse in HIV/AIDS Progression at the Annual Meeting of the Society of NeuroImmune Pharmacology (SNIP), Clear Water, FL, April 5-10, 2005. Drs. David Vlahov and Aftab Ansari served as the discussants. Dr. Robert Muga from Spain and Dr. Maria Prinz from Amsterdam, The Netherlands, presented data on drug abuse and HIV disease from two different cohorts that have been followed for disease progression. A brief summary of the findings presented will be placed on NIDA's website.

Dr. Jag Khalsa along with other colleagues (Drs. Vocci, Montoya, and Elkashef) from DPMC delivered talks on the Medical Consequences of Cocaine and Marijuana at the International Society of Addiction Medicine, in Buenos Aires, Argentina, April 19-24, 2005. In addition, Dr. Khalsa and colleagues met with investigators from Buenos Aires and discussed future collaborations.

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Media and Education Activities

Press Releases

January 5, 2005 — **Brief Encounters Can Provide Motivation To Reduce or Stop Drug Abuse**
Research supported by NIDA, showed that meeting with an addiction peer counselor just once at the time of a routine doctor visit with a follow-up booster phone call can motivate abusers of cocaine and heroin to reduce their drug use.

January 10, 2005 — **NIDA NewScan #34**

- Abstaining From Marijuana Associated With Better Quality of Life
- Sight, Smell of Favorite Foods Are Related to Drug Craving
- Earning a Reward Elicits Greater Brain Activity Than Merely Receiving One
- Novel Compounds Reduce Cocaine Toxicity in Mice
- Studies Suggest Common Factors Responsible for Marijuana and Co-Occurring Drug Abuse
- Activity, Involvement Key to Adolescents Not Smoking
- Experimental Compound May Lead to New Anti-Addiction Medications
- Death Risk Rises for New Injection Drug Users
- Short-Term Treatments Benefit Women With Coexisting Substance Abuse and Post-Traumatic Stress Disorder
- Research Examines Patient Placement Criteria in Addiction Treatment

February 9, 2005 — **NIDA-Funded Studies Show Expanding HIV Screening is Cost Effective**.
Two multicenter research teams have independently determined through the development of computer models that routine screening for HIV in health care settings is as cost effective as screening for such other conditions as breast cancer and high blood pressure, and can provide important health and survival benefits. The studies also suggest that screening that leads to a diagnosis of HIV infection may further lower health care costs by preventing high-risk practices and decreasing virus transmission.

February 10, 2005 — **Research Identifies Proteins Crucial to Construction of Brain's Information Superhighway**.
Communication in the brain travels from one nerve cell to another through critical connections called synapses. These neuron-to-neuron junctions form early in brain development, and their construction was thought to be guided by the nerve cells themselves. Now, investigators supported by NIDA have discovered that cells called glia, known to provide support for neurons in the mature brain, also play a crucial role in formation of synapses during the surge of development following birth. This key insight into the process of normal synapse development may lead to improved treatment of conditions such as drug addiction and epilepsy, which are characterized in part by too many synapses.

March 9, 2005 — **NIDA NewsScan #35**

- Medication May Reduce Inhalant-Seeking Behavior in Rats
- Study Examines Rates of Injection Drug Use in Metropolitan Areas

- Formula Can Help Determine Number of Urban Men at Risk for Diseases Associated with Injection Drug Use, Sexual Practices
- Vouchers Help Methadone Patients Kick Cocaine Abuse
- Sex, Drug Use Increase Risk of Teen Depression, Suicide
- Men, Women Use Different Brain Regions in Making Decisions
- Computer Program May Detect Substance Abuse in Older Adults
- Dopamine Connection Seen in HIV Dementia
- Receptors May Be Key to Nerve Damage from Drug Abuse

Articles of Interest

January 24, 2005, *Washington Post*-"Inhalant Abuse on the Rise Among Children"-Interview with Nora D. Volkow, M.D.

Dr. Frank Vocci, DPMCDA, was interviewed by the following reporters on the following topics:
Ina Hunter on Ibogaine on February 15, 2005 for the Village Voice.
Maia Szalavitz on Amphetamines on March 1, 2005 for New Scientist.
Brian Vastag on Ibogaine on March 10, 2005 for JAMA.

Educational Activities

Heads Up: Real News About Drugs and Your Body. Through a renewed contract with Scholastic Inc., NIDA continued in 2005 with Year 3 of its aggressive outreach to middle school students and teachers with the *Heads Up* article inserts for use in the classroom. Magazines such as *Junior Scholastic, Science World*, and *Up Front* have carried articles on inhalant abuse since 2003 as part of the NIDA-Scholastic Inc. partnership. Each NIDA insert is distributed to nearly 2 million students nationwide, with a reach of nearly 7 million-and this occurs 5-6 times per school year. Year 3 inserts included a free-standing fold-out teaching poster, *The Teen Brain: Under Construction*, and articles on HIV and drug abuse; the latest Monitoring the Future findings, focusing on the health effects of abusing inhalants or prescription drugs; and the commonalities in the brain between obesity and drug addiction.

Responding to trends in inhalant abuse. In response to the continuing increasing trends in inhalant abuse among younger teens as noted in the latest *Monitoring the Future* survey, NIDA has enhanced public awareness this year through meetings, the Internet, and through the development and dissemination of science-based materials on inhalant abuse. In January, at CADCA's National Leadership Forum, NIDA emphasized the need for community attention to inhalants by convening a seminar, *Inhalant Abuse: An Increasing Problem in Youth*, with nationally known researchers and other experts in the field. In addition, in March, NIDA published a new *Community Drug Alert Bulletin* on Inhalants, providing a synopsis of some of the latest scientific findings on inhalants and inhalant abuse. Nearly 150,000 copies were distributed to RADAR centers, medical libraries, constituent groups, and exhibits. NIDA's *Research Report* on Inhalant Abuse, which details current research findings, also was updated. Most recently, as part of the *National Inhalants and Poisons Awareness Week* activities in March, NIDA's Dr. David Shurtleff, Director of the Division of Basic Neuroscience and Behavioral Research, joined ONDCP Director John P. Walters, and others in a 2-hour press conference at the National Press Club in Washington, DC.

NIDA once again participated in this year's **Brain Awareness Week** activities at the National Museum of Health and Medicine and Girl Scout Day at the National Air and Space Museum in Washington, D.C., on March 16 & 17, 2005. The Brain Awareness Week activities included middle school girls and boys and the Girl Scout Day activities included girls from elementary school. As in past years, NIDA played "Who Wants to be a NIDA Neuroscientist?" a game that was patterned after "Who Wants to be a Millionaire?" During the game, children have an opportunity to learn information about the brain and how drugs impact the brain and behavior. Each child is given a packet of NIDA publications and each winner of the game receives a certificate declaring them a "Neuroscientist for the Day."

Conferences/Exhibits

National Association of School Psychologists -- March 29-April 2, 2005

National Science Teachers Association National Convention -- March 31-April 3, 2005

PRIDE 2005 -- April 6-9, 2005

Grantee Honors

In Memoriam

Society for Research in Child Development -- April 7-10, 2005

American Alliance for Health, Physical Education, Recreation and Dance April 12-16, 2005

American Society of Addiction Medicine -- April 14-17, 2005

Lonnie E. Mitchell Historic Black Colleges and Universities Substance Abuse Conference -- April 19-22, 2005

National Conference on Tobacco and Health -- May 3-6, 2005

American Psychiatric Association -- May 21-26, 2005

American Psychological Society -- May 26-29, 2005

American Academy of Physician Assistants -- May 28-June 2, 2005

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Planned Meetings

The National Institute on Drug Abuse (NIDA) is presenting a research track at the **American Psychiatric Association's 158th Annual Meeting**, May 21-26, 2005 in Atlanta, Georgia, with some 22,000 conference attendees. The NIDA track includes sessions on increases in opioid analgesic abuse, scientific advances in the neurobiology of behavior, cannabis dependence treatment and the neurobiology of compulsive reward-seeking. This track will raise awareness of new and emerging issues in addiction and psychiatry and provide important information related to best practices and treatment strategies. A number of NIDA staff, including NIDA's Director, Dr. Nora Volkow, will participate in these sessions.

NIDA will host a two-day conference titled: **Smart Practice, Practical Science: Blending Clinical Treatment and Research** at the Sheraton Bal Harbour Hotel, Miami Beach, Florida on June 6-7, 2005. This conference will bring together clinicians and researchers to present and discuss scientific findings related to empirically supported treatments for drug abuse and addiction and their application to clinical practice. NIDA and SAMHSA/CSAT will also sponsor a one-day meeting designed for the National Association of State Alcohol and Drug Abuse Directors (NASADAD) titled: **Forging Federal-State Collaborations to Blend Research and Practice** to provide an update of Federal and state research-practice blending activities currently underway and planned.

On June 21, 2005, NIDA will hold a Grant Writing Workshop at the **2005 College on Problems of Drug Dependence (CPDD) Conference** in Orlando, Florida. Approximately 50 early-career scientists will participate in learning how to apply for NIH grants and the NIDA grant application process. Drs. Timothy P. Condon, Suman King, Cindy Miner, David Shurtleff, and Mark Swieter from NIDA, and Scott Lukas, McLean Hospital, Harvard Medical School, will present. Dr. Denise Pintello, OSPC, is coordinating and chairing this workshop. Drs. King and Pintello are also coordinating two additional research training activities, a NIDA Tutorials Workshop and a Training Mixer.

Drs. Minda Lynch, DBNBR, Larry Stanford, DCNDBT and Teri Levitin, OEA will be co-chairing a symposium at this year's Annual Meeting of the American Psychological Association in July 2005, entitled **Adolescent Brain Development: What Does it Have to do with Cognitive Processes?** Speakers will include Drs. Beatriz Luna, University of Pittsburgh Medical Center, Debbye Yurgelun-Todd, McLean Hospital, Jay Giedd, NIMH and Jim Bjork, NIAAA.

A committee of NIDA divisional representatives is working with Jane Smither (OSPC), to organize a NIDA-sponsored **Early Career Investigator Poster Session** at this year's American Psychological Association Annual Convention. The session will be held in conjunction with the APA Division 28 and 50 Social Hour and NIDA will support the attendance of approximately 50 poster participants who will be provided an opportunity to present their research to clinicians and researchers representing the membership of these APA Divisions. NIDA program staff involved in this initiative include Drs. Mayer Glantz, DESPR, Minda Lynch, David Shurtleff and Cora Lee Wetherington, DBNBR, Melissa Racioppo, DCNCBT, Mary Ellen Michel, CCTN, Lula Beatty, OSP, Teri Levitin, OEA, Kenzie Preston, IRP and Steve Oversby, DPMCDA.

Drs. Elizabeth Ginexi, DESPR and Minda Lynch, DBNBR, along with Drs. Michael Bardo, University of Kentucky and Steve Sussman, University of Southern California, are co-chairing a one-day satellite at this year's CPDD meeting in June 2005, Orlando, FL. This satellite, entitled **Translating Basic Research from Neural, Behavioral**

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and Social Sciences to Prevention: Challenges and Opportunities, is co-sponsored by NIDA and the Center for Drug Abuse Research Translation at the University of Kentucky, and will explore examples of barriers and challenges to a successful bi-directional translational process between basic research in behavior, cognition and neurobiology, and prevention research in drug abuse. Topics to be highlighted include: Executive/Cognitive Functions, Developmental Risk, Stress, Alternative Reinforcement, and Gene X Environment Interactions. The meeting will also include a poster session with contributions from Early Career Investigators.

The Services Research Branch, DESPR, will host a scientific meeting on the Role of Faith-Based Services in the Treatment of Drug Abuse on September 27, 2005, at the Marriott Bethesda North Hotel, Bethesda, MD.

The Behavioral and Integrative Treatment Branch, DCNDBT and DBNBR are partnering with NCI and many other NIH Institutes in a conference on E-Health to be held on June 9-10, 2005.

NIDA will host the second Health Disparities Conference, **"Bridging Science and Culture to Improve Drug Abuse Research in Minority Communities" at the Hyatt Regency in Atlanta, Georgia, October 24-26, 2005**. Conference highlights will include plenary sessions on genetic research, health disparities within rural communities, HIV/AIDS and the criminal justice system, and gender issues associated with drug abuse research. Participants will also have the opportunity to attend a poster session and smaller symposia on numerous drug abuse research concerns, including social, cognitive, behavioral, health and medical consequences as they relate to minority populations.

Dr. Jag Khalsa, DPMCDA, will present a mini-symposium on **Metabolic and Endocrine Disorders and Interventions in Drug Abusers Co-infected with HIV and HCV** at the XIII World Psychiatry Congress, in Cairo, Egypt, September 10-15, 2005. Speakers (Dr. Adrian Dobs of Johns Hopkins University, Dr. Tim Flanigan of Brown University, Dr. Charles Hinkin of UCLA, and Christine Wanke of Tufts) will present current research findings on the subject. A brief summary of the symposium will be placed on NIDA's website.

On June 17, 2005, just prior to the CPDD meeting in Orlando, NIDA DPMCDA and DBNBR will hold a consultants meeting entitled **Review and Evaluation of NIDA Targets for Potential NIH Roadmap Library Screening Efforts**. A series of 30-minute presentations will be given by NIDA-funded researchers whose findings suggest specific targets for potential library screening efforts within the NIH Roadmap-supported Molecular Libraries High Throughput Screening Centers. The potential targets under discussion will range from traditional receptors (such as the D-1 dopamine receptor) that are highly validated as targets for medications discovery to less traditional targets (such as protein scaffolds) that may yield useful research tools. A group of five consultants, with pharmaceutical and biotechnology company experience in target identification/validation and high-throughput screening assay development, will answer questions related to the perceived merits and readiness of each potential target for high-throughput screening and will be asked for specific recommendations regarding additional target validation and/or assay development efforts that may be desirable. The consultant recommendations will help NIDA to prepare NIDA-relevant targets for incorporation into the NIH Roadmap library screening effort. The meeting organizers are Drs. David McCann, Jane B. Acri and Frank Vocci, DPMCDA, and Drs. David Shurtleff, Paul Schnur, and Christine Colvis, DBNBR.

CTN Related Meetings

National CTN Steering Committee Meetings are planned for the following dates and locations: June 8-10, 2005, Miami, Florida, and October 24-28, 2005, Bethesda, MD.

The CTN Data and Safety Monitoring Board will meet July 21-22, 2005 in Rockville, Maryland. The group will review the new CTN0030 and continuing progress of the active CTN's protocols.

An invited symposium on special design challenges in multi-site trials involving behavioral interventions is scheduled for Tuesday, May 24, 2005, as part of the annual meeting of the Society for Clinical Trials in Portland, Oregon. Paul Wakim, Ph.D., CCTN senior statistician, is chairing the symposium. Planned speakers are: Daniel Feaster, University of Miami School of Medicine; Paula Schnurr, VA National Center for PTSD and Dartmouth Medical School; Rickey Carter, Medical University of South Carolina; and Ellen Hodnett, University of Toronto Faculty of Nursing. At that meeting, Janet Levy, Ph.D., and Paul Wakim, Ph.D., will also present a poster, titled:

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"The Selection of Population-average Versus Subject-specific Models for Analyzing Longitudinal Data from Clinical Trials of Treatments for Drug Addiction".

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Publications

NIDA Publications

National Survey Results on Drug Use — Overview of Key Findings 2004
NIH Pub. No.: 05-5726
This publication provides a concise review of the findings of the Monitoring the Future Study and comparison of data from previous years.

Problems of Drug Dependence 2004: Proceedings from the 66th Annual Scientific Meeting of the College on Problems of Drug Dependence
NIH Pub. No.: 05-5290
This publication is more than just a "proceedings" from a meeting-it is valued as one of the only research tools and references for scientists and other professionals in the drug abuse field. It is the most comprehensive gathering of scientific information on all aspects of substance abuse and is invaluable to researchers and other scientists.

Epidemiologic Trends in Drug Abuse — Community Epidemiology Work Group, Volume II — June 2004.
NIH Pub. No. 04-5365A
This report provides an in-depth analysis of the epidemiologic trends and special reports for a limited audience made up primarily of drug abuse researchers who utilize this volume to identify potential areas for further research.

Research Report Series: Heroin Abuse — Revised
NIH No.: 05-4165
This publication provides science-based information on the prevalence of heroin abuse, methods of use, short- and long-term effects of heroin abuse, and medical complications of chronic abuse. It also describes effective treatment for heroin addiction and lists resources for more information.

Research Report Series: Marijuana Abuse -- Revised
NIH No.: 05-3859
This publication discusses the consequences of marijuana use, the effects of using, and peripheral issues such as medical uses.

NIDA Notes

NIDA Notes Volume 19 Issue No. 5
NIH Pub. No.: 05-3478
In the Director's column, Dr. Nora Volkow discusses the increase in misuse and abuse of prescription medications by adolescents and adults. The lead article reports on two recent studies showing that the age of initiation and the pleasure of response to marijuana in adolescence foreshadow adult outcomes. This issue also reports on The National Survey on Drug Use and Health, which has found that inhalant abuse by teenagers is on the rise. In another story, NIDA-supported economists are offering drug treatment program administrators the comprehensive Drug Abuse Treatment Costs Analysis Program, which features a method to put dollar values on the full range of treatment resources. In the final research article, a recent NIDA study provides no confirmation for previous findings that MDMA (Ecstasy) abusers develop problems recalling words, but suggests that heavy use of the drug does cause persistent deficits in mental processing speed and problem solving. Research News covers a NIDA-sponsored conference on lipids, the messenger molecules crucial for the regulation and control of biological processes including those influencing the effects of drugs on cell function. The Bulletin Board reports on the eighth annual PRISM Awards, sponsored by NIDA in recognition of the entertainment industry's

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serious treatment of destructive social issues surrounding drug abuse in film and television. This feature also highlights the appointment of six new members to the National Advisory Council on Drug Abuse. The Tearoff article describes NIDA's latest Research Report on MDMA abuse, part of the continuing effort to provide science-based information to the public.

NIDA Notes Volume 19, Issue No. 6
NIH Pub. No.: 05-3748

The Director's Column addresses health disparities in minority populations compared with the White population, and introduces NIDA's Health Disparities Initiative, which is a three-pronged approach to understanding and researching these differences. The Initiative will expand support of training and career development programs for minority scientists, focus the research agenda to help researchers reach underrepresented populations and study responses to drugs and the consequences of drug abuse in these populations, and disseminate research results to the widest possible audience. The lead article highlights a pilot study on the use of topiramate to help cocaine-addicted outpatients remain abstinent from the drug. Currently used to treat seizure disorders, topiramate helped study participants stay off cocaine longer than control subjects; 60% of patients taking topiramate attained 3 or more weeks of continuous abstinence compared with 26% of those taking placebo. The researchers found that topiramate seems to change the brain's response to cocaine by indirectly influencing dopamine through two other neurotransmitter systems-GABA and glutamate. Additional studies are planned to further evaluate the efficacy of topiramate as a treatment for addiction.

Other research findings include:

- Contrary to previous assumptions, NIDA-funded scientists have found that it takes very little experience with cocaine to establish environmental associations that become powerful cues for cocaine relapse. After exposure to a 2-hour session of access to cocaine, rats continued seeking the drug when cued for up to a year after access had been extinguished. A similar experiment using sweetened condensed milk, a highly palatable food to rats, failed to produce similar long-term cravings.
- A review of the 2000 and 2001 National Household Surveys on Drug Abuse revealed that adolescent inhalant abuse was more likely in the presence of specific behaviors, such as stealing, fighting, or carrying a handgun. Based on the traits the researchers identified, they concluded that adolescents with inhalant abuse or dependence disorders comprise a subgroup of highly troubled youths with multiple vulnerabilities. Girls were just as likely to abuse inhalants as boys, a finding that contradicts most conventional patterns of drug abuse.

The Bulletin Board focuses on two researchers who received awards at the 2004 Society for Neuroscience conference. Dr. Antonello Bonci received the second annual Waletzky Memorial Award for Innovative research in Drug Abuse and Alcoholism for his work on the long-term changes in brain cells that underlie addictive behaviors. Dr. Rochelle Schwartz-Bloom received the annual Science Educator Award for her curriculum models that help high school students learn the biology and chemistry underlying drug addiction. The Tearoff presents results of the most recent Monitoring the Future survey.

CTN-Related Publications

During the months January-April, 2005, eight editions of the **CTN Bulletin Board** were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN.

A **patient recruitment brochure** was approved for CTN Protocol - HIV and HCV Intervention in Drug Treatment Settings (CTN-0017) and printed for distribution throughout the Network.

Other Publications

Sussman, S., Stacy, A.W., Johnson, C.A., Pentz, M.A. and Robertson, E. A Transdisciplinary Focus on Drug Abuse Prevention: An Introduction. Substance Use & Misuse, 39(10-12), pp. 1441-1456, 2004.

Martin, S. E. and White, H.R. Introduction to Still at Risk for Drug Abuse: Transitions, Risks, and Opportunities for Prevention of Drug Abuse during Emerging Adulthood

Journal of Drug Issues 35(2) pp. 229-234, 2005.

Sussman, S., Stacy, A.W., Johnson, C.A., Pentz, M.A. and Robertson, E. A Transdisciplinary Focus on Drug Abuse Prevention: An Introduction. Substance Use & Misuse, 39(10-12), pp. 1441-1456, 2004.

Vocci, F. and Elkashef, A. Pharmacotherapy and Other Treatments for Cocaine Abuse and Dependence. Curr Opin Psychiatry 18, pp. 265-270, 2005.

A special supplement to the journal, Addiction, Volume 100 reporting on the results of clinical studies of potential cocaine treatment medications undertaken under the Cocaine Rapid Efficacy Screening Trials (CREST) program of the Clinical Medical Branch, Division of Pharmacotherapies and Medical Consequences of Drug Abuse, NIDA was published in March 2005. The authors and articles contained are listed below:

Shoptaw, S., Watson, D.W., Reiber, C., Rawson, R.A., Montgomery, A., Majewska, D. and Ling, W. Randomized Controlled Pilot Trial of Cabergoline, Hydergine and Levodopa/ Carbidopa: Los Angeles Cocaine Rapid Efficacy and Safety Trial (CREST).

Leiderman, D.B., Shoptaw, S., Montgomery, A., Bloch, D.A., Elkashef, A., LoCastro, J. and Vocci, F. Cocaine Rapid Efficacy Screening Trial (Crest): A Paradigm for the Controlled Evaluation of Candidate Medications for Cocaine Dependence.

Berger, S.P., Winhusen, T.M., Somoza, E.C., Harrer, J.M., Mezinskis, J.P., Leiderman, D.B. Montgomery, M.A., Goldsmith, J., Bloch, D.A., Singal, B.M. and Elkashef, A. A Medication Screening Trial Evaluation of Reserpine, Gabapentin, and Lamotrigine Pharmacotherapy of Cocaine Dependence.

Winhusen, T.M., Somoza, E.C., Harrer, J.M., Mezinskis, J.P., Montgomery, M.A., Goldsmith, J. Coleman, F.S., Bloch, D.A., Leiderman, D.B., Singal, B.M., Berger, P. and Elkashef, A. A Placebo-Controlled Screening Trial Of Tiagabine, Sertraline, and Donepezil As Cocaine Dependence Treatments.

Reid, M.S., Casadonte, P. Baker, S., Sanfilipo, M., Braunstein, D., Hitzemann, R., Montgomery, M.A., Majewska, D., Robinson, J. and Rotrosen, J. A Placebo-Controlled Screening Trial of Olanzapine, Valproate, and Coenzyme Q10 / L-Carnitine for the Treatment of Cocaine Dependence.

Reid, M.S., Angrist, B., Baker, S., Woo, C., Schwartz, M., Montgomery, M.A., Majewska, D., Robinson, J. and Rotrosen, J. A Placebo-Controlled Screening Trial of Celecoxib for the Treatment of Cocaine Dependence.

Elkashef, A., Holmes, T.H., Bloch, D.A., Shoptaw, S., Kampman, K., Reid, M., Somoza, E., Ciraulo, D., Rotrosen, J., Leiderman, D., Montgomery, M.A. and Vocci, F. Retrospective Analyses of Pooled Data From Crest I and Crest II Trials.

Ciraulo, D.A., Knapp, C., Rotrosen, J., Sarid-Segal, O., Ciraulo, A.M., LoCastro, J., Greenblatt, D.J., Leiderman, D. Nefazodone Treatment of Cocaine Dependence With Comorbid Depressive Symptoms.

Kampman, K.M., Leiderman, D., Holmes, T., LoCastro, J., Bloch, D.A., Reid, M.S., Shoptaw, S., Montgomery, M.A., Winhusen, T.M., Somoza, E.C., Ciraulo, D.A. and Elkashef, A. Cocaine Rapid Efficacy Screening Trials (CREST), Lessons Learned.

Ciraulo, D.A., Sarid-Segal, O., Knapp, C.M., Ciraulo, A.M., LoCastro, J., Bloch, D.A., Efficacy Screening Trials of Paroxetine, Pentoxifylline, Riluzole, Pramipexole and Venlafaxine In Cocaine Dependence.

Reid, M.S., Angrist, B., Baker, S.A., O'Leary, S., Stone, J., Schwartz, M., Leiderman, D., Montgomery, M.A., Elkashef, A., Majewska, D., Robinson, J. and Rotrosen, J. A Placebo Controlled, Double-Blind Study Of Mecamylamine Treatment For Cocaine Dependence In Patients Enrolled In An Opiate Replacement Program.

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Staff Highlights

Dr. Timothy P. Condon, Deputy Director, NIDA, received the 2004 Presidential Rank Award for Meritorious Senior Professionals. Each year, the President recognizes and celebrates a small group of career Senior Executives with the Presidential Rank Award for exceptional long-term accomplishments. Winners of this prestigious award are strong leaders, professionals and scientists who achieve results and consistently demonstrate strength, integrity, industry and a relentless commitment to excellence in public service.

Dr. Jag Khalsa, Chief, Medical Consequences of Drug Abuse Branch, was awarded the Distinguished Service Award at the 11th Conference of the Society on NeuroImmune Pharmacology (SNIP), held in Clear Water, FL, April 6-10, 2005. The organization presented the award to Dr. Khalsa in recognition of his outstanding service and commitment to the mission of the Society.

Dr. Cora Lee Wetherington, DBNBR, has been selected as one of the recipients of the American Psychological Association (APA) Meritorious Research Service Commendation. This commendation was initiated by the APA Board of Scientific Affairs (BSA) to recognize outstanding contributions to psychological science through service within the federal government in program development and research facilitation. Dr. Wetherington is being honored for her leadership in the areas of research on women and gender and her contributions to bringing gender issues to the forefront of drug abuse research at NIDA and NIH. Dr. Wetherington will be honored formally at the December 2005 meeting of APA's Board of Directors and an announcement of the commendation will be printed in an upcoming issue of the APA Science Directorate's Psychological Science Agenda newsletter and on the Science Directorate web site.

Dr. Allison Chausmer, DBNBR, was invited to participate in the Author's Meeting for the 2006 Surgeon General's Report, "How Tobacco Causes Disease — The Biology and Behavioral Basis for Tobacco-Attributable Disease".

Dr. Allison Chausmer, DBNBR, was invited to participate in the Interagency Committee on Smoking and Health.

Dr. Nemeth-Coslett continues to serve as VP of Education for Executive Toastmasters. This year, she completed her Advanced Toastmasters Bronze (ATM-B) level, achieved level of Competent Leader (CL), and earned her second Competent Toastmasters (CTM) award.

Dr. Joseph Sanchez, Postdoctoral Fellow, Development and Plasticity Section, Cellular Neurobiology Research Branch, IRP, is the recipient of 2005 American Society for Neural Transplantation and Repair Travel Award for his abstract entitled "Mesencephalic Cell Line Development using SV40 T antigen Fragments T155c and T155g" which will be presented at the annual meeting in Clearwater, Florida, April 28, - May 2, 2005.

Dr. Joseph Sanchez is also the recipient of the Travel Award for the upcoming 9th International Conference on Neural Transplantation and Repair for his abstract entitled "Characterization of Cell Lines Generated from Rat Mesencephalon using T155C and T155G" to be held June 8-11, 2005, in Taipei, Taiwan.

Eric Zatman, Contract Review Administrator, OEA, Representing Executive Toastmasters, won local and area competitions in recent speech contests.

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Staff Changes

Gayathri (Gaya) Dowling, Ph.D. will serve as the Deputy Branch Chief for the Science Policy Branch (SPB) in the Office of Science Policy and Communications (OSPC). Gaya joined SPB in November, 2003, as a Health Scientist Administrator and has been instrumental in our work on Substance Abuse in Aging Populations, Prescription Drug Abuse, and a variety of other projects. Prior to coming to NIDA, she was a Program Director in the Office of Minority Health and Research at NINDS where she managed a portfolio of research and education programs promoting diversity in the neuroscience research workforce. She completed her doctorate in Neurobiology at the University of California, Davis, conducted research at the Parkinson's Institute studying the role of nicotinic acetylcholine receptors in muscle cell degeneration and neuroprotection, and subsequently served as a Scientific Review Administrator at the NIMH.

Dr. Beverly Pringle, DESPR, has been named Chief of the Services Research Branch.

Dr. Redonna Chandler, DESPR, has been named Deputy Chief of the Services Research Branch.

Dr. Diane Lawrence joined the Division of Basic Neuroscience and Behavioral Research (DBNBR) in the Functional Neuroscience Research Branch in April 2005. Dr. Lawrence received her Ph.D. from the University of Rochester Neuroscience Program, and was funded by a NIDA training grant to study opioid receptor expression on T cells, under the direction of Jean Bidlack. After a short postdoctoral fellowship at Temple University to gain additional experience with in vivo models of immunology and pharmacology, she shifted her focus back to neuroscience. She began a second postdoctoral fellowship at the Fox Chase Cancer Center, where she studied infectious diseases and immune responses within the brain using both transgenic mouse model systems and neurons in culture. For the past 5 years, Diane has been a research fellow in the NINDS intramural program, in the Laboratory of Molecular Medicine and Neuroscience. Her work is focused on viral infection of the brain, particularly HIV-1, and the role of inflammation in neuropathology. She has been working with a cell culture system of human neural progenitor cells that can be differentiated toward astrocyte or neuronal phenotypes.

Diane has also worked in the extramural division of NINDS, where she was on detail as a program director, an SRA, and did a rotation in Office of Communications and Public Liaison. More recently, Diane was on detail with CSR where she managed the Mitochondria and Neurodegeneration SEP for the NDBG study section in MDCN. In addition to research and administrative work, Diane founded a postdoctoral association at the Fox Chase Cancer Center in Philadelphia, and served as the Basic Science Co-Chair for the NIH Fellows Committee for one year (following in the footsteps of Christine Colvis and Joni Rutter). She also serves on the board of the Bethesda Chapter of the Association for Women in Science.

Dr. Shakeh Kaftarian, DESPR, was invited by the White House Office of National Drug Control Policy (ONDCP) to provide guidance to the Deputy Director of ONDCP and the Acting Administrator of the Drug Free Communities (DFC) program in the design of a national evaluation study of the DFC program, as well as the administration of the DFC grant program across partner organizations (i.e., SAMHSA/CSAP and CADCA Institute). During her six-month detail to ONDCP, Dr. Kaftarian assisted with designing a scientifically sound national cross-site evaluation project; revising and strengthening the theoretical and methodological components of the DFC program; promoting conceptually and technically complementary work across ONDCP and its partners; and improving the quality and delivery of technical assistance and training to DFC program grantees.

Dr. Khursheed Asghar, OEA, has retired after 32 years of government service of which over 24 years were served in NIDA. He served as an SRA, as a pharmacologist and program officer in DBNBR (formerly known as Division of Basic Research). He was Chief of the Extramural Policy and Project Review Branch, Office of Extramural Program Review and after its reorganization in 1990, he served as the Chief of Basic Sciences Review Branch in OEA until retiring on April 30, 2005. Prior to joining NIDA in 1981, he served as a pharmacologist in the FDA and as a Health Scientist Administrator in NINDS.

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Dr. James Alexander of the University of Utah received the 2004 American Psychological Association, Division 43 Distinguished Contribution to Family Psychology Award.

Dr. Richard Clayton, Senior Science Scholar at the University of Kentucky Center for Drug Abuse Research Translation received the 2005 Society for Prevention Research Presidential Award.

Dr. Hendree Jones, Associate Professor, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University in Baltimore, has received the 2005 American Psychological Association (APA) Distinguished Scientific Award for Early Career Contribution to Psychology in the area of Applied Psychology.

Dr. Kevin LaBar of Duke University's Center for Cognitive Neuroscience received the Young Investigator Award at the annual meeting of the Cognitive Neuroscience Society held in New ork City on April 9-12, 2005.

Dr. Mary Jane Rotheram-Borus, University of California, Los Angeles, has received the following honors in 2005: 1) the International Collaborative Prevention Research Award, presented by the Society for Prevention Research for outstanding contributions to advancing the field of prevention science; 2) appointed Chair, Childhood Psychiatry and Biobehavioral Sciences (Dena Bat-Yaacov Endowed Chair); and 3) is serving as Program Chair, Society for Prevention Research (SPR).

Dr. Shiela Strauss of the National Development Research Institute (NDRI) has been awarded a Fulbright Senior Specialist grant to present a series of workshops at Ben Gurion University of the Negev, Beersheva, Israel in May, 2005. She will discuss the findings of her NIDA-funded research concerning the US drug treatment system's response to hepatitis C, and explore the potential for future collaborative efforts to advance knowledge about and advocacy for HCV infected substance abusers in the Middle East.

On April 4, 2005, **Dr. Helene White** of Rutgers University received the Woman of Achievement Award from the New Jersey State Federation of Women's Clubs of GFWC.

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Richard Harrison, Chief of the Contracts Review Branch, Office of Extramural Affairs, National Institute on Drug Abuse, passed away on January 19, 2005. He joined NIDA in the early 1980s, transferring from the National Institute on Alcohol Abuse and Alcoholism where he administered a grants program for Native Americans. Harrison quickly rose to Chief of NIDA's Contracts Review Branch, maintaining a standard of excellence throughout his career. He is remembered as a capable and involved leader who worked tirelessly on behalf of NIDA's mission to bring the power of science to bear on the problems of drug abuse and addiction. Harrison received several NIDA Director's Awards of Merit for his accomplishments, including exemplary service as Contracts Review Branch Chief and work on NIDA's health disparities committee. He was a member of the equal employment opportunity advisory committee and also served on the first NIH Diversity Council.

Harrison was born in Pawhuska, Oklahoma on the Osage Indian Reservation. As a member of the Osage Tribal Nation, he made an annual pilgrimage to Fairfax, Oklahoma to participate in a 4-day tribal ceremony. While at NIH, he was active in recruiting Indian youth to consider careers in government by serving as interns. He was a key participant in the recent opening ceremonies of the National Museum of the American Indian, and loved to demonstrate his Indian dances and share his culture with children in area schools. In addition, Harrison volunteered his skills to Family Services of Montgomery County and the National Minority Organ/Tissue Transplant Education Program. He was a member of the American Indian Society of Washington, Americans for Indian Opportunity, American University/Washington Internships for Native Students, the Kiwanis Club of Rockville, Toastmasters International and the Bahai community of Montgomery County Northwest.

He is survived by his wife Joan; his son John; his brothers David, Henry and John; his stepchildren Deborah Ward, Sandra Meinberg, Linda Hazlewood, Patricia Haga, Michael and David Doyle; and 16 grandchildren.

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