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Research Findings

Basic Research

Dopamine Transport

The human dopamine transporter (hDAT) serves to regulate the ratio of extracellular to intracellular levels of the neurotransmitter dopamine. Inward transport or influx involves binding of synaptic dopamine at the surface of a neuron, transport across the cell membrane, and release to the intracellular plasma. The process is saturable, and is coupled with the inward transport of sodium and chloride ions. In the reverse or efflux direction, dopamine or related monoamines can be released to the outside of the cell. For kinetic analysis of influx and efflux, useful models of the transporter have proposed an "outward-facing" DAT conformation(s), and an "inward-facing" conformation(s) which would allow external or internal binding of ligands, respectively. One feature of these models is that they might operate in a gated fashion, alternately providing binding sites at the extracellular side of the membrane while blocking the intracellular side, and vice versa. It is presently not known whether the same set of amino acid residues control such transporter conformations of the DAT in both directions, and mutational studies are being extensively carried out to identify the critical residues of dopamine and drugs of abuse. Transport and the DAT are of considerable significance in drug abuse research because monoamines such as amphetamine can be transported, the neurotoxic cation MPP+ can be internalized by transport, and cocaine is known to block or inhibit the uptake of dopamine, by binding to the DAT at one or more sites. Dr. Ulrik Gether and collaborators have previously identified an endogenous high affinity zinc binding site on the DAT which involves the close association in space of histidine at position 193 (extracellular loop 2), histidine 375 (transmembrane helix 7), and glutamate 396 (extracellular loop 4, top of transmembrane helix 8). This zinc binding site, which is largely extracellular, has been shown to act as a noncompetitive inhibitor of dopamine uptake at micromolar zinc concentrations. As an extension of this work, Dr. Gether's research group has now reported that when the intracellular loop 3 residue tyrosine 355 was mutated to alanine, dopamine uptake velocity (Vmax) was reduced to less than 1% of the DAT wild type velocity, and produced a twenty fold increase in the inhibition constant Ki for dopamine binding, all in the absence of zinc. In the presence of ten micromolar zinc, the velocity of uptake was 75% restored. This work was done with COS-1 cells transiently expressing the hDAT. Double mutations, such as mutating both histidine 335 and positions 193, 375, or 396, were not effective in promoting transport of dopamine. The authors have separately shown that the DAT mutated at position 355 appeared to be functional, in that it could be tagged with green fluorescent protein, expressed in HEK-293 cells, and visualized at the cell surface, and then internalized by activating a protein kinase. It has also been possible to show that the binding of cocaine (which is not transported) was reduced over one hundred fold by the single mutation at position 355, in the absence of zinc, and this reduction was partially reversed in the presence of zinc. The authors have suggested a model in which histidine 355 is needed to stabilize conformations permitting inward transport, with zinc influencing the equilibrium distribution of these conformations. Loland, C.J., Norregaard, L., Litman, T., and Gether, U. Proceedings of the National Academy of Sciences, 99(3), pp. 1683-1688, 2002.

Crystal Structure of Biphalin - Multireceptor Opioid Peptide

The opioid system plays the most important role in pain signal modulation. This system combines transmembrane G-protein coupled receptors, and their endogenous ligands and opioid peptides released by neurocells. It is widely accepted that there are at least three opioid receptor types, μ, λ, and κ. All opioid receptors have binding sites for benzomorphan alkaloids. Extensive structure-activity studies have shown that recognition of benzomorphan tyramine moiety is a common feature of all opioid receptors. The same tyramine moiety is a part of N-terminal tyrosine, the

active site of endogenous opioid peptides. Large numbers of endogenous opioid peptides, which have been identified, could be divided into groups represented by the endomorphins (large peptide with preference to μ), enkephlins (with affinity with both μ and γ), dynorphins (with selectivity to K), and endomorphins (with selectivity to μ). Opioid analgesic drugs, like morphine, activate opioid receptors that initiate a cascade of events, which results in blocking the pain signal. However, the opioid system is involved in a number of homeostatic neurological and immunological functions. As a result, activation of the opioid system results in a number of side effects, including respiratory depression and dependency. Therefore, one of the most common ways of searching for new opioid analgesic drugs is developing the compounds that have the highest possible selectivity to the receptor and the least unwanted side effect(s). Nevertheless, all opioid receptors are involved in pain transmission modulation. Therefore, the contradictory approach of opioid analgesic development is to search for drugs with affinities to the very broad spectrum of receptors modulating the pain signals. The discovery of biphalin is the best example of the success of using this type of approach. This peptide expresses high affinity to all three opioid receptor types, with some preference for μ receptors. When administered directly into the brain, it has been shown to be more potent than morphine and etorphine at eliciting antinociception (pain relief). Currently biphalin is under intensive preclinical studies. Benzomorphan alkaloid analogues that express different receptor activity, as agonist or antagonist, all possess tyramine moiety in common freeze conformation. This may suggest that opioid peptides, during interaction with receptors, also adopt respective conformation of the tyramine part of N-terminal tyrosine. The presence of other functional groups in opioid peptide analogue and possibility of adopting specific topographical conformation(s) by these groups, determine receptor selectivity and potency. Topographical requirements of different opioid receptors are different even for the same group. Biphalin expresses high affinity to all opioid receptor types. This means that biphalin (i) possesses groups which guarantee high affinity to all types of opioid receptors, (ii) does not possess groups which could negatively interfere with particular receptor subtypes, and (iii) has a peptide chain that is flexible enough to adopt topographical requirements of all opioid receptor types. Flippen-Anderson, J.L., Deschamps, J.R., George, C., Hruby, V.J., Misicka, A., and Lipkowski, A.W. Journal of Peptide Research, 59, pp. 123-133, 2002.

Epileptiform Events in CA3 Hippocampus Depressed by Activation of the Opioid-Receptor-like-1 Receptor

The CA3 hippocampal region is important in the generation of hippocampal seizures. The opioid-receptor-like-1 (ORL-1) shares a high sequence homology with opioid receptors and is highly expressed in rat hippocampus. Activation of the receptor robustly depressed spontaneous epileptiform bursting without desensitization, and this was reversed by application of the receptor antagonist. This depressive action is consistent with the general inhibitory nature that occurs as a result of the activation of the ORL-1 receptor as it reduces the spontaneous miniature excitatory post synaptic currents (EPSCs) as well as electro-stimulation induced EPSCs. These observations also indicate that both pre- and post-synaptic mechanisms are involved in the depressive effect of epileptiform activity in CA3. This is interesting as it was thought that in CA1, CA3 and dentate, the ORL-1 receptor had inhibitory postsynaptic actions and seemed to lack the disinhibitory actions. Two membrane currents (channels) activated by the ORL-1 receptor agonist nociceptin were found to mediate the depressive effect of this drug on the epileptiform activity. The relation of the cell membrane outward potassium current (the M-current activated by nociceptin) to the CA3 epileptiform activity is confirmed by two observations. Similar to the effect of nociceptin, activation of the M-channel (by the channel activator retigabine) reduces epileptiform bursting. Blockade of this outward current (with channel blocker Linopirdine) increased the duration of CA3 epileptiform bursting. A cellular membrane inward rectifier potassium current (and therefore the channel, activated by nociceptin) was also identified. Blockade of the inward current (by adding Ba++ to the superfusion solution), while leaving the M-current intact, diminished the depressive effect of nociceptin on the spontaneous epileptiform bursting. Madamba, S.G., Schweitzer, P., and Siggins, G.R. J Neurophysiol, 82(4), pp. 1776-1785, 2001.

Ultrastructural Immunocytochemical Localization of the Dopamine D2 Receptor and Tyrosine Hydroxylase in the Rat Ventral Pallidum

The mesopallidal dopamine system plays a role in locomotor activity and reward. To understand the potential contribution of the dopamine D2 receptor (D2R) to the action of dopamine in the ventral pallidum (VP), investigators used electron microscopic immunocytochemistry to examine the cellular and subcellular localization of an antipeptide antiserum against the D2R in both ventromedial and dorsolateral VP compartments. In each region the majority of the total D2R-labeled profiles (n = 1,132) were axon terminals (55%) and small unmyelinated axons (27%). These terminals were often apposed to other axon terminals or dendrites and formed almost exclusively symmetric, inhibitory-type axodendritic synapses. Immunogold D2R labeling in axon terminals was seen on the plasmalemma and membranes of nearby synaptic vesicles. In ventral pallidal sections processed for dual detection of D2R peptide and the catecholamine-synthesizing enzyme tyrosine hydroxylase (TH), D2R labeling was detected in a few axons and axon terminals containing TH immunoreactivity as well as in axons contacted by TH-labeled terminals. In most cases,

however, the D2R-labeled profiles were located at a distance from small axons and terminals containing TH. The results provide the first ultrastructural evidence that D2Rs in the two VP subterritories are strategically located for primary involvement in modulation of the presynaptic release of nondopaminergic inhibitory transmitters. They also suggest that in this region the presynaptic D2 receptors are 1) minimally involved in autoregulation of dopaminergic transmission, and 2) differentially activated by dopamine, depending in part on levels and distance from release sites. Mengual, E., and Pickel, V.M., Synapse, 43, pp. 151-162, 2002.

Impaired Prohormone Convertases in Cpe(fat)/Cpe(fat) Mice

A spontaneous point mutation in the coding region of the carboxypeptidase E (CPE) gene results in a loss of CPE activity that correlates with the development of late onset obesity. Examination of the level of neuropeptides in these mice showed a decrease in mature bioactive peptides as a result of a decrease in both carboxypeptidase and prohormone convertase activities. A defect in CPE is not expected to affect endoproteolytic processing. Drs. Berman and Devi and their research team at New York University have addressed the mechanism of this unexpected finding by directly examining the expression of the major precursor processing endoproteases, prohormone convertases PC1 and PC2 in Cpe(fat) mice. They found that the levels of PC1 and PC2 are differentially altered in a number of brain regions and in the pituitary. Since these enzymes have been implicated in the generation of neuroendocrine peptides (dynorphin A-17, beta-endorphin, and alpha-melanocyte-stimulating hormone) involved in the control of feeding behavior and body weight, they compared the levels of these peptides in Cpe(fat) mutant and wild type mice. They found a marked increase in the level of dynorphin A-17, a decrease in the level of alpha-melanocyte-stimulating hormone, and an alteration in the level of C-terminally processed beta-endorphin in Cpe(fat) mice. These results suggest that the impairment in the level of these and other peptides involved in body weight regulation is mainly due to an alteration in carboxypeptidase and prohormone convertase activities and that this may lead to the development of obesity in mice. Berman, Y., Mzhavia, N., Polonskaia, A., and Devi, L.A.. Impaired Prohormone Convertases in Cpe(fat)/Cpe(fat) Mice. J Biol Chem, 276(2), pp. 1466-1473, Jan 12, 2001.

Possible Role of Basal μ Opioid Receptor Signaling in Narcotic Dependence

The μ opioid receptor (MOR) displays spontaneous agonist-independent (basal) G protein coupling *in vitro*. To determine whether basal MOR signaling contributes to narcotic dependence, antagonists were tested for intrinsic effects on basal MOR signaling *in vitro* and *in vivo*, before and after morphine pretreatment. Intrinsic effects of MOR ligands were tested by measuring GTPγgS binding to cell membranes and cAMP levels in intact cells. β-CNA, C-CAM, BNTX, and nalmefene were identified as inverse agonists (suppressing basal MOR signaling). Naloxone and naltrexone were neutral antagonists (not affecting basal signaling) in untreated cells, whereas inverse agonistic effects became apparent only after morphine pretreatment. In contrast, 6α- and 6β-naltrexol and -naloxol, and 6β-naltrexamine were neutral antagonists regardless of morphine pretreatment. In an acute and chronic mouse model of morphine-induced dependence, 6β-naltrexol caused significantly reduced withdrawal jumping compared to naloxone and naltrexone, at doses effective in blocking morphine antinociception. This supports the hypothesis that naloxone-induced withdrawal symptoms result at least in part from suppression of basal signaling activity of MOR in morphine-dependent animals. Neutral antagonists have promise in treatment of narcotic addiction. Wang, D., Raehal, K.M., Bilsky, E.J. and Sadée, W. Inverse Agonists and Neutral Antagonists at μ Opioid Receptor (MOR): Possible Role of Basal Receptor Signaling in Narcotic Dependence J. of Neurochem., 77(6), pp. 1590-1600, 2001.

Neural Systems involving Cannabinoids: Focusing on the CB1 Receptors

Current dogma focuses on CB1 as the main cannabinoid receptor in the brain and CB2 as the main cannabinoid receptor in the periphery. Although microglia are brain cells, their systems are much different from those of nerve cells and considered to have actions commensurate with those systems of the macrophages of the peripheral immune cells. Herein, the authors have described a cannabinoid system in microglia more similar to that of nerve cells involving the CB1 receptor system. However, in these microglia, they utilized stimulation by lipopolysaccharide (LPS) to study the actions, an activator often used to modulate peripheral lymph cell systems. Activated brain microglial cells release inflammatory mediators such as nitric oxide (NO) that may play important roles in central nervous system antibacterial, antiviral, and antitumor activities. However, excessive release of these factors has been postulated to elicit immune-mediated neurodegenerative inflammatory processes and to cause brain injury. Recent studies using the rat animal model indicate that select cannabinoids may modulate production of these inflammatory factors. Treatment of neonatal rat brain cortical microglial cells with the cannabinoid paired enantiomers CP55940 and CP56667 resulted in a stereoselective differential effect on inducible NO production. The analog CP55940 exerted a dose-dependent inhibition of interferon gamma (IFN gamma)/bacterial lipopolysaccharide (LPS)-inducible NO production which was significantly greater than that exerted by CP56667. Pretreatment of microglial cells with the CB1 cannabinoid receptor-selective antagonist SR141716A reversed this CP55940-mediated inhibition. MRT-PCR demonstrated the presence of CB1 receptor mRNA within microglial cells consistent with the presence of CB1

receptors. Collectively, these results indicate that the cannabinoid analog CP55940 selectively inhibits inducible NO production by microglial cells and that this inhibition is effected, at least in part, through the CB1 receptor. Cabral, G.A., Harmon, K.N., and Carlisle, S.J. Cannabinoid-Mediated Inhibition of Inducible Nitric Oxide Production by Rat Microglial Cells: Evidence for CB1 Receptor Participation. Adv. Exper. Med. Biol., 493, pp. 207-214, 2001.

Peripheral Systems Involving Cannabinoids: Focusing on the CB1/CB2 Receptors in Lymphocytes

Although studies have shown that CB2 cannabinoid receptors are more abundant in immune cells than are CB1 receptors, both are increased/decreased by different classes of activators when immune cells are stimulated to proliferate and differentiate into different types of mature lymphocytes. Thus, it appears that cannabinoid receptors are playing unique, but different roles in the presence of different antigens. The following two studies report how each type of cannabinoid receptor is down-regulated under different conditions by particular antigens. In the first study, cannabinoid receptor 2 (CB2) was identified as the most abundant cannabinoid receptor subtype in the immune system. Bacterial lipopolysaccharide (LPS) is a potent stimulant of B cells, inducing proliferation and differentiation into antibody secreting cells. It has been reported that CB2 receptor expression is upregulated during human, tonsillar B cell activation through CD40. It was of interest to investigate the expression of CB2 mRNA using another B cell activator, LPS. Using northern blot analysis, they measured CB2 mRNA levels in murine splenocytes and enriched B cells. Results indicated that the 4.0 kb CB2 transcript was 2 fold higher in abundance in murine B cells than in whole splenocyte preparations. This observation confirmed data from others and from their previous RT-PCR studies that the expression of CB2 mRNA is more abundant in B cells. Upon LPS stimulation, CB2 transcripts were decreased 46% and 42% at 4 hours and 24 hours, respectively, when compared to unstimulated populations. An examination by flow cytometry of the CD69, early activation marker, on splenocytes, showed that the majority of the B cells were activated at 24 hrs. Thus, these results suggested that LPS stimulation of murine B cells caused a decrease in CB2 mRNA expression in contrast to the increase observed following human B cell stimulation through CD40. Lee, S.F., Newton, C., Widen, R., Friedman, H., and Klein, T.W. Down-regulation of Cannabinoid Receptor 2 (CB2) Messenger RNA Expression during *in vitro* Stimulation of Murine Splenocytes with Polysaccharide. Adv. Exper. Med. Biol., 493, pp. 223-228, 2001.

The second study showed significant evidence that cannabinoids have the ability to exert immunomodulatory effects. The identification of cannabinoid receptors in immune tissues has therefore led to questions about whether these immunomodulatory effects occur via these cannabinoid receptors. The cannabinoid receptor 1 (CB1), although expressed primarily in the brain, is also expressed in lower amounts in peripheral tissues. Of interest is the fact that CB1 is expressed in immune tissues such as spleen, albeit at lower levels than the peripheral cannabinoid receptor, CB2. To examine the function of CB1 in immune cells, activation experiments were performed using different stimuli e.g., anti-CD3, phorbol 12-myristate 13-acetate (PMA)/Ionomycin (Io), and PMA/Io + IL-2. Whole spleen cells were cultured in the presence of different stimuli for 0, 2, 4, and 24 hours, harvested at each time point, RNA isolated, and RT-PCR performed. FACS analysis was also performed using CD69 (an early activation marker) to determine whether cells were actually being activated. Results from anti-CD3 stimulation indicated a decrease in CB1 mRNA expression following activation. CB1 mRNA expression in murine splenocytes that were stimulated with PMA/Io in the presence or absence of IL-2 was also modulated. Expression of the message was enhanced upon stimulation with PMA/Io and PMA/Io + IL-2, however, stimulation with PMA/Io + IL-2 led to a stronger increase within 2 to 4 hours with CB1 returning to at or below baseline levels by 24 hours. Expression of CD69 was detected in all stimulated samples thereby indicating that the splenocytes were becoming activated. In summary, anti-CD3 stimulation appeared to decrease CB1 mRNA expression while PMA/Io + IL-2 stimulation significantly increased CB1 mRNA expression. These results demonstrate that the expression of CB1 mRNA is modulated upon cellular activation and that this modulation is dependent on the stimulus that is used. Noe, S.N., Newton, C., Widen, R., Friedman, H., and Klein, T.W. Modulation of CB1 mRNA Upon Activation of Murine Splenocytes Adv. Exper. Med. Biol. 493, pp. 215-221, 2001.

Functional Phenotypic Switch of RVM Neurons Provides a Novel Mechanism of Inflammatory Pain

NIDA-grantee Dr. Ronald Dubner of the University of Maryland and his colleagues examined N-methyl-D-aspartate (NMDA) receptor gene expression and neuronal activity in the rostral ventromedial medulla (RVM), an important area in the pain modulatory circuitry, after hindpaw inflammation in rats. Reverse transcription polymerase chain reaction analysis showed that there was an upregulation of mRNA encoding NMDA receptor subunits in the RVM after inflammation that lasted for up to 7 days. Electrophysiological studies demonstrated that this increased NMDA-gene expression correlated with the activation of RVM of cells that are normally not active during pain states. This functional phenotypic switch of RVM neurons appears to provide a novel mechanism underlying inflammatory pain states. Miki, K., Zhou, Q.Q., Guo, W., Guan, Y., Terayama, R., Dubner, R. and , Ren, K. Changes in Gene Expression and Neuronal Phenotype in Brain Stem Pain Modulatory Circuitry after Inflammation. J Neurophysiol., 87(2), pp. 750-

760, Feb 2002.

Regulation of Opioid Receptor Trafficking and Morphine Tolerance by Receptor Oligomerization

Opiates such as morphine, can be and are used as analgesics. However, treatment of chronic pain means long-term use and this can lead to tolerance and even dependence. While morphine acts by binding to the mu opioid receptor, it does not induce desensitization and endocytosis. These investigators looked at the effect of a mu opioid receptor agonist, DAMGO, on endocytosis of the mu-opioid receptor itself and consequently the effect of DAMGO on tolerance. What they observed was that HEK 293 cells treated with a saturating concentration of DAMGO show robust endocytosis of the mu opioid receptors. HEK 293 cells treated with morphine at the same concentration show that the receptors generally have not been internalized. Those cells that are treated simultaneously with morphine and a sub-saturating dose of DAMGO show endocytosis of the mu opioid receptor like that seen with a saturating dose of DAMGO alone. DAMGO and morphine have a similar affinity for the mu-opioid receptor. If the mu opioid receptors in a cell are independent of one another (monomers), in the last scenario one would expect that the saturating dose of morphine would cause a morphine-like response. Instead, a DAMGO-like response was observed. That is, many of the mu opioid receptors were internalized. Therefore, the investigators suspect that the activated receptors are not monomeric, but instead form oligomeric complexes. In order to test the hypothesis that endocytosis of the mu opioid receptor delays tolerance, these investigators examined the effect of DAMGO, morphine and co-administration of both drugs on the development of tolerance in an animal model. In their *in vivo* model, they found that some of the mu opioid receptors of lamina II of the spinal cord had moved to intracellular compartments in response to sub-antinociceptive levels of DAMGO administered twice daily to animals receiving nociceptive levels of morphine. The presence of these receptors in intracellular compartments suggests endocytosis of those receptors. Furthermore, these animals did not develop tolerance to morphine during the seven days of the experiment. This is in contrast to tolerance developed within four days in the animals receiving morphine alone. The precise mechanism by which this response is elicited is unclear. Nonetheless, these results have important implications for the treatment of chronic pain and suggest that the development of tolerance to morphine can be delayed by co-administration of drugs that promote endocytosis. He, L., Fong, J., von Zastrow, M. and Whistler, J.L. Cell,108, pp. 271-282, January 25, 2002.

Mutation of Drosophila Homer Disrupts Control of Locomotor Activity and Behavioral Plasticity

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. One class of receptors activated by glutamate is the metabotropic Class I glutamate receptors. This class consists of mGluR1 and mGluR5 glutamate receptors. These receptors are coupled to phospholipase C. Activation of these receptors causes the hydrolysis of phosphoinositides to produce diacylglycerol, an activator of protein kinase c and inositol-3-phosphate (IP3), a molecule that releases intracellular calcium stores. Research has shown that knockout of mGluR5 or pharmacological blockade of mGluR5 blocks both the reinforcing and locomotor stimulant effects of cocaine without affecting food reward. In related work NIDA grantee Dr. Paul Worley has shown that homer proteins play an important role in regulating the function of mGluR1 and mGluR5. Homer proteins act as scaffolding proteins to couple the mGluR5 receptor to inositol-3-phosphate receptor. By regulating the coupling of the mGluR5 receptor to the IP3 receptor, homer may modulate the amount of intracellular calcium released. In addition, homer proteins bind to shank, a post synaptic protein associated with the NMDA glutamate receptors. Shank has been shown to regulate dendritic morphology. The changes in dendritic morphology are dependent on shank forming a complex with homer. This result suggests that homer may play an important role in regulating synaptic plasticity at glutamatergic synapses. To test the role of homer in synaptic and behavioral plasticity, Dr. Worley and colleagues isolated and characterized the gene for homer in drosophila. As in mammals, the drosophila homer protein is localized to dendrites and the endoplasmic reticulum. The drosophila mutation, lacking the homer gene, are viable and show coordinated locomotor activity. This suggests that homer is not essential for normal synaptic transmission. However, the mutants displayed deficits in courtship conditioning, an associative learning paradigm in drosophila. In addition, the homer mutant flies showed increased spontaneous locomotor activity. These results suggest that homer may play a role in modulating locomotor activity and behavioral plasticity. Behavioral and synaptic plasticity have been implicated in the cellular processes mediating addiction. Future studies on homer in mammals may reveal the role of homer in regulating synaptic plasticity and the role that homer plays in cocaine addiction. Diagana, T.T., Ulrich Thomas, U., Sergei, N. Prokopenko, S.N., Xiao, B., Worley, P.F., and Thomas, J.B. J. Neuroscience 22, pp. 428-436, 2002.

Mu Knockout Mice and Immune Function

To understand the role of the mu opiate receptor in the modulation of immune function, several studies have used mu knockout mice to study this system. There are still several actions of morphine that modulate immune functions

in these mu knockout mice. This study identifies the kappa opioid system as a site where morphine may elicit action. Opioids such as morphine are potent analgesic and addictive compounds. Chronic morphine use also induces immunomodulatory and immunosuppressive effects, as especially evident in HIV-infected patients. Morphine acts on the immune cells primarily through its binding to mu-opioid receptors on the plasma membrane. However, morphine modulation of immune functions still exists in mu-opioid receptor knockout mice, suggesting that in addition to the mu opioid receptors, morphine may also act by mechanisms mediated by either delta or kappa opioid receptors. To determine whether morphine activates kappa opioid receptors (KOR), a quantitative competitive RT-PCR procedure was utilized to quantify the KOR gene expression of morphine-treated cells. A segment of KOR transcript spanning the second extracellular loop, which has the reported dynorphin specificity, and the seventh transmembrane domain of the receptor was amplified from the total RNA of morphine-treated CEM x174 lymphocytes, along with a competitor molecule. The competitor was constructed by deleting a 33-nucleotide fragment from KOR. The results of the competitive RT/PCR indicated that CEMx174 cells expressed KOR mRNA constitutively, in the order of femtograms. Treatment of 10 muM of morphine resulted in the up-regulation of KOR gene expression 24 hr post-treatment. The observed morphine effect could be reversed by treating the cells with either naloxone (a KOR-partially selective antagonist) or nor-Binaltorphimine (a KOR-selective antagonist). Suzuki, S., Chuang, T.K., Chuang, L.F., Doi, R.H. and Chuang, R.Y. Morphine Upregulates Kappa-Opioid Receptors of Human Lymphocytes. Adv Exper Med Biol, 493, pp. 81-87, 2001.

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Research Findings

Behavioral Research

Role of the Rostral and Caudal Basolateral Amygdala on the Maintenance and Reinstatement of Cocaine-Seeking Behavior in Rats

Associative learning mechanisms within the basolateral amygdala have been hypothesized to control the salience of cues associated with cocaine self-administration and thereby induce drug-seeking behavior. Recent research by Dr. Kantak and her associates employs a second-order operant schedule to investigate whether sites in the rostral-(BLA) and caudal-(cBLA) would provide a critical neuroanatomical substrate for drug seeking and drug taking behavior during the maintenance and reinstatement of self-administration. The use of this second-order schedule allows for drug intake to be measured independently of drug-seeking so that the neuroanatomical basis of drug seeking may be dissociated from that of drug taking. In the second order schedule, rats were trained to self-administer 1 mg/kg of cocaine under an FI 5-min (FR5:S) second-order schedule of drug delivery, where every fifth lever press (FR5) during the 5-min fixed interval (FI 5-min) resulted in the delivery of a 2-sec brief light stimulus located above the lever. Cocaine delivery was contingent on the completion of an FR5 after the FI had elapsed. The stimulus light remained on for the duration of the drug infusion as well as for the 20 sec following infusion. Thus, the light was associated with cocaine delivery. Following a period of extinction and abstinence, reinstatement of responding by the stimulus light alone and by the light + drug prime were examined. Results indicated that lidocaine inactivation of both structures attenuated the reinstatement induced by light + drug prime. In contrast, lidocaine inactivation of only the rBLA blocked reinstatement induced by light alone. Similarly, during cocaine maintenance sessions, inactivation of rBLA did not modify drug seeking, whereas inactivation of the cBLA during maintenance sessions reduced drug-seeking behavior. By contrast, drug taking was not altered under maintenance or reinstatement conditions. Thus, the rBLA and cBLA appear to selectively and dissociably regulate drug-seeking behavior under conditions of cocaine abstinence, as well as maintenance. These findings suggest that the BLA may be more functionally heterogeneous than commonly thought for regulating drug-seeking behavior. Kantak, K.M., Black, Y., Valencia, E., Green-Jordan, K., and Eichenbaum, H.B. Dissociable Effects of Lidocaine Inactivation of the Rostral and Caudal Basolateral Amygdala on the Maintenance and Reinstatement of Cocaine-Seeking Behavior in Rats. Journal of Neuroscience, 22 (3), 1126-1136, 2002.

Prenatal Exposure to Cocaine Decreases the Survival and Growth of Neurons Involved in Attentional Processes

Problems of attention can arise in the young children of individuals who use cocaine during pregnancy. Dr. Diane Snow and her collaborators at the University of Kentucky are using a clinically relevant rodent model of prenatal cocaine exposure to investigate dysfunction in noradrenergic neurons of the locus coeruleus (LC), an area that has been associated with attentional deficits in previous studies. Dr. Snow is using a unique approach in which she measures cell survival and neurite outgrowth in LC neurons cultured from fetal rat brains. With this technique, she can compare the consequences of *in vivo* prenatal exposure, which could result from either direct or indirect effects on the cells of interest, with the direct effects of cocaine applied *in vitro* to neurons cultured from fetuses of untreated dams. Another virtue of this approach is that it permits the delineation of critical periods of drug exposure during prenatal development. In her first study, Dr. Snow found that both *in vivo* and *in vitro* cocaine exposure decreased neuron survival, the number of cells that extended neurites, the number of neurites elaborated per neuron and total neurite length. The two treatments produced consistent results, which suggests that prenatal exposure may alter the

growth potential of LC neurons via direct effects on these cells. Snow, D.M., Smith, J.D., Booze R.M., Welch, M.A., and Mactutus, C.F. Cocaine Decreases Cell Survival and Inhibits Neurite Extension of Rat Locus Coeruleus Neurons. Neurotoxicology and Teratology, 23, pp. 225-234, 2001.

Discovery of a Novel Family of Neuropeptides that Contribute to Switching Between Behavioral Patterns

One characteristic of drug addiction is compulsive seeking and taking of a drug. We have some understanding of the neural circuitry involved in switching between behavioral actions, but only a rudimentary understanding of how dysregulation of this circuitry leads to compulsive behaviors. Recent findings suggest that various classes of peptides are involved in the control of behaviors such as feeding, maternal behavior, and drug ingestion. Dr. Ferdinand Vilim is using a model invertebrate system, the feeding behavior of Aplysia, to discover new neuropeptides and investigate their role in the modulation, coordination, and pattern selection of neural circuits. The advantage of this system is that the neural circuitry underlying the behaviors is well defined at the single neuron level, and new techniques for measuring peptides at the single cell level have been pioneered in Aplysia, because their neurons are very large. Dr. Vilim and his colleagues recently reported their discovery of a novel family of neuropeptides they call enterins, which are present in both the gut and central nervous system of Aplysia. Using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) they were able to characterize the precursor processing and determine post-translational modifications of the multiple enterins. Using electrophysiological techniques, they showed that enterins are likely to be involved in switching between ingestive and egestive motor programs. While it remains to be seen whether enterins are found in the mammalian nervous system, this study demonstrates the potential of using invertebrate model systems for the discovery and characterization of new neuroactive molecules. Since the biological functions of such molecules are often evolutionarily conserved, studies in Aplysia can provide new targets and methods for future drug abuse studies. Furukawa Y., Nakamaru K., Wakayama H., Fujisawa Y., Minakata H., Ohta S., Morishita F., Matsushima O., Li L., Romanova E., Sweedler J.V., Park J.H., Romero A., Cropper E.C., Dembrow N.C., Jing J., Weiss K.R., and Vilim F.S. The Enterins: A Novel Family of Neuropeptides Isolated from the Enteric Nervous System and CNS of Aplysia. Journal of Neuroscience, 21, pp. 8247-8261, 2001.

Prior or Concurrent Exposure to Environmental Novelty Decreases Drug Self-Administration in Rats

When natural rewards such as food or sucrose are provided during the availability of drug self-administration, these consummatory rewards attenuate the intake of both psychostimulant drugs and opiates. Dr. Michael Bardo and his colleagues recently conducted a series of investigations to determine if nonconsummatory rewards would also act as alternative reinforcers when provided along with d-amphetamine (amp). Rats were trained to self-administer amp and when response rates were stable they were provided with novel objects in the self-administration environment. The investigators report an attenuation of responding for drug each time novel objects were introduced. In a second study, they sought to determine if pre-exposure to this form of alternative reward might attenuate the acquisition of self-administration. In this study, one group of animals was given an opportunity to explore novel objects for 15 min prior to each drug self-administration session during acquisition and this group was compared to handled-only animals. Exposure to the novel objects delayed acquisition of amp self-administration, but once the behavior was acquired there was no difference between the two groups. These observations suggest that environmental novelty, which activates the same central dopaminergic pathways as drugs of abuse such as amp, may attenuate the vulnerability to acquire self-administration. However, these effects appear to be transient. Klebaur, J.E., Phillips, S.B., Kelly, T.H., and Bardo, M.T. Exposure to Novel Environmental Stimuli Decreases Amphetamine Self-Administration in Rats. Exp Clin Psychopharm., 9, pp. 372-379, 2001.

Amotivational Effects of Acute Smoked Marijuana in Human Drug Abusers

It has been suggested that marijuana (mj) abuse is associated with an "amotivational" syndrome characterized by apathy, lethargy and a general loss of productivity. NIDA-funded investigators Don Cherek and Scott Lane have been testing mj abusers in the laboratory setting, using operant conditioning techniques to assess responding for monetary reinforcers. In their procedure, subjects respond under progressive ratio (PR) schedules to receive varied amounts of monetary reward. The investigators first demonstrated that under non-drug conditions, greater progressive ratio segments were completed, greater responses made per minute and more monetary rewards earned, with increasing values of available monetary rewards. The authors argue that these response indices assess motivation, since they rose in a direct relationship to increasing value of the reinforcer. They then used this procedure to demonstrate that decreases in responding, under unchanging reinforcement conditions, can index decreases in motivation. In this second study, they treated mj abusing subjects with three different doses of smoked mj or placebo. They found decreases on all three response measures, that were related in a dose-dependent fashion to the dose of mj smoked

just prior to testing. In a second phase of this acute mj study, increasing the monetary value of the reward was found to attenuate mj induced reductions in the size of the largest PR completed (i.e., number of responses the subject is willing to make to receive a monetary reward). Thus, to the extent that reductions in PR size reflect decreased motivation for monetary rewards under the effects of acute mj, this effect can be overcome by increasing reinforcing value of the reward. The authors argue that the PR procedure appears to be a sensitive technique for detecting motivational changes in human drug abusers and suggest that it might be useful for assessing residual effects in chronic mj smokers. Cherek, D.R., Lane, S.D., and Dougherty, D.M. Possible Amotivational Effects Following Marijuana Smoking Under Laboratory Conditions. Exp Clin Psychopharmacol, 10, pp. 26-38, 2002.

Neurotoxicity Induced by Repeated MDMA Treatment Does Not Affect Performance on Repeated Acquisition Tests of Cognitive Performance

Abuse of the drug "ecstasy" (3,4-methylenedioxy-methamphetamine) has shown alarming trends on several epidemiological indices of drug abuse in this country. This trend is of great concern because both preclinical neurobiological data and findings from human neuroimaging studies reveal that this drug induces neurotoxicity in central serotonergic (5-HT) transmitter systems. Studies in human abusers also suggest that chronic MDMA administration produces functional deficits on memory tasks, and possibly on measures of higher order cognition. The challenge has been to model some of these functional deficits in preclinical studies and ascertain whether or not they can be linked to toxic effects in central neurotransmission. Recent studies by Dr. Peter Winsauer and colleagues employed a repeated acquisition learning paradigm in squirrel monkeys to assess the effects of a neurotoxic MDMA regimen on working memory. Animals were trained on the task until they demonstrated stable performance and then tested with drugs that stimulate 5-HT release. After dose-response determinations were made for the effects of these drugs on response rate and errors made on the task, half of the animals were treated with 2.5 mg/kg MDMA twice per day for four days. Dose response determinations were repeated under effects of two 5-HT releasers, mCPP and fenfluramine. The MDMA treatment was then repeated in the same monkeys, only for this second regimen animals received 5 mg/kg twice per day for four days. Again, MDMA-treated and non-treated controls were retested under effects of the two 5-HT releasing drugs. While these drugs decreased response rates on the task, in a dose-dependent fashion, they produced no effect on response accuracy (i.e., correct responses to different stimulus Ôsignals'). Most notably, MDMA treated rates performed no differently from untreated controls when assessed under non-challenge conditions (without mCPP or fenfluramine), and there were no differences in the effects of these 5-HT releasing drugs within animals at pre- and post- MDMA time points. The failure to observe a functional effect of repeated MDMA treatment is surprising, given that post-mortem measures showed severe reductions of [3H]citalopram-labled SERT and significant reductions of 5-HT and its metabolites over multiple brain regions. It is possible that compensatory changes in other neurotransmitter systems sustain the integrity of the cognitive processes assessed by this task, that residual 5-HT is adequate for mediating this behavioral effect, or that well-learned cognitive tasks may be difficult to disrupt with repeated MDMA treatment. Winsauer,P.J., McCann, U.D., Yuan, J., Delatte, M.S., Stevenson, M.W., Ricaurte, G.A. and Moerschbaecher, J.M.. Effects of Fenfluramine, m-CPP and Triazolam on Repeated-acquisition in Squirrel Monkeys before and after Neurotoxic MDMA Administration. Psychopharmacology, 159, pp. 388-396, 2002.

The Effects of Smoked Cocaine during the Follicular and Luteal Phases of the Menstrual Cycle in Women

Dr. Suzette Evans and colleagues of the New York State Psychiatric Institute and the College of Physicians and Surgeons of Columbia University have found that phase of the menstrual cycle is a determinant of cocaine craving as well as of the subjective response to smoked cocaine. Eleven females research volunteers who were currently using cocaine were recruited for participation in this study. Their mean amount spent per week on cocaine was $397 and their average use was 3-4 days per week. Each subject was tested in both the luteal and the follicular phase and in each phase subjects received four cocaine sessions in which they could smoke up to six doses of cocaine (either 0, 6, 12, for 25 mg cocaine base) at 14-min intervals. Under placebo conditions, resting heart rate, reports of dysphoria (e.g, ratings of "depressed," "irritable," "miserable"), and cocaine craving were greater during the luteal phase than in the follicular. Following cocaine administration, luteal phase dysphoric ratings were dose-dependently improved. Cocaine craving was greater during the luteal phase than during the follicular under 3mg and 25 mg, but not after 12 mg at which time craving was higher in the follicular phase. Cocaine-produced ratings of mood states (alert, friendly, self-confident, social, talkative), positive drug effects (good drug effect, high, stimulated), and drug quality ratings were generally greater during the follicular phase than the luteal phase. Heart rate increase was also greater during the follicular phase. Plasma cocaine levels increased with increasing cocaine dose, but did not differ in the follicular and luteal phases. The differential subjective effects of cocaine in the luteal and follicular phases as well as the cocaine-produced amelioration of mild luteal phase dysphoria observed in this study warrant investigation of the mechanisms underlying these effects as well as an exploration of treatment implications of these findings. Evans,

S.M., Haney, M, and Foltin, R.W. The Effects of Smoked Cocaine during the Follicular and Luteal Phases of the Menstrual Cycle in Women. Psychopharmacology, 159, pp. 397-406, 2002.

Social Factors Can Ameliorate Vulnerability to Drug Abuse in Cynomolgus Monkeys

In an investigation of the relationship between social rank and cocaine self-administration, Dr. Mike Nader and colleagues at Wake Forest School of Medicine report in Nature Neuroscience that cocaine functions as a reinforcer for subordinate, but not dominant monkeys. For the first 18 months of the study, monkeys were individually housed and then were housed socially in groups of four. Following the emergence of a dominance hierarchy, the monkeys were given the opportunity to acquire cocaine self-administration. In subordinate monkeys, cocaine self-administration was an inverted U-shaped function of dose, whereas in dominant monkeys, responding for cocaine did not exceed responding for saline at any of the study doses. The investigators also assessed D2 receptor binding via PET imaging before the monkeys were individually housed and again after they were group housed. When individually housed, D2 receptor binding levels did not differ between the monkeys that eventually became dominant and those that became subordinate. Following group housing, however, D2 receptor binding increased in the dominant monkeys, but not the subordinate monkeys. The investigators suggest that switching from individual housing to social housing "normalized" dopamine functioning in the dominant monkeys, but not in the subordinate monkeys. Thus, low D2 binding in the basal ganglia of socially housed monkeys appears to be associated with a greater vulnerability to acquire drug self-administration with cocaine. Morgan, D., Grant, K.A., Gage, H.D., Mach, R.H., Kaplan, J.R., Prioleau, O., Nader, S.H., Buchheimer, N., Ehrenkaufer and Nader, M.A. Social Dominance in Monkeys: Dopamine D2 Receptors and Cocaine Self-Administration. Nature Neuroscience, 5(2), pp. 169-174, Feb 2002.

Wheel Running Attenuates the Antinociceptive Properties of Morphine and Its Metabolite, Morphine-6-Glucuronide, in Rats

Prior studies conducted by Dr. Robin Kanarek of Tufts University, (in conjunction with contributions from other research programs) have established that chronic running in an activity wheel is associated with a reduction in the pain-relieving actions of opioid drugs in laboratory animals. Dr. Kanarek has suggested that this effect results from cross-tolerance between the endogenous opioid peptides released during exercise and exogenously administered opioid agonists. Alternatively, given that exercise affects opioid metabolism, the effect could result from altered opioid metabolism. Dr. Kanarek and her colleague, Wendy Foulds Mathes, tested these alternative explanations by examining the effect of chronic exercise on the pain-relieving effects of the morphine metabolite, morphine-6-glucuronide (M6G). M6G itself is not further metabolized, and it also is capable of producing profound antinociception. She found that, like morphine, the antinociceptive response to M6G also was attenuated by chronic wheel running, thus lending support to the hypothesis that there is cross-tolerance between chronic exercise and exogenously administered opioids. Mathers, W.F. and Kanarek, R.B. Wheel Running Attenuates the Antinociceptive Properties of Morphine and Its Metabolite, Morphine-6-Glucuronide, in Rats. Physiology & Behavior, 74, pp. 245-251, 2001.

Chronic Sucrose Intake Enhances Nicotine-Induced Antinociception in Female But Not Male Long-Evans Rats

Previous work has shown that in rats and mice, chronic consumption of palatable foods and fluids enhances the antinociceptive effects of morphine and other opioid agonists. Dr. Robin Kanarek and her colleague, Silvia Mandilo, of Tufts University have now shown that this effect extends to nicotine-induced antinociception. They found that nicotine administration produced dose-related increases in antiociception, but only in female subjects. Other animal studies have also shown sex differences in response to nicotine, e.g, females exhibit a greater antinociceptive effect of centrally-administered nicotine, a greater effect of nicotine on food intake and body weight, and greater motivation to self-administer nicotine. In the present study, the authors speculate that the sucrose enhancement of nicotine-induced antinociception in females, but not males, could be due to the fact that because female rats are smaller than males, their percent daily calories obtained from sucrose was greater. This study, along with prior research demonstrating sucrose enhancement of opioid-induced antinociception, highlights the need for additional research on the role of diet in effects of psychoactive drugs as well as highlights the importance of examining the role of gender in these effects. Mandilo, S. and Kanarek, R.B. Chronic Sucrose Intake Enhances Nicotine-Induced Antinociception in Female but not Male Long-Evans Rats. Pharmacology, Biochemistry and Behavior, 68, pp. 211-219, 2001.

Ketaconazole Suppresses Food Restriction-Induced Increases in Heroin Self-Administration in Rats: Sex Differences

In animal laboratory studies, augmentation of drug self-administration by food restriction is well established, although the mechanism for this effect is not well understood. Given that food restriction produces an increase in

corticosterone, it has been hypothesized that food deprivation is a stressor and thus acts as other stressors to elevate drug self-administration. This hypothesis was tested in a recent study by Dr. Marilyn Carroll and colleagues at the University of Minnesota who sought to determine whether ketaconazole, a corticosterone synthesis blocker, would suppress the increase in heroin self-administration produced by food restriction. In both male and female rats, heroin self-administration was increased approximately two-fold by food restriction. Under conditions of food satiation, ketaconazole had no effect on heroin self-administration in either males or females. Under conditions of food restriction, ketaconazole suppressed the food-restriction increase in heroin self-administration in females, but not males. This outcome in females lends support to the hypothesis that stress mediates the effects of food restriction on increased drug self-administration, and also has implications for the development for medications to be used in opiate abuse. Carroll, M.E., Campbell, U.C., and Heideman, P. Ketaconazole Suppresses Food Restriction-Induced Increases in Heroin Self-Administration in Rats: Sex Differences. Experimental and Clinical Psychopharmacology, 9, pp. 307-316, 2001.

Sex Differences in the Effects of Baclofen on the Acquisition of Intravenous Cocaine Self-Administration in Rats

Previous work by Dr. Marilyn Carroll and colleagues at the University of Minnesota has shown that female rats acquire i.v. cocaine self-administration faster than male rats and that a larger percentage of female than male rats acquire cocaine self-administration. These researchers now report that baclofen differentially affects acquisition of i.v. cocaine self-administration in male and female rats. Prior animal studies have shown the GABA agonist, baclofen, to be effective in reducing both the maintenance of i.v. cocaine self-administration as well as the reinstatement of i.v. cocaine self-administration following extinction. Dr. Carroll and her colleagues have now extended baclofen's effects to the acquisition phase of i.v. cocaine self-administration. They found that baclofen not only reduced the rate of acquistion of i.v. cocaine self-administration, but it also reduced the percentage of subjects that acquired i.v. cocaine self-administration. For both outcomes, the reduction was greater in females than males. Whereas 77.7% of the males met criterion for acquisition of cocaine self-administration under baclofen, only 15.4% of the females met criterion. These data join a growing body of behavioral research with animals indicating sex differences in drug effects. Campbell, U.C., Morgan, A.D., and Carroll, M.E. Sex Differences in the Effects of Baclofen on the Acquisition of Intravenous Cocaine Self-administration in Rats. Drug and Alcohol Dependence, 66, pp. 61-69, 2002.

Chronic Cocaine Increases Perseverative Responding and Impairs Reversal Learning in Monkeys

Several lines of evidence support the hypothesis that compulsive drug seeking and drug taking behavior are attributable, in part, to dysfunctions in the neural systems mediating incentive motivation and behavioral regulation (e.g., the striatum, amygdala and ventral frontal cortex). Specifically, impairments of frontal lobe function have been thought to release well-learned conditioned responses, resulting in compulsive drug seeking and taking that characterize addictive behavior patterns. Few studies, however, have directly investigated the long-term consequences of prolonged exposure to addictive drugs on frontal cortex cognitive function in non-human primates. The present experiments investigated the effects of acute and chronic administration of cocaine on the acquisition and reversal of object discriminations in male and female Vervet monkeys to test the hypothesis that cocaine affects performance of tasks that depend upon the functions of the orbitofrontal cortex and amygdala. It was hypothesized that cocaine would impair reversal learning without affecting the acquisition of novel discriminations. In the first experiment, an acute dose of cocaine (1 mg/kg) impaired reversal of a previously acquired object discrimination, but did not affect learning of a novel discrimination. Moreover, an analysis of the errors made indicated that cocaine did not increase perseverative responding, but rather produced disorganized behavior during reversal learning. In the second experiment, monkeys were treated repeatedly with cocaine (2 or 4 mg/kg) or saline once daily for 14 days. At nine and 30 days after the last drug treatment, acquisition and reversal of a novel discrimination were assessed under drug free conditions. On both tests, reversal learning was impaired, but there was no effect of drug treatment on acquisition. Moreover, the pattern of errors indicated that reversal learning was impaired as a result of perseverative responding. These data suggest that monkeys treated repeatedly with cocaine exhibit interference from previously conditioned stimulus-reward contingencies and/or develop an inability to inhibit irrelevant responses in the face of new reinforcement contingencies. The results suggest that long-term cocaine administration may disrupt orbitofrontal efferents to the striatum, resulting in impaired inhibition of established conditioned responses. Jentsch, J.D., Olausson, P., De La Garza, II, R., and Taylor, J.R. Impairments of Reversal Learning and Response Perseveration after Repeated, Intermittent Cocaine Administrations to Monkeys. Neuropsychopharmacology, 26 (2), pp. 183-190, 2002.

Neurons in Nucleus Accumbens Maintain Firing Patterns Related to Responses for Cocaine more Strongly than those Related to Water Reinforcement during Extinction

Dr. Regina Carelli is studying electrophysiological responses of neurons in the nucleus accumbens (Nas) in rats performing operant behaviors such as lever pressing to receive cocaine or natural rewards. She previously found that some Nas neurons increase their activity just prior to a lever press, and that these cells usually discriminate between type of reinforcer. For example, the vast majority of neurons that show anticipatory responses when the rat presses a lever associated with water reward, do not also increase their firing for a cocaine-associated lever, and vice versa. In two recent studies, Dr. Carelli and her graduate students asked whether Nas neurons maintain such firing patterns during extinction, when lever presses are no longer reinforced with water or cocaine. In experiments with cocaine self-administration, cells showed anticipatory firing during extinction trials at the same level as was recorded during earlier reinforced trials. In contrast, under conditions of water reinforcement, neuronal responses during extinction were greatly attenuated, and they did not return to pre-extinction levels even during reinstatement trials, at least over the short term. These findings are intriguing, but they also pose new questions for future experiments. First, anticipatory responses of Nas neurons have generally been thought to signal the expectation of reward in conditioning experiments, but the maintained firing of cocaine-associated neurons was not correlated with a slower extinction rate in the present experiments. In fact the opposite was true -- during the extinction from cocaine reinforcement, animals pressed about once per minute for about 25 minutes, whereas rats undergoing extinction from water reinforcement continued non-reinforced responding at this rate for about one hour. Thus, it would be of interest to determine if neuroadaptations produced by cocaine exposure uncouple the firing properties of Nas neurons from expectations of reward. Second, differences in Nas activity were not correlated with ease of reinstatement in either experiment -- rats resumed responding after a period of 30 minutes of no lever presses when primed with a cocaine infusion or with water plus a reward-associated auditory signal. Also, it is not known how long cocaine-associated neural responses are maintained and whether they might contribute to reinstatement at much later time points when, perhaps, reinstatement might fail to be produced in animals previously responding for water reinforcement. Carelli, R.M. and Ijames, S.G. Nucleus Accumbens Cell Firing during Maintenance, Extinction, and Reinstatement of Cocaine Self-administration Behavior in Rats. Brain Research, 866, pp. 44-54, 2000; Hollander, J.A., Ijames, S.G., Roop, R.G., and Carelli, R.M. An Examination of Nucleus Accumbens Cell Firing during Extinction and Reinstatement of Water Reinforcement Behavior in Rats. Brain Research, 929, pp. 226-235, 2002.

Environmental and Social Enrichment Protect against Vulnerability to Acquire Amphetamine Self-administration

Environmental enrichment (EC) in a preclinical model consists of placing novel and interesting objects into the housing environment and varying these objects over days. In the laboratory of Dr. Michael Bardo at the University of Kentucky, adolescent rats reared in EC environments are also socially housed. Another group of rats are reared in a social environment (SC) but without the rotating novel objects. Dr. Bardo recently compared rats exposed to these environments, starting at 21 days of age, to animals reared in isolation (IC), on responding for sucrose reinforcement and on the acquisition of self-administration for d-amphetamine (amp). EC has previously been shown to increase dopamine in the same nucleus accumbens (Nas) region that is involved in amphetamine reinforcement. Previous studies have revealed that animals exposed to EC conditions show enhanced locomotor stimulation, conditioned place preference, and DA release in the Nas in response to amp when compared to control rats. In the present study animals were tested for operant responding to receive sucrose at age 45 days and began i.v. self-administration for amp at age 62-63 days. The authors found that both EC and SC animals had higher response rats for the natural sucrose reinforcer on a fixed rate operant schedule, but as the schedule requirements were increased this difference dissipated. When self-administration rates were compared for the three groups there were no differences for responding to receive 0.1 mg/kg/infusion amp, but at 0.03 mg/kg/infusion both EC and SC animals made significantly fewer responses to receive drug. When the groups were compared on a progressive ratio operant schedule, that more precisely assesses magnitude of drug reinforcement, again EC rats self-infused significantly less amp. No differences were noted on an inactive lever on either procedure. These observations suggest that environmental enrichment is capable of reducing reinforcing impact of the psychostimulant d-amphetamine, and may therefore be an environmental variable that can affect vulnerability. It is not clear, however, why these results differ from those previously observed using other procedures to measure sensitivity to amphetamine. As it is possible that this protective effect is dose-dependent (i.e., not seen with higher doses of drug), further parametric analysis of the effect is warranted. Differences between these and previous data may also be attributed to different routes of administration (e.g., i.v. versus oral versus central infusion). Bardo, M.T., Klebaur, J.E., Valone, J.M. and Deaton, C. Environmental Enrichment Decreases Intravenous Self-administration of Amphetamine in Female and Male Rats. Psychopharmacology, 155, pp. 278-284, 2001.

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Director's Report to the National Advisory Council on Drug Abuse
May, 2002

Research Findings

Treatment Research and Development

Contingency Management to Enhance Naltrexone Treatment of Opioid Dependence: A Randomized Clinical Trial of Reinforcement Magnitude

Dr. Kathleen Carroll and colleagues at Yale University School of Medicine randomly assigned detoxified opioid-dependent individuals to 1 of 3 treatments delivered over 12 weeks: standard naltrexone maintenance, standard naltrexone plus low-value contingency management (CM), or standard naltrexone plus high-value CM. Results suggest that (a) assignment to either CM condition was associated with significant reductions in opioid use over time compared with standard naltrexone treatment; (b) contrasts of high- versus low-value reinforcement magnitude were not significant, suggesting no relative benefit of higher over lower value incentives in this population; (c) participants assigned to either CM group reported significant reductions in readiness to change compared with participants assigned to standard naltrexone treatment. These findings suggest that targeted behavioral therapies can play a substantial role in broadening the utility of available pharmacotherapies. Carroll, K.M., Sinha, R., Nich, C., Babuscio, T., and Rounsaville, B.J. Experimental and Clinical Psychopharmacology, 10, pp. 54-63, 2002.

Personality, Drug of Choice, and Co-morbid Psychopathology Among Substance Abusers

Researchers at Yale University investigated the association between substance abuse/dependence, drug of choice, and the personality traits of negative emotionality, positive emotionality, and constraint (disinhibition) as measured by the Multidimensional Personality Questionnaire. Of the sample of 325 subjects, a total of 205 (63%) met criteria for lifetime substance abuse/dependence, with the remainder comprising the comparison group. The substance abusers were placed into one of four predominant drug of abuse/dependence categories (opioid, cocaine or stimulants, marijuana or sedatives, or alcohol) based upon best-estimate diagnoses and one of five self-reported drug of preference groups (polysubstance, opioid, cocaine or stimulants, marijuana or sedatives, and alcohol). Findings demonstrated that individuals with substance abuse/dependence, compared to those without, scored lower on constraint even after adjusting for socio-demographic factors, comorbid psychiatric disorder, and current/remitted substance-use disorder. Individuals with substance abuse/dependence scored marginally higher on negative emotionality, but this difference was statistically significant only when co-morbid psychopathology was not controlled. Findings also showed that individuals who differ with respect to drug of choice-whether defined in terms of the predominant drug of abuse/dependence or self-reported drug of preference-vary in terms of constraint. After controlling for socio-demographic indicators and co-morbid psychopathology, scores on constraint generally decreased with the social deviance of the drug of choice, thereby underscoring a potentially important link between disinhibition and drug selection. Conway, K.P., Swendsen, J.D., Rounsaville, B.J., and Merikangas, K.R. Drug and Alcohol Dependence, 65, pp. 225-234, 2002.

Challenges In the Transfer of Contingency Management Techniques

Nancy Petry from the University of Connecticut critiqued the Therapeutic Workplace intervention. Strengths described include studying a patient population of major public health concern, expanding contingency management techniques to a vocational training setting, reinforcing gradual approximations, implementing the intervention for a long duration, and carefully designing and executing the experimental procedures. However, she emphasized many of these strengths also may be interpreted as weaknesses if the ultimate goal is to apply contingency management

techniques in self-sustaining, community-based settings. She noted the need for long-term cost-effectiveness of these procedures, and discussed the difficulties in transferring contingency management techniques to real-world settings. Petry, N.M. Experimental and Clinical Psychopharmacology, 9, pp. 35-39, 2001.

A Promising Intervention For A Daunting Problem: Comment On Silverman Et Al. (2001)

Researcher Steve Higgins from the University of Vermont provided a commentary on Kenneth Silverman's Therapeutic Workplace Intervention. He asserted that the therapeutic workplace represents a creative and promising new approach to drug abuse treatment that to the author's knowledge, is the first intervention that has been shown in a randomized clinical trial to significantly reduce cocaine abuse among pregnant women. He commended the rigor of the work and the science-based approach that integrates concepts and principles from several behavioral science literatures. He remarked that the intervention offers a potentially practical way of extending incentive-based drug abuse treatments to community clinics and suggested that the report has the potential to provoke serious consideration of what more might be done to combat chronic unemployment and drug abuse in poor communities. Higgins, S.T. Experimental and Clinical Psychopharmacology, 9, pp. 27-28, 2001.

Clinical Features of Pathological Gambling in an Addictions Treatment Cohort

Dr. James Langenbucher and colleagues at the Rutgers Center for Alcohol Studies examined the prevalence and descriptive psychopathology of pathological gambling in a heterogeneous treatment sample of 372 substance users. Of all participants, about 14% of men and 10% of women were identified by the South Oaks Gambling Screen (SOGS) as likely pathological gamblers (PGs). Compared with the 323 participants who were not pathological gamblers (NPGs), the 49 PGs showed more disturbance than NPGs on some measures of premorbid risk, pathological substance use, social consequences of use, and psychiatric comorbidity. Gambling status may be an important comorbid condition in addictions treatment settings and a significant covariate in research. Langenbucher, J., Bavly, L., Labouvie, E., Sanjuan, P.M., and Martin, C.S. Psychology of Addictive Behaviors, 15, pp. 77-79, 2002.

The Brief Abstinence Test: Effects of Continued Incentive Availability on Cocaine Abstinence

This study tested the efficacy of varying levels of incentives to initiate and sustain short-term abstinence from cocaine use. Cocaine-abusing methadone patients were randomized to one of 4 study conditions: In 3 conditions, patients could earn $100 for 2 days of cocaine abstinence; 2 of these conditions offered, on either a continuous or interrupted schedule, an additional $300 for evidence of sustained abstinence over the next 9 days. Patients in the 4th condition were offered no incentives. In the 3 incentive conditions, 70-80% of patients initiated abstinence, compared with 48% in the no-incentive condition. Both continuing reinforcement conditions produced higher rates of sustained abstinence than the single and no-voucher conditions. The study confirmed the utility of quantitative urine-testing methods combined with high valued incentives to promote cocaine abstinence initiation in methadone maintenance patients. Katz, E.C., Robles-Sotelo, E., Correia, C.J., Silverman, K., Stitzer, M.L., and Bigelow, G. Experimental & Clinical Psychopharmacology, 10, pp. 10-17, 2002.

Interest in and Obstacles to Pursuing Work Among Unemployed Dually Diagnosed Individuals

This study investigated interest in and perceived barriers to pursuing work, and the utilization of vocational rehabilitation services among 130 unemployed members of a dual recovery self-help fellowship. Members generally expressed high interest in working, although they perceived multiple barriers to attaining and maintaining employment. Based on a path model predicting interest in working, both substance use status and physical health rating were found to be significant contributors to interest in working. As expected, mental health symptoms and greater perceived obstacles (e.g., stigma, fear of failure, and insufficient skills) were significant contributors to perceived difficulty in pursuing work, whereas substance use, physical health, and recency of employment were not. Finally, perceived barriers to pursuing work, but not interest in work, were related to utilizing vocational rehabilitation services. There was also a significant gender difference, with men more likely than women to use these vocational rehabilitation services. Laudet, A.B., Magura, S., Vogel, H.S., Knight, E. L.. Substance Use & Misuse, 37, pp. 145-170, 2002.

Inhibition of Synthesis of Stress Hormones Does Not Reduce Drug Abuse

Stress plays an important role in substance abuse problems. For example, in studies with rodents stress induces reinstatement of opioid and cocaine self-administration. In addition, attenuation of the stress response by pharmacological adrenalectomy using ketoconazole, a cortisol synthesis inhibitor, reduces cocaine self-administration

in rodents. In contrast, studies in primates and humans have produced conflicting results using cortisol synthesis inhibitors for attenuating cocaine-related behaviors and subjective effects. To explore the treatment implications of these findings, ketoconazole's (600-900 mg daily) ability to reduce heroin and cocaine use was compared with placebo in 39 methadone maintained patients with a history of cocaine abuse or dependence during a 12-week double blind trial. Contrary to the predicted effects, both heroin and cocaine use increased after patients were stabilized on methadone and ketoconazole. Depressive and withdrawal symptoms improved no more with ketoconazole than with placebo treatment, and side effects were greater on ketoconazole than placebo. As reported before with methadone treatment, morning cortisol levels were significantly lower than normal values throughout the clinical trial, but were not lower with ketoconazole than placebo treatment. Thus, in agreement with the negative results from acute dosing studies in primates and humans, chronic ketoconazole treatment does not appear to reduce cocaine or opioid use in humans maintained on methadone. Kosten, T.R., Oliveto, A., Sevarino, K.A., Gonsai, K.,and Feingold, A. Ketoconazole Increases Cocaine and Opioid Use in Methadone Maintained Patients. Drug Alcohol Depend., 66(2), pp.173-180, 2002.

Predictive Validity of the CSSA and Urine Toxicology Results in Drug Abuse Treatment

Both cocaine withdrawal symptoms, measured by an instrument called the Cocaine Selective Severity Assessment (CSSA), and urine toxicology results obtained at the start of treatment have been shown to predict treatment outcome in outpatient cocaine dependence treatment. This study further evaluates the predictive validity of the CSSA and urine toxicology results, alone and in combination. Subjects included 76 cocaine-dependent individuals who participated in 7-week, outpatient, pilot medication trials for cocaine dependence. Predictor variables included CSSA scores and results from a urine toxicology screen obtained on the first day of medication treatment. Successful outcome was defined as 3 continuous weeks of self-reported abstinence from cocaine confirmed by urine toxicology screens. Predictive validity was assessed by logistic regression analysis. Both the urine toxicology screen and the CSSA scores were significant predictors of 3 weeks of continuous abstinence from cocaine, and the inclusion of both variables significantly improved the predictive validity of either variable alone. Urine toxicology results and CSSA scores obtained at treatment entry are useful predictors of outcome in outpatient cocaine dependence treatment. Kampman, K.M., Volpicelli, J.R., Mulvaney, F., Rukstalis, M., Alterman, A.I., Pettinati, H., Weinrieb, R.M., and O'Brien, C.P. Cocaine Withdrawal Severity and Urine Toxicology Results from Treatment Entry Predict Outcome in Medication Trials for Cocaine Dependence. Addict Behav., 27(2), pp. 251-260, 2002.

Depot Formulation of Naltrexone Provides a Safe, Effective, Long-lasting Antagonism of the Effects of Heroin

Naltrexone, an opioid antagonist, is currently approved as a treatment for heroin dependence. However, naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment. A sustained-release form of naltrexone may improve compliance. The present study was designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex). Twelve heroin-dependent individuals participated in an 8-week inpatient study. After a 1-week detoxification period, six participants received 192 mg naltrexone base and six participants received 384 mg naltrexone base. For safety, the low dose of depot naltrexone was tested before the high dose. The effects of heroin (0, 6.25, 12.5, 18.75, 25 mg, ivy.) were evaluated for the next 6 weeks. One dose of heroin was tested per day on Mondays through Fridays, and the entire dose range was tested each week. Active heroin doses were administered in ascending order during the week, while placebo could be administered on any day. Subjective, performance, and physiological effects were measured both before and after heroin administration. The hypotheses were that depot naltrexone would antagonize the effects of heroin, and that the high dose of depot naltrexone would produce a more effective and longer-lasting antagonism than the low dose. The low and high doses of depot naltrexone antagonized heroin-induced subjective ratings for 3 and 5 weeks, respectively. Plasma levels of naltrexone remained above 1 ng/ml for approximately 3 and 4 weeks after administration of 192 mg and 384 mg naltrexone. Other than the initial discomfort associated with the injection of depot naltrexone, there were no untoward side effects. These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin. Comer, S.D., Collins, E.D., Kleber, H.D., Nuwayser, E.S., Kerrigan, J.H., and Fischman, M.W. Depot Naltrexone: Long-lasting Antagonism of the Effects of Heroin in Humans. Psychopharmacology (Berl); 159(4), pp. 351-360, 2002.

Buprenorphine May Have Abuse Liability in Nonopioid-dependent Individuals who Abuse Heroin

Several sources indicate that intravenously administered buprenorphine may have significant abuse liability in humans. The present study evaluated the reinforcing effects of intravenously administered buprenorphine (0, 2, and 8 mg) in detoxified heroin-dependent participants during a 7.5-week inpatient study. Participants (n = 6) were

detoxified from heroin over a 1.5-week period immediately after admission. Testing subsequently occurred in three 2-week blocks. During the first week of each 2-week block, the reinforcing effects of buprenorphine were evaluated. Participants first received a dose of buprenorphine and $20 and then were given either the opportunity to self-administer the dose or $20 during choice sessions. During the second week of each 2-week block, the direct effects of heroin were measured to evaluate potential long-lasting antagonist effects of buprenorphine. Progressive ratio break-point values were significantly higher after 2 and 8 mg of buprenorphine compared with placebo. Correspondingly, several positive subjective ratings increased after administration of active buprenorphine relative to placebo. Although there were few differences in peak effects produced by 2 versus 8 mg of buprenorphine, the higher buprenorphine dose generally produced longer-lasting effects. Heroin also produced dose-related increases in several subjective effects. Peak ratings produced by heroin were generally higher than peak ratings produced by buprenorphine. There was little evidence of residual antagonism produced by buprenorphine. These results demonstrate that buprenorphine served as a reinforcer under these conditions, and that it may have abuse liability in nonopioid-dependent individuals who abuse heroin. Comer, S.D., Collins, E.D., and Fischman, M.W. Intravenous Buprenorphine Self-administration by Detoxified Heroin Abusers. J Pharmacol Exp Ther., 301(1), pp. 266-276, 2002.

Prefrontal Dysfunction in Methamphetamine-Dependent Subjects

Paulus and colleagues at the Department of Psychiatry, University California, San Diego used fMRI to demonstrate decision-making deficits in a two-choice prediction task and reduced task-related neural activation in different prefrontal areas in subjects dependent on methamphetamine. The performance of 10 methamphetamine abusers during early stages of abstinence was compared to ten age- and education-matched, non-drug using controls. Relative to comparison subjects methamphetamine abusers more influenced by the immediately preceding outcome during the two-choice prediction task, i.e. relied on stimulus-contingent response selection. Methamphetamine-dependent subjects failed to activate ventromedial cortex (BA 10,11) during the task, and exhibited less task related activation of the dorsolateral prefrontal cortex (BA 9) than the comparison subjects. These results demonstrate that decision-making deficits in methamphetamine abusers are related to orbitofrontal and dorsolateral prefrontal dysfunction. Paulus, M.P. et al., Neuropsychopharmacology, 26, pp. 53-63, 2002.

Prefrontal and Anterior Cingulate Activity during Decision-Making Depend on Error Rate and Outcome Predictability

Paulus and colleagues at the Department of Psychiatry, University California, San Diego used fMRI to demonstrate that the rate of errors during decision-making differentially affects activation of the prefrontal and cingulate cortex in normal, healthy subjects. BOLD fMRI scans were obtained while normal, healthy subjects performed a two-choice prediction task across 90-s blocks with 20, 50, or 80% error rates. As reported previously, activation of the right dorsolateral (BA 9, 46), inferior prefrontal (BA 44), and precuneus (BA 7) was observed when error rates were set at chance level (50%). In contrast, premotor (BA 6) and parahippocampal (BA 36) areas were relatively more active at high error rates. During low error rates, the dorsolateral (BA 9, 46) and inferior prefrontal cortex (BA 44) as well as parietal (BA 40) and cingulate cortex (BA 25, 32) were more active. In addition, error rate or outcome predictability influenced the relationship activation in the dorsolateral prefrontal cortex and the anterior cingulate and the dominant strategy underlying decision-making (e.g., win-stay/lose-shift). These results suggest that these structures maintain a representation of the reinforcement history and available response alternatives that contribute to selection of optimal decision-making strategies. Paulus, M.P., Hozack, N., Frank, L., and Brown, G.G. Neuroimage, 15(4), pp. 836-846, 2002.

Reward Prediction Errors Selectively Activate Ventral Striatum in Humans

Berns and colleagues in the Department of Psychiatry at Emory University used fMRI to test whether the ventral striatum plays a specific role of signaling errors in the prediction of rewards in normal, healthy subjects. Subjects performed either a simple operant conditioning task involving delivery of small quantities of fruit juice rewards or a control task where the outcome event was a neutral visual stimulus instead of juice. Increased BOLD signal in the ventral striatum occurred when the juice was withheld at the expected time of delivery, but not when the visual outcome stimulus was unexpectedly withheld. These data provide evidence for time-locked processing of reward prediction errors in human ventral striatum. Pagnoni, G. et al., Nature Neuroscience, 5, pp. 97-98, 2002.

Changes in Gene Expression Linked to Methamphetamine-Induced Dopaminergic Neurotoxicity

The effects of the mRNA synthesis inhibitor, actinomycin-D, and the protein synthesis inhibitor, cycloheximide, were examined by Dr. Ricaurte and colleagues at the Johns Hopkins School of Medicine. Both agents afforded complete

protection against methamphetamine- (METH) induced DA neurotoxicity and did so independently of effects on core temperature, DA transporter function, or METH brain levels, suggesting that gene transcription and mRNA translation play a role in METH neurotoxicity. Next, microarray technology, in combination with an experimental approach designed to facilitate recognition of relevant gene expression patterns, was used to identify gene products linked to METH-induced DA neurotoxicity. This led to the identification of genes in the ventral midbrain associated with the neurotoxic process, including genes for energy metabolism [cytochrome c oxidase subunit 1 (COX1), reduced nicotinamide adenine dinucleotide ubiquinone oxidoreductase chain 2, and phosphoglycerate mutase B], ion regulation (members of sodium/ hydrogen exchanger and sodium/bile acid cotransporter family), signal transduction (adenylyl cyclase III), and cell differentiation and degeneration (N-myc downstream-regulated gene 3 and tau protein). It was elected to further examine the increase in COX1 expression, because of data implicating energy utilization in METH neurotoxicity and the known role of COX1 in energy metabolism. On the basis of time course studies, Northern blot analyses, in situ hybridization results, and temperature studies, it was shown that increased COX1 expression in the ventral midbrain is linked to METH-induced DA neuronal injury. The precise role of COX1 and other genes in METH neurotoxicity remains to be elucidated. Xie, T., Tong, L., Barrett, T., Yuan, J., Hatzidimitriou, G., McCann, U.D., Becker K.G., Donovan, D.M. and Ricaurte, G.A. Changes in Gene Expression Linked to Methamphetamine-Induced Dopaminergic Neurotoxicity. Journal of Neuroscience, 22(1), pp. 274-281, 2002.

Altered Prolactin Response to M-chlorophenylpiperazine in Monkeys Treated Previously with 3,4-Methylenedioxymethamphetamine (Ecstasy, MDMA) and Fenfluramine

3,4-Methylenedioxymethamphetamine (ecstasy, MDMA) and fenfluramine are potent brain serotonin (5-HT) neurotoxins in animals. There is concern that humans previously exposed to these amphetamine derivatives may have incurred brain 5-HT neurotoxicity. To determine whether MDMA- and/or fenfluramine-induced 5-HT neurotoxicity can be detected during life using neuroendocrine methods, groups of monkeys previously treated with neurotoxic regimens of MDMA or fenfluramine underwent neuroendocrine challenge with the direct 5-HT agonist and 5-HT-releasing drug, m-chlorophenylpiperazine (m-CPP). Animals treated 2 weeks previously with MDMA exhibited a nonsignificant reduction in the prolactin response to m-CPP. In contrast, monkeys treated 3 1/2 years previously with MDMA or 2 years previously with fenfluramine exhibited significantly increased prolactin responses to m-CPP. No significant differences in cortisol concentrations were noted between groups at any time point. These data indicate that neuroendocrine challenge with m-CPP is capable of detecting substituted amphetamine-induced 5-HT neurotoxicity in living primates, but that the recency of drug exposure is an important consideration. Changes in the neuroendocrine response to m-CPP over time in animals with substituted amphetamine-induced neurotoxicity may be related to aberrant 5-HT reinnervation of the basal forebrain that occurs over time in monkeys previously treated with neurotoxic doses of MDMA or fenfluramine. Hatzidimitriou, G., Tsai, E.H., McCann, U.D., and Ricaurte, G.A. Altered Prolactin Response to M-chlorophenylpiperazine in Monkeys Previously Treated with 3,4-methylenedioxymethamphetamine (MDMA) or Fenfluramine. Synapse, 44(1), pp. 51-57, 2002.

A Comprehensive Review of Two Common Club Drugs

Evidence indicates that 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) is toxic to serotonergic neurons in animals and may be a neurotoxin in humans as well. The use of gamma-hydroxybutyrate (GHB), although not as popular as MDMA, is also a significant problem. The pharmacokinetics of MDMA and GHB, appear to be nonlinear, making it difficult to estimate a dose-response relationship. Symptoms of an MDMA toxic reaction include tachycardia, sweating, and hyperthermia. Occasional severe sequelae include disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure. Treatment includes lowering the body temperature and maintaining adequate hydration. Symptoms of GHB intoxication include coma, respiratory depression, unusual movements, confusion, amnesia, and vomiting. Treatment includes cardiac and respiratory support. Because of the popularity of these agents and their potentially dangerous effects, health care professionals must be familiar with these substances and the treatment options for patients who present with symptoms of a toxic reaction. Because of the increasing popularity of club drugs and their dangerous adverse effects, health care professionals must be familiar with these substances. No standard treatment protocols exist for the intoxication syndromes associated with MDMA or GHB, and supportive care is currently the standard of treatment. Teter, C.J., and Guthrie, S.K., A Comprehensive Review of MDMA and GHB: Two Common Club Drugs. Pharmacotherapy, 21(12), pp. 1486-1513, 2001.

Risperidone Pre-Treatment Reduces the Euphoric Effects of Experimentally Administered Cocaine

The effects of stimulants seem to be critically dependent on dopaminergic (DA) neurotransmission in preclinical research; however, stimulant challenge studies using volunteers treated with DA antagonists have generally failed to demonstrate a reduction of subjective effects. To further test the role of DA, a study to determine whether repeated

dosing with risperidone reduced the subjective effects of experimentally administered cocaine was conducted. Nine non-treatment seeking hospitalized cocaine-dependent volunteers received 40 mg cocaine IV before and following 5 days of treatment with 2 mg per day of risperidone, a D2 antagonist. Risperidone pre-treatment reduced the self-rated `high' produced by cocaine. Repeated, rather than single dosing may be necessary to reduce the subjective effects produced by cocaine. The degree of D2 receptor blockade produced by risperidone appears to be greater than the reduction in euphoric effects produced by cocaine, suggesting that mechanisms other than those involving D2 receptors may be important in drug-induced euphoria. Newton, T.F., Ling, W., Kalechstein, A.D., Uslaner, J., and Tervo, K. Risperidone Pre-Treatment Reduces the Euphoric Effects of Experimentally Administered Cocaine. Biology Psychiatry, 102, pp. 227-233, 2001.

Sensitivity of Prefrontal Cortex to Changes in Target Probability: A Functional MRI Study

Electrophysiological studies suggest sensitivity of the prefrontal cortex to changes in the probability of an event. The purpose of this study by Dr. Steven Forman and colleagues at the University of Pittsburgh was to determine if subregions of the prefrontal cortex respond differentially to changes in target probabilities using functional magnetic resonance imaging (fMRI). Ten right-handed adults were scanned using a gradient-echo, echo planar imaging sequence during performance of an oddball paradigm. Subjects were instructed to respond to any letter but X. The frequency of targets (i.e., any letter but X) varied across trials. The results showed that dorsal prefrontal regions were active during infrequent events and ventral prefrontal regions were active during frequent events. Further, we observed an inverse relation between the dorsal and ventral prefrontal regions such that when activity in dorsal prefrontal regions increased, activity in ventral prefrontal regions decreased, and vice versa. This finding may index competing cognitive processes or capacity limitations. Most importantly, these findings taken as a whole suggest that any simple theory of prefrontal cortex function must take into account the sensitivity of this region to changes in target probability. Casey, B.J., Forman, S.D., Franzen, P., Berkowitz, A., Braver, T.S., Nystrom, L.E., Thomas, K.M., and Noll, D.C. Sensitivity of Prefrontal Cortex to Changes in Target Probability: A Functional MRI Study. Human Brain Mapping, 13, pp. 26-33, 2001.

Quantitative EEG (QEEG) Defined a Group of Treatment-receptive Cocaine-Dependent Males and Females

Dr. Leslie Prichep and colleagues at NYU School of Medicine used EEG analyzed by sophisticated quantitative measures and somatosensory evoked potential features to group 16 female and 41 male cocaine-dependent subjects into three clusters. All subjects were in treatment and had been drug free for 5 to 14 days. The clusters were compared on a median split of length-of-stay (</> 25 weeks) in treatment. Eighty percent of the subjects in one cluster remained in treatment more than 25 weeks, while only 22% and 35% of the subjects in the other clusters did. There were no differences among the clusters in length or amount of cocaine use. The EEG patterns of the clusters differed in a number of ways of relative and absolute power in various frequency bands. Understanding the bases of these electrocortigrams will aid in understanding the individual differences among recovering cocaine-dependent individuals. Prichep, L.S., Alper, K.R., Sverdlov, L., Kowalik, S.C., John, E.R., Merkin, H., Tom, M.L., Howard, B., and Rosenthal, M.S. Clin Electroenceph, 33(1), pp. 8-20, 2002.

Fluoxetine was Shown to Reduce the Probability of Dropout and Increase the Probability of Abstinence in Smoking Cessation Treatment

Hitsman and colleagues demonstrated in a two-level dose (30 mg and 60 mg) of fluoxetine that there was a dose-response improvement in dropout and abstinence rates and a behavioral treatment paradigm. The study was devised to answer questions of whether side effects to such treatment would have the opposite, deleterious effect or would have a positive effect at the lower dose and a negative effect at the higher dose. In further analysis it was shown that the probability of improved performance was correlated linearly with blood levels (for moderate levels and above) for both men and women, though men had an overall better outcome. Hitsman, B., Spring, B., Borelli, B., Niura, R., and Papandonatos, G.D., Exptl Clin Psychopharm, 9(4), pp. 355-362, 2001.

Impulsivity Has an Important Role in Severity of Drug Use and in Retention in Treatment

Moeller and colleagues assessed treatment-seeking cocaine-dependent subjects on a questionnaire (BIS-11) measurement of impulsivity. The subjects then participated in a 12-week double-blind placebo-controlled trial of buspirone. Both amount of cocaine use and severity of withdrawal were significantly correlated with impulsivity scores. While the effect of buspirone was modest and not significant in percentage of subjects who remained in the trial, scores on the impulsivity measure were: higher scores predicted early drop-outs with 25% remaining at 12 weeks compared to 70% with low impulsivity scores. While the numbers in the study were small (n=35), the results

suggest that impulsivity is an important consideration for both cocaine use and for treatment outcome. Moeller, F.G., Dougherty, D.M., Barrattt, E.S., Schmitz, J.M., Swann, A.C., and Grabowski, J. J Subst Abuse Treat., 21, pp. 193-198, 2001.

Serum Prolactin, as a Measure of Central Dopamine, Is Related to Some Successful Outcomes in Treatment

Dr. Ashwin Patkar and associates assayed serum prolactin and found that cocaine-dependent subjects with levels above the median in treatment had fewer negative urine screens and received less favorable ratings by the treatment counselors. While it was true that neither discharge status nor retention in treatment were related to prolactin levels, the results do indicate activity of cerebral activity-presumably in the dopaminergic system-modulate treatment goals. It should be noted that prolactin levels in the cocaine patients were significantly higher than controls by nearly 30% (9.12 ng.ml vs. 7.14 ng/ml). Patkar, A.A., Hill, K.P., Sterling, R.C., Gottheil, E., Berrettinin, W.H., and Weinstein, S.P. Addiction Biology, 7(1), pp. 45-53, 2002.

Preliminary Evidence Suggests an Allele of the Serotonin Transporter is Related to Cocaine Abuse

Dr. Patkar and colleagues compared Long (L) and Short (S) alleles of the serotonin transporter between cocaine-dependent subjects and controls in an association study. The alleles differed by a 44-bp insertion or deletion involving repeat elements. Those with an L-allele (and those with the LL genotype) were more frequent among the cocaine patients; the SS genotype was less frequent. All the patients were African-American (N=197); these results were significant only when compared to a heterogeneous control group (N=101) while failing to reach significance when compared only to the African-American controls (N=61). There were no differences between the groups in allele frequencies and it is tentatively concluded that the failure to reach significance was due to reduced sample size, since the trends were the same. These results therefore suggest that allelic variants of the serotonin transporter may be related to cocaine susceptibility. Patkar, A.A., Berrettini, W.H., Hoehe, M., Hill, K.P., Sterling, R.C., Gottheil, E., and Weinstein, S.P. Addiction Biology, 6, pp. 337-345, 2001.

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Director's Report to the National Advisory Council on Drug Abuse
May, 2002

Research Findings

Research on AIDS and Other Medical Consequences of Drug Abuse

AIDS-Associated Mild Neurocognitive Impairment is Delayed in the Era of Highly Active Antiretroviral Therapy

Highly active antiretroviral therapy (HAART), the clinical strategy of combining antiretroviral medications from different classes, has restored immune function for many immunosuppressed individuals infected with HIV. Because some antiretroviral agents penetrate poorly into the central nervous system (CNS), patients may remain susceptible to HIV-associated neurocognitive disorders despite viral suppression in other tissues. Recent results suggest that HAART helps to maintain intact cognitive functioning in high-risk patients with relatively unrestricted access to HAART. This protection is predominantly mediated by a HAART-induced improvement in immune function reflected by the CD4 cell count. To examine whether specific classes of antiretroviral drugs afford protection, Dr. Igor Grant and colleagues at the University of California San Diego plan to investigate the role of HIV-RNA viral load, and to extend the observations to individuals in the medically asymptomatic stages of disease. Deutscha, R., Ellisa, R.J., McCutchana, J.A., Marcotte, T.M; Letendrea, S., Grant, I. and the HNRC Group. AIDS-Associated Mild Neurocognitive Impairment is Delayed in the Era of Highly Active Antiretroviral Therapy. AIDS, 15, pp. 1898-1899, 2001.

HIV/AIDS Risk Behaviors among Female Jail Detainees: Implications for Public Health Policy

Women are currently a primary focus in the battle against HIV/AIDS. This study examines the sex- and IDU-HIV/AIDS risk behaviors of female jail detainees and assesses the potential impact of interventions targeting this population. A sample of 948 participants stratified by charge type (i.e., felony vs. misdemeanor) and by race/ethnicity formed be basis of this study. Results indicate that non-hispanic white women, women arrested for less serious charges, women who have prior arrests, women arrested on drug charges, and women with severe mental disorders are at especially high risk for sexual and IDU transmission of HIV/AIDS. Investigators conclude that many women at particular risk of HIV/AIDS - women who use drugs, women who trade sex for money or drugs, homeless women, and women with mental disorder - will eventually cycle through the jail. Because most jail detainees return to their communities within days, providing HIV/AIDS education in the jail must become a public health priority. McClelland, G.M., Teplin, L.A., Abram, K.M., and Jacobs, N. American Journal of Public Health, 92(5), pp. 818-825, 2002.

HIV-1 RNA Viral Load Monitoring in HIV-infected Drug Users on Antiretroviral Therapy - Relationship with Outpatient Care Patterns

HIV-1 viral load (VL) testing is a standard component of HIV care. Investigators examined the use and predictors of VL testing in drug users, a group at risk for problematic care. Using 1996 to 1998 New York State (NYS) Medicaid files, the authors studied drug users who had been enrolled >10 months, had been prescribed antiretroviral agents in 1997 and 1998, and who had undergone any VL testing in 1997. The authors found that nearly half this cohort of drug users did not have regular VL testing. Drug users with HIV-focused care or with regular drug treatment are more likely to have regular VL testing. Laine, C., Zhang, D.Z., Hauck, W.W., and Turner, B.J. Journal of Acquired Immune Deficiency Syndromes, 29(3), pp. 270-274, March 1, 2002

Psychiatric Symptoms, Health Services, and HIV Risk Factors among Homeless Women

The authors determined whether psychiatric symptoms and lack of health and/or social services contacts were associated with HIV risk behaviors among a probability sample of homeless women. Women were interviewed regarding socioeconomic indicators, psychiatric symptoms, health and/or social services contacts, and past-year HIV risk behaviors. Overall, 8 percent of the women injected drugs, 64 percent engaged in unprotected sex, and 22 percent traded sex. Substance abuse was positively associated with injection drug use and trading sex. Homeless women with case managers were less likely to inject drugs. Although barriers to obtaining drug treatment were associated with trading sex, women attending self-help meetings for substance abuse were also more likely to trade sex. Homeless women who are substance abusers are vulnerable to HIV risk behaviors. Risk reduction interventions for homeless women should be implemented through substance abuse and intensive case management programs. Kilbourne, A.M., Herndon, B., Andersen, R.M., Wenzel, S.L., and Gelberg, L. Journal of Health Care for the Poor and Underserved, 13(1), pp. 49-65, February 2002.

Differential Predictors of Emotional Distress in HIV-infected Men and Women

Changes in the AIDS epidemic in many areas of the United States require information about the experience of the growing segment of women afflicted. The authors compared patterns of emotional distress between men and women with symptomatic HIV and examined potential predictors of different levels of vulnerability. A sample of 126 low socioeconomic men and women seeking care from HIV treatment centers was surveyed using measures of physical and psychological well-being. Women had more HIV symptoms, poorer functioning, and greater disruptions in physical and psychosocial well-being. Physical health status and optimism were primary predictors of emotional distress in both men and women. More than 50% of men and women had scores indicative of clinical anxiety. Approximately 1 out of 10 had clinically relevant scores for depression. Gender differences may provide potentially useful information for tailoring assessment interventions for emotional distress in people infected with HIV. van Servellen, G., Aguirre, M., Sarna, L., and Brecht, M.L. Western Journal of Nursing Research, 24(1), pp. 49-72, February 2002.

Real and Perceived HIV Risk by Population Density: An Exploratory Examination

Little is known about HIV and its primary routes of transmission in less populated areas. The purpose of this exploratory study was to contrast the real and perceived HIV risk among out-of-treatment drug users in a multi-site sample of low-, medium-, and high-population density counties in six states and Washington, D.C. Drug users in medium density areas "perceived" their risk of acquiring HIV/AIDS as lower than those in the high-density areas. The perceived risk could be predicted primarily as a function of lifetime HIV, lifetime STDs, needle use, having multiple sexual partners, and community population density. Because of different risk patterns and a "false" sense of risk, it is important to expand HIV risk reduction activities to include less populated areas. Leukefeld, C.G., Farabee, D., McDermeit, M., Dennis, M.L., Wechsberg, W.M., Inciardi, J.A., Surratt, H.L., Compton, W.M., Cottler, L.B., Klein, H., Hoffman, J.A., Desmond, D., and Logan, T.K. Journal of Drug Issues, 31(4), pp. 889-903, Fall 2001.

Analysis of a Population-based Pneumocystis Carinii Pneumonia Index as an Outcome Measure of Access and Quality of Care for the Treatment of HIV Disease

A population-based Pneumocystis carinii pneumonia (PCP) Index was developed in New York City to identify geographic areas and subpopulations at increased risk for PCP. A zip code-level PCP Index was created from AIDS surveillance and hospital discharge records and defined as (number of PCP-related hospitalizations)/(number of persons living with AIDS). Results indicated that in 1997, there were 2262 hospitalizations for PCP among 39,740 persons living with AIDS in New York City (PCP Index=.05691). PCP Index values varied widely across neighborhoods with high AIDS prevalence (West Village=.02532 vs Central Harlem=.08696). Some neighborhoods with moderate AIDS prevalence had strikingly high rates (Staten Island=.14035; northern Manhattan=.08756). The PCP Index highlights communities in particular need of public health interventions to improve HIV-related service delivery. Arno, P.S., Gourevitch, M.N., Drucker, E., Fang, J., Goldberg, C., Memmott, M., Bonuck, K., Deb, N., and Schoenbaum, E. American Journal of Public Health, 92(3), pp. 395-398, March 2002.

Drug Use During Pregnancy and Short-Term Maternal Outcomes

Findings from the largest study of illicit drug use during pregnancy have replicated many of the associations found in studies involving smaller samples. Over a 2-year period, 19,079 mother-infant pairs were screened after delivery for cocaine and opiate exposure at four clinical centers, located in Detroit, Memphis, Miami, and Providence. Of those screened, 16,988 met eligibility criteria, and 11,811 agreed to participate. Analyses involved 8,627 mother-infant pairs, based on ability to confidently classify participants as exposed or not exposed. Exposure was defined as

admission of use of cocaine or opiates or both, or the presence of cocaine or opiate metabolites in meconium (using gas chromatography-mass spectroscopy methodology). Nonexposure was defined as a negative drug use history by interview and a negative immunoassay screen. Exposed mothers had a significantly higher risk of infections, including syphilis, gonorrhea, hepatitis, and HIV; psychiatric, nervous, and emotional disorders; and abruptio placenta. However, it should be noted that in this large, sociodemographically diverse cohort study, the prevalence of these risk outcomes was lower than typically reported in previous reports. The authors point out that although the prevalence of serious and life-threatening medical outcomes is low in drug-abusing pregnant women, disadvantaged social and environmental conditions that are often characteristic of the lifestyle of these women may compound these problems. Bauer, C.R., Shankaran, S., Bada, H.S., et al. The Maternal Lifestyle Study: Drug Exposure During Pregnancy and Short-Term Maternal Outcomes. American Journal of Obstetrics and Gynecology, 186, pp. 487-495, 2002.

Current and Former Marijuana Use: Effects on IQ in Young Adults

Studying a cohort of young individuals who have been followed since birth, Peter Fried and colleagues have been able to assess IQ before and after onset of marijuana use. Seventy individuals aged 17-20 years old were involved in the analyses, using self-report of drug use and urinalysis. IQ in the 17-20 year-old period was compared with IQ in the 9-12 year-old period (pre-marijuana use). In addition, IQ differences across the two time periods were compared for current heavy users (at least 5 joints per week), current light users (less than 5 joints per week), former users (had not smoked regularly for at least 3 months), and non-users (never smoked more that once per week and no smoking in the past 2 weeks). Among the factors controlled for in the analyses are socioeconomic status variables (e.g., family income and parental education), education level of participant, age, sex, maternal use of cigarettes, marijuana and alcohol during pregnancy, participant's exposure to secondhand marijuana smoke, and participant's use of alcohol and tobacco. Current marijuana use was negatively associated with global IQ score only in the current heavy users (average decrease of 4.1 points over the time periods, current average IQ of 105.1). A negative effect was not found among subjects who had been heavy users but were no longer using marijuana. The authors caution that the negative effects of current heavy use and the lack of long-term effects found in this study should be interpreted carefully. The relatively small number of subjects for whom data were available, the length of time that the drug was used, the estimated total number of joints smoked, and the young age of the subjects all may serve to moderate effects. The authors also emphasize that broad intellectual functioning was examined in this report (i.e., only overall IQ), and it remains to be ascertained whether the absence of a residual marijuana effect of past use would also be evident in more specific cognitive domains such as memory and attention. Fried, P., Watkinson, B., James, D., and Gray, R. Current and Former Marijuana Use: Preliminary Findings from a Longitudinal Study of Effects on IQ in Young Adults. Canadian Medical Association Journal, 166, pp. 887-891, 2002.

Changes in HIV and Risk Behaviors Among Male IDUs in New York City, 1990-1999

Male IDUs who have sex with men (MSM) continue to be at particularly high risk for HIV infection. In 1999, over 23% of AIDS patients in the U.S. with a history of injecting drugs were MSM. MSM IDUs may be more likely than other IDUs to engage in some injection and sexual risk behaviors, and these behaviors may serve as a bridge for HIV transmission to various other groups. In New York City, HIV prevalence, HIV incidence, and injection risk behaviors have declined among IDUs, but relatively little is known about differences between MSM IDUs and other male IDUs regarding trends in risk behaviors and HIV prevalence. In this study, data were collected as part of an ongoing series of studies of entrants to a drug detoxification program at Beth Israel Medical Center in New York City. Male subjects entering the program between January 1990 and July 1999, who were 18 or older and had injected illicit drugs within the previous 6 months were eligible for inclusion. Participants were classified as MSM if they reported sexual intercourse with a man in the 5 years prior to the interview. The period of observation was dichotomized into 1990-1994 and 1995-1999, and analyses compared male IDUs who were and were not MSM within and between periods. In general, MSM IDUs tended to be at least as likely as other male IDUs to engage in high-risk injection and sexual behaviors. Both groups of men reduced high-risk injection behaviors and increased protective injection behaviors over time. However, neither group reduced its participation in commercial sex exchange, and only the non-MSM IDU group increased condom use between the first and second periods. MSM IDUs were significantly more likely to be HIV+ than were other male IDUs during the first period, and they tended to be so during the second period as well, even after adjusting for changes in the demographic and behavioral composition of the two groups. Overall, HIV prevalence declined by approximately 15% between periods in each group. The use of needle exchange increased from 21% to 57% for MSM IDUs and from 25% to 47% for non-MSM IDUs. Declining prevalence among MSM IDUs may be partially attributable to the effects of intervention efforts targeting MSM, as well as IDU populations, although it appears that such interventions have primarily affected injection risk. Injection risk behaviors declined among the IDUs in this study, whereas sexual risk behaviors did not. This study highlights the need for multidimensional interventions with heightened sensitivity to and awareness of sexual orientation. Given the high-risk profile of MSM

IDUs, such approaches should be prioritized for implementation and assessment in the near future. Maslow, C.B., Friedman, S.R., Perlis, T.E., Rockwell, R., and Des Jarlais, D.C. Changes in HIV Seroprevalence and Related Behaviors Among Male Injection Drug Users Who Do and Do Not Have Sex with Men: New York City, 1990-1999. Am J Public Health, 92, pp. 382-384, 2002.

Differential Effects of Face-to-Face and Computer Interview Modes

Researchers assessed the differential effects of face-to-face interviewing and audio-computer assisted self-interviewing (audio-CASI) on categories of questions. Syringe exchange participants (n=1417) completed face-to-face interviews or audio-CASI. The questionnaire was categorized into the groups "stigmatized behaviors," "neutral behaviors," and "psychological distress." Interview modes were compared for questions from each category. Audio-CASI was found to elicit more frequent reporting of stigmatized behaviors than face-to-face interviews. The researchers found that the interview mode differences between the "stigmatized" HIV risk behaviors and "psychological distress" were notable. There was also significantly more reporting of stigmatized behaviors with audio-CASI and significantly more reporting of "psychological distress" in the face-to-face interviewing. It appears that the process of collecting information regarding depression is facilitated by the face-to-face interview process; respondents may underreport to the computer because the impersonal nature of a computer interview is incongruent with the personal nature of questions regarding one's emotional or mental health. Responding to potentially sensitive questions should not be seen as merely "providing data" but rather as an activity with complex motivations. These motivations can include maintaining social respect, obtaining social support, and altruism. Ideally, procedures for collecting self-report data would maximize altruistic motivation while accommodating the other motives. Clark Newman J., Des Jarlais, D.C., Turner, C.F., Gribble, J., Cooley, P., and Paone, D. The Differential Effects of Face-to-Face and Computer Interview Modes. Am J Public Health, 92, pp. 294-297, 2002.

Validity of Self-Reported NEP Attendance Has Implications for Program Evaluation

Some studies have indicated that needle exchange programs (NEPs) can be effective in reducing drug-related risks for HIV seroconversion; however, others have reported higher HIV incidence rates among NEP attendees. Since many studies rely on self-reports of NEP attendance, the authors investigated the extent to which differential misreporting of NEP attendance could bias risk estimates. Over a 3-year period from 1994 to 1997, self-reports of NEP attendance from participants in a prospective study in Baltimore, Maryland, were compared with NEP records. Of 1,315 participants, 459 (35%) had registered with the Baltimore NEP. There was 86.7% concordance between self-reported and actual NEP use; 11.0% reported NEP attendance but did not attend (overreported), and 2.2% reported not attending NEP but did attend (underreported). In multivariate analyses using generalized estimating equations, persons who overreported NEP attendance were more likely to have injected frequently (adjusted odds ratio (AOR) = 1.29, 95% confidence interval (CI): 1.04, 1.61), denied needle sharing (AOR = 0.69; 95% CI: 0.52, 0.89), and been an HIV seroconverter (AOR = 1.83, 95% CI: 1.11, 3.01). With Poisson regression to model predictors of HIV seroconversion, models that included measures of NEP attendance based on self-reports compared with actual program data underestimated a protective association by 18%. These findings have important implications for evaluations of NEPs. Safaeian, M., Brookmeyer, R., Vlahov, D., Latkin, C., Marx ,M., and Strathdee, S.A.. Validity of Self- Reported Needle Exchange Attendance Among Injection Drug Users: Implications for Program Evaluation. Am J Epidemiol, 155(2), pp. 169-175, 2002.

Effects of Sponsorship in 12-Step Treatment of Injection Drug Users

What contributes to sustained abstinence from injection drug use by those who participate in community-based Narcotics Anonymous (NA) and Alcoholics Anonymous (AA) is not well understood. We know that sponsorship is a central element in these programs. To investigate the relationship between sponsorship and abstinence, researchers evaluated NA/AA sponsorship over a1-year period in a longitudinal study of 500 former and current injection drug users in inner-city Baltimore recruited from the community-at-large, independent of treatment center affiliation. The findings indicated that having a sponsor in NA/AA for this population was not associated with any improvement in 1-year sustained abstinence rates than a non-sponsored group. However, being a sponsor over the same time period was strongly associated with substantial improvements in sustained abstinence rates for the sponsors, controlling for involvement with community organizations, NA/AA meeting attendance, marital status, employment, participation in drug and alcohol treatment centers and HIV status. Involvement in community organizations was also strongly associated with successful abstinence, controlling for the same variables. Of those participants involved with community organizations, more than half reported involvement in church activities. This investigation suggests that, for NA/AA sponsors in this study population, providing direction and support to other addicts is associated with improved success in sustained abstinence for the sponsors but does little to improve the short-term success of the persons being sponsored. Crape, B.L., Latkin, C.A., Laris, A.S., and Knowlton, A.R. The Effects of Sponsorship in 12-Step Treatment of Injection Drug Users. Drug Alcohol Depend, 65, pp. 291-301, 2002.

Selection Effect of Needle Exchange in Anchorage, Alaska

Participation bias (selection bias) may be a problem in studies that attempt to evaluate the effects of needle-exchange programs (NEPs). The present study looked at only those injection drug users (IDUs) who were randomly placed in the needle-exchange condition in a two-arm randomized clinical trial of needle exchange. Time to follow-up between the experimental NEP condition (n = 296; median = 261 days) and pharmacy sales condition (n = 304; median = 256 days) was not statistically different [chi (2) (1, N = 600) = 0.42, P =.52]. Within the NEP condition, a similar analysis comparing time to follow-up between IDUs who used the NEP (n = 65; median = 199 days) and those who refrained from using the NEP (n = 231; median = 286 days) was highly significant, chi (2) (1, n = 296) = 17.3, P=.0001. The final logistic regression model predicting use of the NEP was the log 10 transformation of the number of times injected heroin in the last 30 days (odds ratio [OR]=4.9, confidence interval [CI] 2.8, 8.9), ever injected amphetamine in the last 30 days (OR =4.9, CI 1.09, 22.5), and ever shared injection equipment in the last 30 days (OR =2.9, CI 1.5, 5.5). Within the NEP condition, follow-up rates differed between those who used the NEP and those who did not use it. Of drug users randomly assigned to an NEP, the ones who actually used the NEP had higher levels of drug use. Predictors of who used the NEP were consistent with those reported by other researchers. This study demonstrates that selection bias occurs among IDUs who use NEPs. Fisher, D.G., Reynolds, G.L., and Harbke, C.R. Selection Effect of Needle Exchange in Anchorage, Alaska. J Urban Health, 79(1), pp. 128-135, 2002.

Cultural Factors Influencing HIV Risk Behavior Among Dominicans in N.Y.City

Hispanics in the U.S. have disproportionately high rates of HIV. The existence of ethnically and culturally diverse Hispanic communities in the U.S. suggests that qualitative research on HIV-related attitudes and behaviors within Hispanic subgroups can help to inform the development of successful interventions. In this paper, the authors present findings from interviews with 20 Dominicans involved in drug- or sex work-related activities in New York City in terms of predominant cultural influences and specific issues regarding sex work, drug use, and HIV/AIDS. Several directions for interventions in the Dominican community are also discussed, including outreach efforts sensitive to the stigmatization of behaviors such as needle use and homosexuality, and messages to sex workers to use condoms with their partners as well as their clients. The authors discuss how improved knowledge of cultural norms can serve as a foundation for interventions within this community, especially given the need for additional information on contraception, family planning, and drug treatment services. Shedlin, M.G. and Deren, S. Cultural Factors Influencing HIV Risk Behavior Among Dominicans in New York City. J Ethnicity in Subst Abuse,1(1), pp. 71-95, 2002.

Gender-Related Social Factors Associated with Syringe Sharing Among Injecting Partners

The study of social networks has become an increasingly utilized method of examining the relationship between injection drug users' social environment and risk of HIV. This study examined relational aspects of two injection drug users (IDUs) within a single social network as they relate to sharing syringes. Data presented in this study were derived from baseline interviews of 508 IDUs from Baltimore, MD. Analyses were performed separately for male and female participants in an effort to understand gender differences in social aspects of syringe sharing. Among this sample, women shared syringes with a significantly higher percentage of injecting partners compared to men. In separate multilevel logistic regression models, significant variables associated with males' and females' syringe sharing were: sharing drugs daily with female injecting partners, injecting partners' provision of drugs when indexes' were withdrawing, being sexual partners, and injecting partners' injecting speedballs. Factors associated with male injecting dyads sharing of syringes were: being kin, injecting partners' injection of heroin and daily drug use, and drinking alcohol together. Results from this study demonstrate the usefulness of examining relationship characteristics of injecting dyads related to syringe sharing as they differ between men and women. Sherman, S.G., Latkin, C.A., and Gielan, A.C. Social Factors Related to Syringe Sharing Among Injecting Partners: A Focus on Gender. Subst Use Misuse, 36(14), pp. 2113-2136, 2001.

Gender Differences in HIV Risk Behaviors of PR IDUs and Awareness of Serostatus

Researchers examined HIV injection and sex-related risk behaviors among Puerto Rican injecting drug users by gender, separately for those who were aware of being HIV positive and those who believed they were seronegative or were unaware of their serostatus. The participants (N= 873; 561 in New York and 312 in Puerto Rico) were recruited from January 1998 to July 1999 in the two sites by street outreach workers. Of the participants, 81% were males and 19% self-reported that they were previously told that they had been infected with HIV. More significant gender differences in risk behaviors were found in bivariate analyses among those who were not told they were infected than among those who were aware of their HIV+ status. The factors related to HIV risk behaviors between males and females differed after controlling for the impacts of other variables in multivariate analysis. Among those who were never told they were infected, men were more involved in risky injection behaviors than women. Even among those

who knew they were HIV+, men were more likely than women to engage in distributive sharing of injection equipment. Men also used paraphernalia and shared their needles/syringes or paraphernalia with others. Regardless of awareness of infection, women were more likely than men to engage in sex, to exchange sex for drugs or money, and to have multiple sexual partners. The levels of unsafe injection and sexual practices found in this study indicate a critical need for continuing intervention programs to reduce the risk of becoming HIV infected in these communities. Kang, S.Y., Deren, S., Andia, J., Colon, H.M., and Robles, R. Gender Differences in HIV Risk Behaviors Among Puerto Rican Drug Injectors by Awareness of HIV Seropositive Status. AIDS and Behavior, 5(3), pp. 241-249, 2001.

Public Health and Criminal Justice Policy Issues Related to High-Risk Women

Researchers have documented the linkages between sex-for-crack exchanges, prostitution, and rising rates of HIV and other sexually transmitted diseases among cocaine-dependent women. As crack began to fade from the headlines in the 1990s, however, it was assumed by many that crack had declined in popularity in the street drug culture. In this study, researchers describe crack use, street crime, and sex-for-drug exchanges collected during the mid-1990s in Miami, Florida from interviews with a sample of 851 multi-ethnic/racial women. Of the women, 708 or 83.2% were cocaine dependent and reported trading sex (defined as periodic exchange of sex for money or drugs, as opposed to regular or commercial sex work) in the past 30 days. All the women also had criminal histories, used illicit drugs 2-3 years before the initiation of reported criminal activity, and traded sex before the initiation of crack cocaine. The women are at high risk for HIV/AIDS, given their histories of injecting drug use, sex with an IDU who is HIV+, unprotected sex, and number of sex partners. Recent studies of HIV infection among crack-using women in Miami have reported HIV prevalence as high as 24% in non-sex traders and 35% in sex traders. The authors conclude that crack use continues to occupy a prominent place in the culture of drug-dependent women in Miami. They argue that their data contradict the argument that legalizing drugs would reduce crime associated with drug use, and suggest instead that drug addiction is a disorder of the whole person, including cognitive problems, psychological dysfunctions, and educational and employment deficits. Moreover, they found significant gaps in conventional HIV prevention outreach activities: of 53 women participating in focus groups, almost none had ever come into contact with an HIV prevention outreach worker, largely because outreach occurs during the day and early evening and sex trading occurs late at night. The HIV prevention messages must also be made more relevant to the lives, culture, and concerns of the drug-involved women they are intended to reach. Inciardi, J.A. and Surratt, H.L. Drug Use, Street Crime, and Sex-Trading Among Cocaine- Dependent Women: Implications for Public Health and Criminal Justice Policy. J Psychoactive Drugs, 33(4), pp. 379-389, 2001.

Ethnographic Accessing, Sampling, and Screening of Heroin Sniffers in N.Y. City

In this article, researchers describe various ways in which ethnographic methods were used in a cohort study of HIV risk and transitions to injecting among non-injecting heroin users (NIUs) or "sniffers" in New York City. In preparation for and in conjunction with an epidemiological questionnaire survey and biological specimen collection, ethnographic methods were used to explore the meaning of non-injecting and injecting rates of heroin administration for NIUs, how non-injecting heroin use was imbedded in the everyday life of the user, and the relationship of users to the retail markets for heroin. The study utilized different ethnographic techniques to access, sample, and screen heroin "sniffers" for the epidemiological survey. These techniques included ethnographic accessing, targeted canvassing, and interactive screening. The article concludes that ethnographic methods can be fruitfully integrated with epidemiological survey research and are necessary for conducting research among non-institutionalized, hard-to-reach or hidden populations of drug users. Sifaneck, S.J. and Neaigus, A. The Ethnographic Accessing, Sampling, and Screening of Hidden Populations: Heroin Sniffers in New York City. Addiction Research and Theory, 9(6), pp. 519-543, 2001.

Health Care Utilization in Female African-American Crack Cocaine Users

Researchers examined utilization of health care services by urban female African-American crack cocaine users recruited for a larger study developing HIV risk reduction interventions. Structured interviews were conducted with 149 women at a community-based field site. Nearly all women regularly sought health care during the past year, although only 40% had any type of health insurance. Two- thirds had no regular primary care provider, with the highest percentage among women who did not have health insurance. Typically, women received care at public hospital outpatient clinics or emergency rooms and the most common care issues were female-related health issues and substance use. Many women reported having had routine exams such as general medical, pelvic, or pap smear in the past 2 years. However, fewer had dental, eye or mammogram exams during that same time period, with many never having had such exams. Twenty-three percent of the women reported a lifetime diagnosis of a mental illness. Analyses by amount of crack use indicated that those who used most were least likely to be insured, and most likely to seek care at hospital emergency rooms. Multivariate analyses revealed that self-rated health and having a minor child predicted amount of health care received in the past year. Many female African American crack cocaine users

are not receiving important health care exams and services. Steps must be taken to improve preventive and primary care to female African American crack cocaine users prior to the necessity of care in a more expensive hospital setting. Kidder, D.P., Elifson, K.W., and Sterk, C.E. Health Care Utilization in Female African-American Crack Cocaine Users. Women and Health, 34(1), pp. 79-97, 2001.

Practical Guidelines on Research and Services Projects for Hard-to-Reach Populations

Researchers from the National Development and Research Institutes (NDRI) in New York City have prepared a recent book to serve as a practical guide for conducting research and delivering services to marginalized groups and populations. The knowledge and expertise represented in the book span more that 15 years of accumulated experience in working with people outside the mainstream, including drug users, the homeless, street prostitutes, runaway teenagers, and drug dealers. The book follows a step-by-step format, with guidelines on setting up research projects; the outreach process and qualities that make a good outreach worker; conducting clinical and research interviews; strategies for locating, following up, and maintaining contact with hard-to- reach study participants; managing service delivery projects; the importance of community collaborations; ethical considerations; and the integration of service provision and research in a single setting. Tortu, S., Goldsamt, L.A., and Hamid, R. (eds.). A Practical Guide to Research and Service With Hidden Populations, Boston: Allyn & Bacon, 2002.

The Pharmacokinetics of Methadone Following Co-Administration with a Lamivudine/ Zidovudine Combination Tablet in Opiate-Dependent Subjects

The investigators determined methadone pharmacokinetics in an open-label, within subject study in 16 methadone-maintained, non-HIV-infected subjects prior to and following administration of one lamivudine 150-mg/zidovudine 300-mg combination tablet to determine whether this antiretroviral therapy alters methadone serum concentrations. No significant differences in the mean area under the serum concentration-time curve (AUC0-24h; 8753 ±4280 vs. 8641 ± 4431 g-h/L), oral clearance (CL/F; 9.9 ± 4.9 vs. 10.3 ± 5.5 L/h), oral volume of distribution (Vd/F; 647 ±465 vs. 481 ± 305 L), maximum serum concentration (Cmax; 514 ± 223 vs. 5510 ± 237 µ g/L), or terminal elimination half-life (t1/2; 55.3 ± 61.0 vs. 35.0 ± 17.5 h) were detected. These results suggest that methadone dose change is not likely to be necessary for patients treated with lamivudine/ zidovudine combination pharmacotherapy. Rainey, P.M., Friedland, G.H., Snidow, J.W., McCance-Katz, E.F., Mitchell, S.M., Andrews, L., Lane, B., and Jatlow, P., Am J. Addictions, 11(1), pp. 66-74, 2002.

High Prevalence of Iron Deficiency and Anemia Among Female Injection Drug Users with or Without HIV Infection

Based on the fact that anemia is associated with HIV disease progression and high mortality, Semba et al. measured hemoglobin and plasma ferritin in a cohort of 136 HIV+ and 61 HIV-negative women IDUs in Baltimore, Maryland. The prevalence of anemia was 44.1% and 26.2%; iron deficiency was 37.5% and 42.6%; and the iron deficiency anemia 20.6% and 14.7%, in HIV+ and HIV- women, respectively. The overall prevalence of hepatitis C infection was 90.5%. Iron deficiency accounted for 46.7% and 56.1% of the anemia among HIV+ and HIV- negative female IDUs. The iron deficiency accounted for about half of the anemia among female IDUs. However, they stated that although iron supplementation is indicated for anemia in patients, such treatment should be approached with caution in women co-infected with HIV and hepatitis C virus, because iron supplementation and overload have been associated with increased progression of HIV infection, worsening of hepatitis C infection and higher mortality. Semba, R., Shah, N., Strathdee, S.A., and Vlahov, D. JAIDS, 29, pp. 142-144, 2002.

Impact of Selenium Status on Pathogenesis of Mycobacterial Disease in HIV-1-infected Drug Users During the Era of Highly Active Antiretroviral Therapy

The risk of Mycobacterial disease is significantly increased in drug users as well as in immunocompromised HIV-1-infected individuals. Since the essential trace element selenium has an important function in maintaining processes and may, thus, have a critical role in clearance of mycobacteria, the investigators examined the impact of selenium status on the development of mycobacterial disease in HIV-1-seropositive drug users over a 2-year period (1999-2000). Twelve cases of mycobacterial disease (tuberculosis, 9; infection due to atypical Mycobacterium species, 3) occurred; these 12 cases were compared with 32 controls with no history of respiratory infections that were matched on age, sex, and HIV status. Significant risk for mycobacterial disease was associated with a CD4 cell count of <200/mm3, malnutrition, and selenium levels of 135 g/L (patients with these levels were 13 times more likely to develop mycobacterial disease). Multivariate analyses controlling for antiretroviral treatment and CD4 cell count revealed that both body mass index and selenium level remained significant factors in the relative risk for developing mycobacterial disease (RR=3, p=0.015); these findings suggest that selenium status may have a profound impact on

the pathogenesis of mycobacterial disease. Shor-Posner, G., Miguez-Burbano, M.J., Pineda, L.M., Rodriguez, A., Ruiz, P., Castillo, G., Burbano, X., Lecusay, R., and Baum, M., JAIDS, 29, pp., 169-173, 2002.

The Effects of Cannabinoids on the Pharmacokinetics of Indinavir and Nelfinavir

Dr. Abrams and colleagues present pharmacokinetic data from a randomized placebo-controlled study showing that the magnitude of pharmacokinetic parameter changes in two protease inhibitor antiretroviral medications, indinavir and nelfinavir, in marijuana users are likely to have no significant short-term clinical consequences, and that the use of marijuana or dronabinol is unlikely to impact antiretroviral efficacy. The investigators conducted a placebo-controlled randomized clinical in-patient study in HIV+ subjects who were on indinavir (n=28; 800 mg tid) or nelfinavir (n=34; 750 mg, tid) randomized to either arm: marijuana smoke (3.9% THC; up to 3 complete marijuana cigarettes daily, 1 hr prior to meals) or dronabinol (2.5 capsules, oral) or placebo capsules. Serial blood sampling was performed at baseline and on day 14 of treatment. Data showed that a statistically significant but clinically insignificant decrease (14%, p=0.074) occurred in median Cmax of indinavir in the marijuana group of patients. Statistically non-significant changes occurred in the nelfinavir concentrations in the marijuana group. Due to large inter-subject variability, there were no significant changes in the PI levels in the dronabinol group either. In summary, the use of marijuana did not impact adversely on the pharmacokinetics of protease inhibitors used in the treatment of HIV infection. Kozel, B.W., Aweeka, F.T., Benowitz, N.L., Shade, S.B., Hilton, J.F., Lizak, P.S., and Abrams, D.I., AIDS, 16, pp. 543-550, 2002.

Use of Highly Active Antiretroviral Therapy in HIV-Infected Women: Impact of HIV Specialist Care

The objectives of this analysis were to evaluate factors associated with use of HIV specialist care by women, and to determine whether medical indications for therapy validate lower rates of antiretroviral use in women not using HIV specialty care. Results indicate that 81% of 273 women included in the analysis used HIV specialists vs. 19% who did not. Predictors of use of specialty care included having health insurance, not being an IDU, and the presence of depression (p< =.05). Medical indications for therapy were comparable between the users of HIV specialty care vs. non-users, but the use of HAART was significantly greater for those women using specialty care (27%) vs. those who did not (7.8%). Lower rates of HAART and other antiretroviral therapies (ART) at all CD4 cell count levels occurred in women not receiving specialty care. In the six months prior to study interview, women who utilized specialty care received significantly more advice to initiate ART vs. those not receiving such care (RR, 2.4). Among women with CD4 cells <500 who were current IDUs, the proportion receiving HAART was very low, irregardless of whether or not they were in specialty care (14% vs. 17%, p=NS). For women with CD4 cells <500 who were not IDUs, 31% in specialty care received HAART vs. 0% not in specialty care (p=.002). The overall low level of HAART use (23%) and use of any ART (47%) in this study of HIV-infected women indicate that substantial gaps remain for HIV-infected women in access to specialty care and therapy. Gardner, L.I., Holmberg, S.D., Moore, J., Arnsten, J.H., Mayer, K.H., Rompolo, A., Schuman, P., Smith, D.K. for the HIV Epidemiology Research Study Group, JAIDS, 29, pp. 69-75, 2002.

Cocaine Modulation of HIV Growth in SCID Mice

Epidemiologic studies have identified cocaine as a co-factor for development of acquired immunodeficiency syndrome (AIDS). In a recent study published in the February 2002 issue of Journal of Infectious Diseases, Dr. Michael Roth and his associates at University of California, Los Angeles, School of Medicine clearly show a link of cocaine exposure to accelerated HIV replication. This study was undertaken to examine whether systemic exposure of severe combined immunodeficient (huPBL-SCID) mice to cocaine would affect HIV burden and alter distribution of T cells subsets *in vivo*. The researchers observed that systemic cocaine administration resulted in accelerated infection of human peripheral blood leukocytes (PBL), a decrease in CD4 cells, a decrease in the CD4:CD8 ratio, and a dramatic rise in circulating virus load. Since exposure to cocaine alone did not affect the implantation of PBL, it suggested a specific interaction between cocaine and HIV. These findings are important as they suggest a causal relationship between cocaine exposure and enhanced HIV replication *in vivo*, supporting the role of cocaine as an important cofactor in the pathobiology of AIDS. Roth, M.D., Tashkin, D.P., Choi, R., Jamieson, B.D., Zack, J.A., and Baldwin, G.C. Cocaine Enhances Human Immunodeficiency Virus Replication in a Model of Severe Combined Immunodeficient Mice Implanted with Human Peripheral Blood Leukocytes. J Infect Diseases, 185, pp. 701-705, 2002.

Studies of Opiate-Systems Regulation of Immune Function

Studies continue to correlate opiate action with HIV growth in human lymphocytes, macrophages and microglia. Herein, methadone was shown to enhance growth of HIV under *in vitro* conditions. Methadone also activated latent viruses in the lymphocytes, *in vitro*, of HIV-infected populations. As this action correlates with the up-regulation of the CCR5 receptor, a coreceptor for HIV, this is of great interest and it is important that work continues to clarify the

nature of this action. Opiate abuse has been postulated to be a cofactor in the immunopathogenesis of acquired immunodeficiency syndrome (AIDS). This study evaluated whether methadone, a drug widely prescribed for the treatment of drug abusers with opioid dependence, affects human immunodeficiency virus (HIV) infection of human immune cells. When added to human fetal microglia and blood monocyte-derived macrophage cultures, methadone significantly enhanced HIV infection of these cells. This enhancement was associated with the up-regulation of expression of CCR5, a primary coreceptor for macrophage-tropic HIV entry into macrophages. Most importantly, the addition of methadone to the cultures of latently infected peripheral blood mononuclear cells from HIV-infected patients enhanced viral activation and replication. Although the *in vivo* relevance of these findings remains to be determined, the data underscore the necessity of further studies to define the role of opioids, including methadone, in the immunopathogenesis of HIV infection and AIDS. Li,Y., Wang, X., Tian, S., Guo, C.J. Douglas, S.D. and Ho, W.Z. Methadone Enhances Human Immunodeficiency Virus Infection of Human Immune Cells. J Infect Diseases, 185, pp. 118-122, 2002.

Effects of Fetal and Adolescent Nicotine Exposure on CNS Vulnerability

It is widely believed that nicotine is a neuroteratogen that targets synaptic function during critical developmental stages. Recent studies indicate that central nervous system (CNS) vulnerability extends into adolescence, the time that smoking typically commences. In the past year, NIDA supported researchers, Dr. Theodore Slotkin and his associates at Duke University Medical Center have demonstrated that nicotine administration during development alters the functioning of the serotonergic (5-HT) systems, the neurotransmitter pathway closely associated with depression, throughout the brain. Dr. Slotkin examined indices of the development of 5-HT projections and 5-HT presynaptic activity following prenatal and adolescent nicotine exposure of rats. These studies used the nicotine dose rates that replicate the plasma nicotine levels found in smokers. Fetal nicotine exposure (gestational days 4-21) showed a decrease in the cerebrocortical binding of paroxetine (PXT), a marker for the 5-HT transporter, indicative of a decrease in nerve terminals in that region. This effect lasted into adulthood. There was a corresponding increase in PXT binding in the midbrain and brainstem, the region containing the 5-HT cell bodies that project to the cerebral cortex, a pattern typical of reactive sprouting in response to nerve terminal damage. After adolescent nicotine treatment (postnatal days 30-47), PXT binding was reduced in the hippocampus and striatum instead of the cerebral cortex, again accompanied by increased binding in the midbrain and brainstem. These effects within each region were gender selective, although both males and females displayed abnormalities. Superimposed on this overall effect, there were transient changes of 5-HT transporter expression likely due to the acute stimulant effects of nicotine. Additional studies showed that withdrawal from adolescent nicotine treatment led to suppression of activity in the cerebral cortex and activation in the midbrain. These results indicate that both fetal and adolescent nicotine exposure elicit apparent damage to 5-HT projections with reactive increases in regions containing 5-HT cell bodies. These findings are important as long-term changes in 5-HT innervation and /or synaptic activity may play a role in the subsequent development of depression in the offspring of women who smoke during pregnancy or in adolescent smokers. Xu, Z., Seidler, F.J., Ali, S.F., Slikker Jr., W., and Slotkin, T.A. Fetal and Adolescent Nicotine Administration: Effects on CNS Serotonergic Systems. Brain Research, 914, pp.166-178, 2001.

Offspring of Women who Smoke during Pregnancy Show Behavioral Abnormalities

Behavioral abnormalities, including increased incidence of attention deficits, learning disabilities, and cognitive dysfunction are shown by the offspring of women who smoke. Researchers at Duke University Medical Center, Dr. Theodore Slotkin and his team recently reported alterations in cellular morphology and regional architecture in the juvenile and adolescent brain regions involved in learning and memory (hippocampus) and in pain pathways (somatosensory cortex) in rats previously exposed to nicotine prenatally. These investigations were designed to compare the vulnerabilities of neuronal populations arising from different germinal zones as well as similar types of cells located in different regions. Their data showed that prenatal nicotine exposure, at blood levels comparable to those seen in human smokers or in user of transdermal nicotine patches, elicited structural abnormalities in the hippocampus and somatosensory cortex before the reemergence of functional deficits. Nicotine appeared to target specific sub-regions and cell types, including cells with postnatal birth dates, indicating that exposure alters the program for brain cell development and for architectural assembly of critical regions involved in learning and memory. Roy, T.S., Seidler, F.J. and Slotkin, T.A. Prenatal Nicotine Exposure Evokes Alterations of Cell Structure in Hippocampus and Somatosensory Cortex. J. Pharmacology Experimental Therapeutics, 300, pp. 124-133, 2002.

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May, 2002

Research Findings

Epidemiology, Etiology and Prevention Research

Television Viewing and Aggressive Behavior during Adolescence and Adulthood

Television viewing and aggressive behavior were assessed over a 17-year interval in a community sample of 707 individuals. There was a significant association between the amount of time spent watching television during adolescence and early adulthood and the likelihood of subsequent aggressive acts against others. Specifically, researchers reported that 5.7 percent of the study participants who watched less than an hour of TV a day committed a violent act that resulted in serious injury, such as broken bone. Among those who watched one to three hours, 18.4 percent had been violent. Of those who watched more than three hours a day, the rate of aggression was 25.3 percent. This association remained significant after previous aggressive behavior, childhood neglect, family income, neighborhood violence, parental education, and psychiatric disorders were controlled statistically. This study is the first long-term longitudinal study to link television exposure during adolescence and young adulthood to aggressive behaviors in adults. Although this study's design (observational) is potentially limited in its ability to, in its self, establish that a direct causal link between television watching and aggression exist, it does, nonetheless, provide empirical data that adds to the pattern of accumulated evidence that supports the plausibility that television watching is causally connected to future aggressive behaviors. Johnson, J.G., Cohen, P., Smailes, E.M., Kasen, S., and Brook, J.S. Science, 295(5564), pp. 2468-2471, March 29, 2002.

Early Adolescent Marijuana Use: Risks for the Transition to Young Adulthood

This study assessed the relationship of early adolescent marijuana use to performance of developmental tasks integral to the transition to young adulthood. The tasks concerned intimacy, education, and work and social conformity. African American (N = 617) and Puerto Rican (N = 531) youths completed questionnaires in their classrooms. Five years later they were individually interviewed. Logistic regression analysis estimated the increased likelihood that early marijuana users would make an inadequate transition to young adult social roles. Analyses examining the association between early marijuana use and 20 outcome variables found significant relationships for 10 of them: (a) having lower educational and occupational expectations; (b) being suspended or expelled from school, fired from jobs, 'high' at school or work, collecting welfare; and (c) rebelliousness, not participating in productive activities, not attending church, and being an unmarried parent. Marijuana use was not related to any of the intimate relationship measures. These findings emerged with controls on gender, ethnicity, age and mother's education. The authors conclude that among African Americans and Puerto Ricans, early marijuana use predicts less adequate performance on some developmental tasks integral to becoming an independent young adult. Marijuana is not a benign drug and is associated with future risks for the individual and society at large. Brook, J.S., Adams, R.E., Balka, E.B., and Johnson, E. Psychol Med, 32(1), pp. 79-91, January 2002.

Relative Effectiveness of Anti-drug PSAs

Whether an anti-drug media campaign can produce behavior change in the target (i.e., youth) population is a critical question. Such change depends on knowing the extent to which that behavior is influenced by attitudes, norms and beliefs, and whether these can be altered by televised public service announcements (PSAs). This study explores the relative perceived effectiveness of 30 anti-drug PSAs and assesses the extent to which judgments of effectiveness are related to judgments of realism, amount learned, and positive and negative emotional responses. A sample of

students in grades 5 through 12 were randomized to 5 experimental (E) conditions to view sets of 6 anti-drug PSAs or a control group that viewed a non-drug-related TV program. Three of the E groups saw ads focused primarily on the negative consequences of using various drugs; the other two E groups saw ads focused on refusal skills. The researchers report wide variation in the perceived effectiveness of the 30 PSAs: 16 were rated as significantly more effective and 6 significantly less effective than the control program. Ratings of effectiveness were highly associated with realism (r = .87), amount learned (r=. 88), and negative emotion (r=. 87). However, the more positive the adolescents' emotional response to the PSA, the less they regarded it as effective (r=-.35; p=. 06). These findings highlight the variation in the effectiveness of ads. While most ads made adolescents less inclined to use drugs, several had little effect and others had negative effects. Moreover, those youth who do not view drug use as risky behavior were least likely to view the ads as effective. These findings suggest that evaluative research is necessary to prevent broadcast of PSAs that could have a negative impact. PSAs should point out the negative consequences of drug use rather than telling adolescents to just say no. Fishbein, M., Hall-Jamieson, K., Zimmer, E., von Haeften I., and Nabi, R. Avoiding the Boomerang: Testing the Relative Effectiveness of Anti-drug Public Service Announcements before a National Campaign. Am. J. Public Health. 99(2) pp. 238-245, 2002.

Having a Teenage Mother is Unrelated To Adolescent's Psychosocial Outcomes

This is a study of psychosocial outcomes of adolescents born to teenage mothers. Adolescents' problem behaviors, psychological well-being, social support, school variables, and sexual behaviors are compared across three groups-those born to mothers 17 or younger, mothers 18-19 years old, and mothers 20 or older. Analyses from two samples of African American adolescents from Maryland and Michigan are reported. The results from both samples indicate that mother's age at birth is unrelated to adolescents' psychosocial outcomes. These two studies add to the limited number of analyses that examine adolescent outcomes for children of teen mothers. The results suggest that efforts to understand social structural determinants of healthy and problematic adolescent development may be more informative than examining the effects of mother's age. They also suggest that teen pregnancy prevention programs may be more effective if they are part of a larger prevention strategy that incorporates social structural change efforts and not only a focus on individual level change. Zimmerman, M.A., Tuttle, L., Kieffer, E., Parker, E., Caldwell, C.H., and Maton, K.I., American Journal of Community Psychology, 29(5), pp. 799-805, 2001.

Treatment Seeking After Onset of Substance Use Disorder

This paper reports results of analyses of survey data on patterns and predictors of treatment seeking after onset of DSM-III-R substance use disorders in three countries. The study utilized population-based survey data from a regional sample in Ontario, Canada, a national sample in the U.S., and local samples in Fresno, California and Mexico City, Mexico. Analyses examined the effects of demographics, symptoms, and types of substances on treatment seeking. Results indicated that between 50% (Ontario) and 85% (Fresno) of people with substance use disorders seek treatment but the time lag between onset and treatment seeking averages ten or more years. Consistent predictors of treatment seeking include: (1) late onset of disorder, (2) recency of cohort, (3) 4 specific dependence symptoms: using larger amounts than intended, unsuccessful attempts to cut down use, tolerance, and withdrawal symptoms, and (4) use versus non-use of cocaine and heroin. Results from this study indicate that treatment seeking has increased in recent years; however, further research is needed to assess whether this is because of increased access, increased demand, increased societal pressures, or other factors. Kessler, R.C., Aguilar-Gaxiola, S., Berglund, P.A., Caraveo-Anduago, J.J., DeWit, D.J., Greenfield, S.F., Kolody, B., Olfson, M. and Vega, W. Patterns and Predictors of Treatment Seeking After Onset of a Substance Use Disorder. Archives of General Psychiatry, 58, pp. 1065-1071, 2001.

Understanding the Differences in Youth Drug Prevalence Rates Produced by the MTF, NHSDA, and YRBS Studies

This paper explores potential reasons for the differences in drug use prevalence rates among youth generated by three nationally representative surveys: The National Household Survey on Drug Abuse (NHSDA), the Monitoring the Future (MTF) survey, and the Youth Risk Behavioral Survey (YRBS). The MTF and YRBS are the most similar of the surveys, being conducted among students in a classroom using self-administered questionnaires. The NHSDA is conducted in the respondent's household, but it has always used self-administered procedures for the drug questions. Nevertheless, the NHSDA generally reports the lowest drug prevalence rates for youth among the three surveys. There are a number of methodological differences across the surveys that cumulatively, probably account for the differences in estimates. Some of the differences appear to be due to telescoping, in that when a calendar was introduced to anchor past 30 day and 12 month time periods in the NHSDA, prevalence rates for illicit drugs were reduced. However, there is substantial similarity in the trends over time among the three surveys, especially for cigarettes, alcohol and cocaine. Many of the estimates generated by the three surveys have overlapping confidence

intervals, which suggests the estimates are not statistically significantly different from one another. Harrison, L.D. Understanding the Differences in Youth Drug Prevalence Rates Produced by the MTF, NHSDA, and YRBS Studies. Journal of Drug Issues, 31(3), pp. 665-694, 2001.

Psychiatric and Substance Use Disorder in South Florida: Racial/Ethnic and Gender Contrasts in a Young Adult Cohort

Authors present their findings of a sub-sample (N = 1,803) of students who entered middle school in 1990, and were interviewed between 1998 and 2000. Using the computer-assisted personal interviews, subjects psychiatric and substance use disorders were evaluated using the DSM IV. Investigators found that over 60% of the sample met lifetime criteria for one or more disorders. Childhood conduct and major depressive alcohol abuse disorders were the most prevalent. The rates of affective and anxiety disorders in females were double that in males, however once attention deficit disorders, conduct disorders, and antisocial personality disorders were considered, the gender difference disappeared. Lower rates were reported among African Americans for depressive disorders and substance abuse dependence. Among Hispanics, rates were found to be lower among the foreign born in comparison with their US born counterparts, especially for substance abuse disorders. This study emphasizes the need for prevention efforts in the school setting and the notion that more research needs to be done on the origins of ethnic and nativity differences. Turner, R.J., Gil, A.G. Archives General Psychiatry, 59, pp. 43-50, 2002.

Estimates of Intra-group Dependence for Drug Use and Skill Measures in School Drug Prevention Trials

Group-randomized drug abuse prevention trials customarily designate schools as the unit of assignment to experimental condition; however, students within schools remain the unit of observation. Students nested within schools may show some resemblance based on common (peer) selection or school climate factors (i.e. disciplinary practices, group norms, or rules). Appropriate analyses of any treatment effects must be statistically correct for the magnitude of clustering within these intact social units (i.e., intra-class correlation coefficient [ICC]). There is little reported evidence, however, of variation in ICCs that might occur with studies of racially or geographically diverse populations. The purpose of this study was to generate estimates of intra-group dependence for drug use and psychosocial measures (hypothesized mediators) from three separate drug abuse prevention trials. Clustering for the drug use measures averaged .02 across studies and age groups (range=. 002 to .053) and was equivalently small for the psychosocial measures (averaging .03 across studies and age-groups; range=. 001 to .149). With few exceptions and across different samples, clustering decreased in magnitude over time. Clustering was largest for peer smoking and drinking norms among white, suburban youth and smallest for alcohol expectancies among urban black youth. Scheier, L.M., Griffin, K.W., Doyle, M.M., and Botvin, G.J. Estimates of Intra-group Dependence for Drug Use and Skill Measures in School-Based Drug Abuse Prevention Trials: An Empirical Study of Three Independent Samples. Health Education & Behavior, 29(1), pp. 85-103, 2002.

Prevention - Effects on Developmental Progression in Drug Use

This study examines the plausibility of the gateway hypothesis to account for drug involvement in a sample of middle school students participating in a drug abuse prevention trial. Analyses focused on a single prevention approach to exemplify intervention effects on drug progression. Improvement in social competence reduced multiple drug use in 1- and 2-year follow-ups. Specific program effects disrupted drug progression by decreasing alcohol and cigarette use over 1 year and reducing cigarette use over a 2-year period. Controlling for previous drug use, alcohol was integrally involved in the progression to multiple drug use. Subgroup analyses based on distinctions of pretest use/nonuse of alcohol and cigarettes provided partial support for the gateway hypothesis. However, evidence also supported alternate pathways including cigarette use as a starting point for later alcohol and multiple drug use. Findings underscore the utility of targeting more than one gateway substance to prevent escalation of drug involvement and reinforce the importance of social competence enhancement as an effective deterrent to early-stage drug use. Scheier, L.M., Botvin, G.J., and Griffin, K.W. Preventive Intervention Effects on Developmental Progression in Drug Use: Structural Equation Modeling Analyses Using Longitudinal Data. Prevention Science, 2(2), pp. 91-112, 2001.

Reliability and Validity of a Brief Measure of Sensation Seeking

Sensation seeking is a powerful predictor of a wide array of problem behaviors. High sensation seekers (HSS) are more likely than low sensation seekers (LSS) to engage in risky behaviors and, subsequently are less likely to label them as risky. The widely used measure of sensation seeking, Form V of the Sensation Seeking Scale (SSS-V), however, has several shortcomings including length, forced-choice format and outdated colloquial language. This article reports on 2 studies that tested a brief alternative measure based on the SSS-V, the Brief Sensation Seeking

Scale (BSSS) and its reliability and validity as a self-report of sensation seeking. Study 1 was administered in mass-testing sessions and found to have suitable item characteristics and internal consistency of responses to items across age (13-17 years), sex and ethnic categories. Study 2 participants completed the BSSS individually using a computer, and also responded to questions about their perceptions of and experiences with drugs and additional risk and protective factors. Their BSSS scores correlated inversely with negative attitudes toward drug use and positively with actual drug use and the BSSS's sensation seeking measure was a strong predictor of intention to use marijuana in the future. Thus, this new brief measure reliably and predictably measures sensation seeking and related factors. Hoyle, R.H., Stephenson, M.T., Palmgreen, P., Lorch, E.P., and Donohew, R.L. Reliability and Validity of a Brief Measure of Sensation Seeking. Personality and Individual Differences, 32, pp. 401-414, 2002.

Inhalant Abuse Among Three Groups of Adolescents

Analyses involving participants from three ethnic populations over the course of ten years suggest that a number of social and perceptual correlates of inhalant use operate similarly across Mexican American, American Indian, and non-Latino white adolescents. These analyses suggest that peer factors, including peer sanctions, peer use, and peer encouragement, were particularly important, though less so for Mexican American and Indian youth. Increased perception of harm is also correlated with less inhalant use for all groups. These data suggest that the historically higher rates of inhalant use for males as compared to females no longer prevail. Furthermore, for the American Indian sample, for both lifetime and 30-day prevalence, males were less likely to have used inhalants than females. Overall, American Indian adolescents participating in the survey showed decreasing rates of inhalant use over time. Beauvais, F., Wayman J.C., Jumper-Thurman, P., Plested, B., and Helm, H. Inhalant Abuse Among American Indian, Mexican American, and Non-Latino White Adolescents. American Journal of Drug and Alcohol Abuse, 28, pp. 171-187, 2002.

Social Information Processing and Aggression

Social information processing (SIP) patterns were conceptualized in independent domains of process and context and measured through responses to hypothetical vignettes in a stratified sample of 387 children (50% boys; 49% minority) from 4 geographical sites followed from kindergarten through 3rd grade. Analyses supported the within-construct internal consistency, cross-construct discrimination, and multidimensionality of SIP patterns. Contrasts among nested structural equation models indicated that SIP constructs significantly predicted children's aggressive behavior problems as measured by later teacher reports. The findings support the multidimensional construct validity of children's social cognitive patterns and the relevance of SIP patterns in children's aggressive behavior problems. Dodge, K.A., Laird, R., Lochman, J.E., and Zelli, A. Multidimensional Latent-Construct Analysis of Children's Social Information Processing Patterns: Correlations with Aggressive Behavior Problems. Psych. Assessment, 14(1), pp. 60-73, 2002.

Pathways to Externalizing Behavior

The roles of peer rejection in middle childhood and antisocial peer involvement in early adolescence in the development of adolescent externalizing behavior problems were examined using longitudinal, prospective data. Classroom sociometric interviews from ages 6-9 yrs, adolescent reports of peers' behavior at age 13 yrs, and parent, teacher, and adolescent self-reports of externalizing behavior problems from ages 5-14 yrs were available for 400 adolescents. Both early starter and late starter pathways were considered. Results indicate that experiencing peer rejection in elementary school and greater involvement with antisocial peers in early adolescence were correlated, but that these peer relationship experiences may represent 2 different pathways to adolescent externalizing behavior problems. Peer rejection experiences, but not involvement with antisocial peers, predict later externalizing behavior problems when controlling for stability in externalizing behavior. Externalizing problems were most common when rejection was repeatedly experienced. Early externalizing problems did not appear to moderate the relation between peer rejection and later problem behavior. Laird, R.D., Jordan, K.Y., Dodge, K.A., Pettit, G.S., and Bates, J.E. Peer Rejection in Childhood, Involvement with Antisocial Peers in Early Adolescence, and the Development of Externalizing Behavior Problems. Dev. & Psychopathology, 13(2), pp. 337-354, 2001.

Early-Adolescent Risk Factors of Youth Violence Mediate Childhood Risks

Analyses were conducted to assess whether risk factors for youth violence measured at 10 yrs of age influenced later violence directly or indirectly through predictors measured in early adolescence (14 yrs of age). Analyses revealed that many childhood risks--which included teacher-rated hyperactivity/low attention, teacher-rated antisocial behavior, parental attitudes favorable to violence, involvement with antisocial peers, low family income, and availability of drugs in a neighborhood--had strong and persistent effects on later violence. However, mediation effects also were noted for most factors. Male gender and low neighborhood attachment measured at 10 yrs of age

were the only 2 risks that appeared not to be mediated partially by predictors at 14 yrs of age. School and peer predictors of violence measured at 14 yrs of age were the strongest mediators of the earlier risk factors. Those predictors consistently added to the explanatory power of each model that was tested. Herrenkohl, T.I., Guo, J., Kosterman, R., Hawkins, J.D., Catalano, R.F., and Smith, B.H. Journal of Early Adolescence, 21(4), pp. 447-469, 2001.

Persistence of Violence In The Transition To Adulthood

Researchers examined violent behavior from ages 13-21 yrs and identified predictors at age 10. Logistic regression was used to assess predictors of developmental patterns of violence. The sample is from a study of 808 youth interviewed annually from age 10 to 16 yrs, and again at ages 18 and 21. Over 28% of the youth in the sample reported nonviolence throughout adolescence and into early adulthood. Most youth (55%) engaged in violence in adolescence but desisted from violence in early adulthood, while 16% persisted in violent behavior at age 21. Violence in adolescence was best predicted by male gender, Asian American ethnicity (a protective factor), childhood fighting, early individual characteristics, and early antisocial influences. Adult persistence of violence was best predicted by male gender, early school achievement (which was protective), and early antisocial influences. Early prosocial development was also protective against violence persistence for females. Implications for prevention are discussed. Kosterman, R., Graham, J.W., Hawkins, J.D., Catalano, R.F., and Herrenkohl, T.I., Violence & Victims,16(4), pp. 355-369, 2001.

Substance Use and Intimate Violence among Incarcerated Males

The purpose of this study was to examine substance use patterns among a sample of incarcerated males who report engaging in levels of intimate violence as well as identifying similarities and differences in demographic, economic status, mental health, criminal justice involvement, relationships, and treatment factors for three groups of incarcerated males - those who report perpetrating low intimate violence; those who report perpetrating moderately intimate violence; and those who report perpetrating extremely intimate violence the year preceding their current incarceration. Findings indicated that low intimate violence group's perpetration consisted almost exclusively of emotional abuse. Moderately intimate violent males and extremely intimate violent males however report not only high rates of emotional abuse but physical abuse as well. The distinction between moderate and extremely violent groups was substantial. Findings also indicated that perpetrators at different levels of violence in this study, did not vary significantly in age, employment history, marital status or race. However, the three groups showed significant differences in three main areas: (1) cocaine and alcohol use patterns (2) stranger violence perpetration and victimization experiences, and (3) emotional discomfort. Implications for substance abuse and mental health treatment interventions and for future research are discussed. Logan, T.K, Walker, R., Staton, M., and Leukefeld, C. Substance Use and Intimate Violence among Incarcerated Males. Journal of Family Violence, 6(2), pp. 93-114, June 2001.

The Drugs-Violence Nexus among American and Canadian Youth

This paper examines the relationship between drug use and violence among representative samples of students in the United States and Ontario, Canada. Canada has significantly lower levels of violent crime than the United States, but students report similar rates of drug use. Using logistic regression analysis, authors found a similar relationship between drug use and violence among adolescents in the two countries. All the drugs considered-cannabis, cocaine, and alcohol binge drinking-are significantly related to violent behavior; whether the perpetrator or the victim. The most noteworthy difference may be that in Ontario, drug use appears to be even more highly correlated with violence than in the United States. Harrison, L.D., Erickson, P.G., Adlaf, E., Freeman, C. The Drugs-Violence Nexus among American and Canadian Youth. Substance Use & Misuse, 36(14), pp. 2065-2086, 2001.

Correlates of Driving Anger

In a survey and a field study involving psychology students at a state university, it was determined that trait driving anger correlated with reports of anger in response to commonly occurring situations on the road. Significant positive correlations were found between trait driving anger and situations where provocation was significant, as in ordinary traffic, rush hour, and when being yelled at by another driver. There was no correlation when provocation was minimal. Moreover, trait driving anger was not correlated with crash rates or moving violations, but trait driving anger correlated with crash-related conditions such as loss of concentration, loss of vehicular control, and close calls. Deffenbacher, J., Lynch, R.S., Oetting, E.R., and Yingling, D.A. Driving Anger: Correlates and a Test of State-Trait Theory. Personality and Individual Differences, 31, pp. 1321-1331, 2001.

Risk and Promotive Effects in the Explanation of Persistent

Serious Delinquency in Boys Risk and promotive effects were investigated as predictors of persistent serious delinquency in male participants of the Pittsburgh Youth Study (R. Loeber, D. P. Farrington, M. Stouthamer-Loeber, & W. B. van Kammen, 1998), living in different neighborhoods. Participants were studied over ages 13-19 years for the oldest sample and 7-13 years for the youngest sample. Risk and promotive effects were studied in 6 domains: child behavior, child attitudes, school and leisure activities, peer behaviors, family functioning, and demographics. Regression models improved when promotive effects were included with risk effects in predicting persistent serious delinquency. Disadvantaged neighborhoods, compared with better neighborhoods, had a higher prevalence of risk effects and a lower prevalence of promotive effects. However, predictive relations between risk and promotive effects and persistent serious delinquency were linear and similar across neighborhood socioeconomic status. Stouthamer-Loeber, M., Loeber, R., Wei, E., Farrington, D.P., and Wikstroem, P-O.H. Journal of Consulting & Clinical Psychology, 70(1), pp. 111-123, 2002.

Test of the Plausibility of Adolescent Substance Use Playing a Causal Role in Developing Adulthood Antisocial Behavior

DSM-IV antisocial personality disorder diagnosis requires that conduct disorder be exhibited before age 15. However, recent studies have reported on men and women without conduct disorder before age 15 but qualified for the adulthood antisocial personality criterion (AAB). This general-population, retrospective study investigated the plausibility of causal relationships between adolescent drug and alcohol misuse (ADAM) and AAB among subgroups who reported childhood-onset conduct problems (CP), adolescent-onset CP, or no more than one conduct problem. Data from the Epidemiological Catchment Area Study (N=8,724) suggested that persons with childhood-onset CP are at much greater risk for AAB than persons with adolescent-onset CP. Nevertheless, large proportions of men and women with AAB had adolescent-onset CP or no CP. Regardless of CP history, being drunk by age 18 or having a drug use-related symptom before age 18 increased AAB risk, even after controlling for having a substance use-related disorder in adulthood. Mechanisms that potentially explain these associations are discussed. Ridenour, T.A, Cottler, L.B, Robins, L.N., Compton, W.M., Spitznagel, E.L., Cunningham-Williams, R.M. Journal of Abnormal Psychology, 111(1), pp. 144-155, 2002.

Workplace Substance Abuse Prevention Training

Supervisor tolerance-responsiveness is defined as the attitudes and behaviors of supervisors associated with either ignoring or taking proactive steps with troubled employees. Two studies examined this construct. The first study used survey methodology to examine supervisor response to and tolerance of coworker substance use in the workplace and ways of interfacing with the Employee Assistance Programs (EAPs). That study suggested that engaging supervisors in a dialogue about tolerance might improve their willingness to become more responsive to employee drug use, and more inclined to refer employees to EAPs. The second study was a randomized control field experiment that assessed a team-oriented training, using a cognitive mapping technique to help improve supervisor responsiveness to employee substance use. Supervisors who received this training showed improvement on several dimensions of responsiveness, including a greater propensity to refer substance-using employees to EAPs, compared to those who received a more didactic/informational training and those in a no-training/control group. Trained supervisors also showed increases in their own help-seeking behavior. Overall, results indicate that while supervisor tolerance of coworker substance use inhibits EAP utilization, it may be possible to address this tolerance using team-oriented prevention training. Bennett, J.B. and Lehman, W.E.K. Supervisor Tolerance-responsiveness to Substance Abuse and Workplace Prevention Training: Use of a Cognitive Mapping Tool Health Education Research, 17, pp. 27-42, 2002.

Treatment for Aggressive Children

This article provides a history and overview of an Anger Coping Program (ACP) for children with a history of aggressive behavior problems. The program uses a cognitive-behavioral approach to address the social-cognitive distortions and deficits of aggressive children. The program structure, its application in residential treatment, and its dissemination are discussed. The ACP has produced significant post-intervention improvements in childrens' behavior and social-cognitive processes. Lochman, J.E., Curry, J.D., Dane, H., and Ellis, M. The Anger Coping Program: An Empirically Supported Treatment for Aggressive Children. Residential Treatment for Children and Youth, 18, pp. 63-73, 2001.

Influence of a Substance-Abuse-Prevention Curriculum on Violence-Related Behavior

The objective of this work was to test the impact of a school-based substance-abuse prevention program, Project Towards No Drug Abuse (TND), on risk for violence. Logistic regression analyses tested whether victimization,

perpetration, or weapon carrying differed for intervention students relative to control students within a sample of 850 continuation high school students followed over 12 months. Data indicate a higher risk for victimization (OR=1.57) among male control students. No intervention effect was observed for female students or for perpetration among males. The findings provide limited support for a generalization of TND's preventive effect. Simon, T.R., Sussman, S., Dahlberg, L.L., and Dent, C.W. Influence of a Substance-Abuse-Prevention Curriculum on Violence-Related Behavior. American Journal of Health Behavior, 26(2), pp. 103-110, 2002.

Support for a Social Contextual Model of Delinquency

Three theoretical approaches designed to predict risk for delinquency were examined empirically. Hypotheses derived from these perspectives, an individual difference perspective, a social interactional model, and a social contextual approach, were tested using two independent samples of early adolescents followed over a four-year period. Results from a series of structural equation models suggested that a social contextual approach provided the best fit with the data across both samples and genders. Consistent with this approach, results indicated that a lack of nurturant and involved parenting indirectly predicted delinquency by increasing children's earlier antisocial behavior and deviant peer relationships. Child antisocial behavior also predicted similar decreases in nurturant parenting over time. Both child antisocial behavior and deviant peer affiliations in the fall of eighth grade predicted delinquency one year later. Scaramella, L.V., Conger, R.D., Spoth, R., and Simons, R.L. Evaluation of a Social Contextual Model of Delinquency: A Cross-Study Replication. Child Development, 73(1), pp. 175-195, 2002.

Deviant Peer Association and Aggression toward Female Partner

Deviancy training was examined as a risk factor for physical and psychological aggression toward a female partner among boys and young men in the Oregon Youth Study. Hostile talk about women during videotaped male friendship interaction was hypothesized to indicate a process by which aggression toward women is reinforced within male peer networks. Both antisocial behavior and hostile talk were predicted to be associated with later aggression toward a female partner. Prospective developmental models were tested from 9-10 years of age through young adulthood. Findings indicated that the relation of deviant peer association in adolescence and later aggression toward a partner was mediated by antisocial behavior; observed hostile talk about women with male peers explained additional variance in aggression toward a partner. Capaldi, D.M., Dishion, T.J., Stoolmiller, M., and Yoerger, K. Aggression Toward Female Partners by at-risk Young Men: The Contribution of Male Adolescent Friendships. Developmental Psychology, 37(1), pp. 61-73, 2001.

The First 3 Years of a Prevention Trial With Children at High Risk For Adolescent Conduct Problems

Fast Track is a conduct-problem prevention intervention derived from longitudinal research on how serious and chronic adolescent problem behaviors develop. Over 9,000 kindergarten children at 4 sites in 3 cohorts were screened, 891 were identified as high risk, and randomly assigned to intervention or control groups. Beginning in Grade 1, high-risk children and their parents were asked to participate in a combination of social skills and anger-control training, academic tutoring parent training, and home visiting. A multiyear universal classroom program was delivered to the core schools attended by these high-risk children. By the end of third grade, 37% of the intervention group was determined to be free of serious conduct-problem dysfunction, in contrast with 27% of the control group. Teacher ratings of conduct problems and official records of use of special education resources gave modest effect-size evidence that the intervention was preventing conduct problem behavior at school. Parent ratings provided additional support for prevention of conduct problems at home. Parenting behavior and children's social cognitive skills that had previously emerged as proximal outcomes at the end of the 1st year of intervention continued to show positive effects of the intervention at the end of third grade. Bierman, K.L., Coie, J.D., Dodge, K.A., et al. Evaluation of the First 3 Years of The Fast Track Prevention Trial With Children At High Risk For Adolescent Conduct Problems. Journal of Abnormal Child Psychology, 30 (1), pp. 19-35, 2002.

Predictor Variables Associated with Positive Fast Track Outcomes at Grade 3

Progress has been made in understanding the outcome effects of preventive interventions and treatments designed to reduce children's conduct problems. However, limited research has explored the factors that may affect the degree to which an intervention is likely to benefit particular individuals. This study examines selected child, family, and community baseline characteristics that may predict proximal outcomes from the Fast Track intervention. The primary goal of this study was to examine predictors of outcomes after 3 years of intervention participation, at the end of 3rd grade. Three types of proximal outcomes were examined: parent-rated aggression, teacher-rated oppositional-aggressive behavior, and special education involvement. The relation between 11 risk factors and these 3 outcomes was examined, with separate regression analyses for the intervention and control groups. Moderate

evidence of prediction of outcome effects was found, although none of the baseline variables were found to predict all 3 outcomes, and different patterns of prediction emerged for home versus school outcomes. Bierman, K.L., Coie, J.D., Dodge, K.A., et al. Predictor Variables Associated with Positive Fast Track Outcomes at the End of Third Grade. Journal of Abnormal Child Psychology, 30(1), pp. 37-52, 2002.

Stress and Smoking in Adolescence: A Test of Directional Hypotheses

The authors conducted a comparative test of the hypotheses that (a) stress is an etiological factor for smoking and (b) cigarette smoking causes increases in stress. Participants were a sample of 1,364 adolescents, initially surveyed at mean age 12.4 years and followed at 3 yearly intervals. Measures of negative affect, negative life events, and cigarette smoking were obtained at all 4 assessments. Latent growth modeling showed negative affect was related to increase in smoking over time; there was no path from initial smoking to change in negative affect. Comparable results were found for negative life events, with no evidence for reverse causation. Results are discussed with respect to theoretical models of nicotine effects and implications for prevention. Wills, T.A., Sandy, J.M., Yaeger, A.M. Health Psychology, 21(2), pp. 122-130, 2002.

Perceived Discrimination and Early Substance Abuse

This study investigated internalizing and externalizing symptoms as potential mediators of the relationship between perceived discrimination and early substance abuse among 195 American Indian 5th through 8th graders from three reservations that share a common culture. It was found that perceived discrimination increased both internalizing and externalizing symptoms among the youth. Perceived discrimination contributed significantly to internalizing symptoms, particularly among female and younger adolescents, but did not contribute to early onset substance abuse. Instead, perceived discrimination acted through externalizing symptoms to increase its likelihood. That is, American Indian early adolescents who experienced discrimination were likely to respond with anger and delinquent behaviors, which in turn were strongly associated with early substance abuse. Whitbeck L.B., McMorris, B.J., Chen, X., and Stubben, J. Perceived Discrimination and Early Substance Abuse among American Indian Children. Journal of Health and Social Behavior, 42, pp. 405-424, 2001.

Traditional Indian Culture Associated with Academic Success

This research examines factors affecting school success for a sample of 196 5th to 8th grade American Indian children from three reservations in the upper Midwest. The investigators assessed enculturation, a multidimensional construct including involvement with traditional activities, cultural identification, and traditional spirituality. The results indicate that traditional culture, as measured by enculturation, positively affects the academic performance of early adolescent American Indian students when controlling for age, participation in clubs, maternal warmth, and self-esteem. These findings are congruent with the growing literature on the positive effects of traditional culture for American Indian children. Whitbeck, L.B. Hoyt, D.R., Stubben, J.D., and LaFromboise, T. Traditional Culture and Academic Success among American Indian Children in the Upper Midwest. Journal of American Indian Education, 40(2), pp. 48-60, 2001.

Gender Labels and Gender Identity Predict Drug Use

This article examines the intertwined roles of gender labels and gender identity in predicting drug use behaviors and experiences of middle school students in a large, ethnically diverse, southwestern city. Gender labels refers to male vs. female while gender identity refers to a subjective sense of maleness/masculinity or femaleness/femininity. Gender labels by themselves appear to be more salient in explaining differences in self-reported drug use than two of the three gender identity measures examined. Boys used more drugs, used them more frequently and were more likely to use marijuana and hard drugs. However, masculine dominance also is associated with drug use, especially for boys. Such boys report more drug use and exposure. Gender identity measures do not supersede gender labels in predicting drug outcomes. However, labels and identity together are more powerful predictors than separately. Kulis, S., Marsiglia, F.F., and Hecht, M.L. Gender Labels and Gender Identity as Predictors of Drug Use Among Ethnically Diverse Middle School Students. Youth and Society, 33(3), pp. 442-475, 2002.

Predicting Smoking Initiation

In an analysis of 810 children drawn from a longitudinal study of students from a suburban school district in the Pacific Northwest, predictor variables for smoking initiation were assessed in second or third grade and smoking initiation was measured in sixth or seventh grade. Measures of family processes were entered separately into logistic regression models that included controls for household structure and income, parent smoking and peer and child characteristics. Measures of child attachment to parent and parent involvement with the child's school were

significantly and negatively associated with smoking initiation. The results suggest that family bonding and parent supportiveness protect youth from early smoking initiation while parent smoking and early childhood antisocial behavior and depression are risk factors for early smoking initiation. Fleming, C.B., Kim, H., Harachi, T.W., and Catalano, R.F. Family Processes for Children in Early Elementary School as Predictors of Smoking Initiation. Journal of Adolescent Health, 30(4), pp. 184-189, 2002.

Family- and Community-Level Factors Predict Parent Support Seeking

This study was designed to elucidate the influences of community- and family-level sociodemographic factors on parent formal and informal support seeking activities. Participants in the study were 1,260 parents of sixth graders from 26 rural communities. Informal support seeking was defined as the frequency with which parents sought parenting information through reading newspaper or magazine articles or talking to friends and relatives. Formal support seeking was defined as participating in support groups for parents, and talking to a family counselor or talking to a religious leader. Findings indicated that at the family level, higher formal support seeking scores were associated with lower household income, being a mother (vs. father), and a greater number of children, while higher informal support seeking was predicted by more parent education and being a mother (vs. father). There was a significant positive effect of community population size on informal parent support seeking. Redmond, C., Spoth, R., and Trudeau, L. Family- and Community-Level Predictors of Parent Support Seeking. Journal of Community Psychology, 30(2), pp.153-171, 2002.

Rural-Urban Differences in Substance Abuse Risk Factors

The authors examined rural-urban differences in cumulative risk for youth substance abuse. Two studies were conducted including samples of midwestern parents interviewed as a part of a state-level needs assessment for prevention program planning purposes (n=339; n=593). A cumulative risk index was constructed using individual and family risk items that have been shown to be associated with adolescent substance use. Rural urban comparisons demonstrated higher levels of cumulative risk among rural youth, which contributes to an explanation of findings from earlier reports of rural-urban differences in substance use. Spoth, R.L., Goldberg, C. Neppl, T., Trudeau, L., and Ramisetty-Mikler, S. Rural-Urban Differences in the Distribution of Parent-Reported Risk Factors for Substance Use Among Young Adolescents. Journal of Substance Abuse, 13, pp. 609-623, 2001.

Family Process Assessment for an African-American Sample

Data from 492 parents and 226 children in the EARLY ALLIANCE (EA) prevention trial were used to explore an assessment of family processes for a sample of African American kindergarten children, their parents, and teachers. Modified versions of the Family Assessment Measure, the Family Adaptability and Cohesion Evaluation Scales, the Family Beliefs Inventory, and the Deviant Beliefs measure were examined for internal consistency. Exploratory and confirmatory factor analyses provided empirical support for a Cohesion factor (cohesion and communication), a Structure factor (support and organization), a Beliefs factor (on family purpose and child development), and a Deviant Beliefs factor. Regression analyses examined the relationship of these measures of family processes to child social and academic competence, problem behavior, and early reading achievement. Family Structure (support and organization), Family and Beliefs were consistently related to parent- and teacher-reported competence and behavioral outcomes. Smith, E.P., Prinz, R.J., Dumas, J.E., and Laughlin, J. Latent Models of Family Processes In African American Families: Relationships to Child Competence, Achievement, and Problem Behavior. J. Marriage & Family, 63(4), pp. 967-980, 2001.

Recruitment and Retention Procedures for Violence Prevention

Participant recruitment and retention problems and strategies of the EARLY ALLIANCE (EA) violence prevention intervention are presented. EA combines home visitation and school-based prevention, and targets entire families in the prevention of child conduct disorder, substance abuse, and school failure. Techniques used to enhance participant recruitment included signing families to a package of programs, presenting EA as a preventive program. Caregivers were directly approached at the beginning of 1st grade, a time when they are particularly motivated to help children. Retention techniques include maintaining flexible schedules, keeping appointments, adhering to procedures, providing support in times of need, and adequately compensating families for their time and inconvenience. Prinz, R.J., Smith, E.P., Dumas, J.E., Laughlin, J.E., White, D.W., and Barron, R. Recruitment and Retention of Participants in Prevention Trials Involving Family-Based Interventions. Am. J. Prev. Med., 20(Suppl1), pp. 31-37, 2001.

Behavior Management to Improve School-Wide Positive Behavior

The Effective Behavior Support program, a consultative approach to assisting middle schools in implementing

empirically based school-wide behavior management practices, involved working with school staff to clarify rules, teach appropriate social behavior, increase positive reinforcement for positive behavior, consistently provide mild consequences for rule violation, and monitor data on student behavior. The intervention was evaluated through records of rewards given, discipline referrals, and frequent surveys of students. Where possible, data from the target school were evaluated against data from comparison schools. Results show effects at the target school on increased positive reinforcement for appropriate social behavior and decreased aggressive behavior among students. Discipline referrals were significantly decreased for 7th graders and for harassment among males. Students' perceptions of school safety improved at the target school but not at comparison schools. Students' reports of being physically or verbally attacked the previous day were reduced at the target school as well, but these changes were also seen at the comparison school. Metzler, C.W., Biglan, A., Rusby, J.C., and Sprague, J.R. Evaluation of a Comprehensive Behavior Management Program To Improve School-Wide Positive Behavior Support. Education & Treatment of Children, 24 (4), pp. 448-479, 2001.

Relationship Quality Of Aggressive Children And Their Siblings

Sibling influence on the learning and enactment of aggressive behavior has been consistently demonstrated in studies of sibling relationships. Available evidence suggests that, compared with nonaggressive children's sibling interactions, the sibling interactions of aggressive children are marked by more frequent, intense, and prolonged aggressive behaviors. Although research on normative and aggressive children's sibling interactions has increased recently, a number of limitations in this literature were addressed in this study by: (1) including both an aggressive and nonaggressive comparison group, (2) examining both positive and negative features of sibling relationships, (3) employing a multi method/multi-informant approach to data collection, and (4) utilizing an improved self-report method. In support of their hypotheses and consistent with previous research, results showed that aggressive children's sibling relationships were marked by higher levels of observed conflict and lower levels of self-reported positive features. When gender was examined, results showed that older brother/younger sister dyads were characterized by higher levels of negative features and lower levels of positive features. Aguilar, B., O'Brien, K.M., August, G.J., et al. Relationship Quality of Aggressive Children and Their Siblings: A Multi-Informant, Multi-Measure Investigation. Journal of Abnormal Child Psychology, 29 (6), pp. 479-489, 2001.

Binge Drinking Trajectories from Adolescence to Emerging Adulthood in a High-Risk Sample: Predictors and Substance Abuse Outcomes

This study describes binge-drinking trajectories from adolescence to emerging adulthood in 238 children of alcoholics and 208 controls. Mixture modeling identified three trajectory groups: early-heavy (early onset, high frequency), late moderate (later onset, moderate frequency), and infrequent (early onset, low frequency). Nonbingers were defined a priori. The early-heavy group was characterized by parental alcoholism and antisociality, peer drinking, drug use, and (for boys) high levels of externalizing behavior, but low depression. The infrequent group was elevated in parent alcoholism and (for girls) adolescent depression, whereas the nonbinger and late-moderate groups showed the most favorable adolescent psychosocial variables. All 3 drinking trajectory groups raised risk for later substance abuse or dependence compared with the nonbingers, with the early-heavy group at highest risk. Chassin, L., Pitts, S.C., Prost, J. Journal of Consulting & Clinical Psychology, 70(1), pp. 67-78, 2002.

Moderators of the Relation between Substance Use Level and Problems: Test of a Self-Regulation Model in Middle Adolescence

The authors tested predictions, derived from a self-regulation model, about variables moderating the relationship between level of substance use (tobacco, alcohol, and marijuana) and problems associated with use. Data were from two independent studies of adolescents, with mean ages of 15.4 and 15.5 years (Ns=1,699 and 1,225). Factor analysis indicated correlated dimensions of control problems and conduct problems. Protective moderation was found for variables indexing good self-control; risk-enhancing moderation was found for variables indexing poor self-control. These effects were generally independent of deviance-prone attitudes and externalizing symptomatology. Multiple-group structural modeling indicated moderation occurred for paths from life stress and coping motives and for paths from level to control and conduct problems. Moderation effects were also found for parental variables, peer variables, and academic competence. Wills, T.A., Sandy, J.M., and Yaeger, A.M. Journal of Abnormal Psychology, 111(1), pp. 3-21, 2002.

Developmental Trajectories of Cigarette Use

This study identified developmental trajectories of cigarette smoking from early adolescence into young adulthood, and delineated whether risk factors derived from a social learning-problem behavior framework could differentiate

among trajectories. Participants (N=374) were interviewed five times from age 12 until age 30/31. Using growth mixture modeling, three trajectory groups were identified - heavy/regular, occasional/maturing out, and non/experimental smokers. Being a female, having higher disinhibition, receiving lower grades, and more frequent use of alcohol or drugs significantly increased the probability of belonging to a smoking trajectory group compared with being a nonsmoker. Higher disinhibition and receiving lower grades also differentiated regular smokers from the rest of the sample. None of the risk factors distinguished occasional from regular smokers. When models were tested separately by sex, disinhibition, other drug use, and school grades were associated with smoking for both sexes. On the other hand, environmental factors, including socioeconomic status, parent smoking and friend smoking, were related to smoking for females but not for males. Sex differences in developmental trajectories and in smoking behavior among regular smokers were notable. The occasional/maturing out group was made up of more females than males and may relate to women stopping or reducing smoking when they begin to have children. In contrast, women were more likely to start regular smoking earlier than males and being female significantly differentiated smokers from nonsmokers. Future research should examine transitions and turning points from adolescence to adulthood that may affect cessation and escalation differently for males and females. White, H.R., Pandina, R.J., and Chen, P.H. Developmental Trajectories of Cigarette Use from Early Adolescence into Young Adulthood. Drug Alcohol Depend., 65, pp. 167-178, 2002.

Risk Factors Vary According to Substance Use Outcome

This longitudinal study investigated Grade 7 and Grade-10 risk factors for alcohol misuse at Grade 12. Alcohol use was conceptualized as problem-related drinking, high-risk drinking and high consumption. Prospective analyses using two-part models predicted any alcohol misuse and the amount of misuse for over 4,200 participants in the RAND Adolescent Pan Study. Predictor variables were: demographics; substance use and exposure; prodrug attitudes; rebelliousness and deviant behavior; self-esteem; family structure and relations; and grades. Grade-7 predictors of alcohol misuse 5 years later included: early drinking onset; parent drinking; future intentions to drink; cigarette offers; difficulty resisting pressures to smoke; being white; being male; having an older sibling; deviant behavior; and poor grades. By Grade 10, predictors of alcohol misuse 2 years later included: drinking and marijuana use by self and peers; future intentions to drink; difficulty resisting pressures to drink and use marijuana; being male; coming from a disrupted family; and deviant behavior. Somewhat different predictors were identified for problem-related, high-risk and high consumption drinking, emphasizing the importance of investigating multiple dimensions of misuse. Ellickson, P.L., Tucker, J.S., Klein, D.J., and McGuigan, K.A. Journal of Studies on Alcohol, 62(6), pp. 773-782, 2001.

Emotional Distress Both Contributes To And Is Influenced By Cigarette Smoking

Empirical evidence regarding the causal nature of the relationship between emotional distress and tobacco use in male and female adolescents provides support for both the distress-to-use and the use-to-distress hypotheses. Using a cross-lagged model with 3 waves of data from 2,961 adolescents followed into young adulthood, the authors tested the hypothesis that this relationship changes over time. As hypothesized, emotional distress in Grade 10 was associated with increased smoking in Grade 12 for both boys and girls. Smoking in Grade 12 was, in turn, associated with increased emotional distress in young adulthood. The addition of 3 factors (rebelliousness, deviance, and family problems) to the model did not alter the results. Results suggest that the relationship between tobacco use and emotional distress is a dynamic one in which distress initially leads to use but then becomes exacerbated by it over time, Orlando, M., Ellickson, P.L., and Jinnett, K., Journal of Consulting & Clinical Psychology, 69(6), pp. 959-970, 2001.

Predictors of Late-Onset Smoking and Cessation Over 10 Years

Researchers examined predictors of smoking onset and cessation between early and late adolescence (13-18 yrs) and between late adolescence and young adulthood (18-23 yrs). Subjects were 3,056 high school students recruited in 1985. Predictors measured at 13 and 18 yrs included sociodemographic and environmental characteristics, smoking attitudes, bonds with school and problem behavior. Results show that robust predictors of initiation and cessation across the 2 developmental periods included doing poorly in school and prior smoking. Predictors common to 3 of 4 developmental models included being young for grade cohort and intention to smoke. Early deviant behavior and drinking fostered initiation among older teenagers, but problem behavior as an older teenager did not predict young adult initiation. Smokers with few or no high school friends who smoked and felt able to resist smoking pressure at age 18 yrs were more likely to quit by age 23 yrs. Being female predicted initiation by age 18 yrs; being African-American, Hispanic, or Asian inhibited this. The strong association of prior smoking behavior and intentions with later smoking among adolescents and young adults is seen to underscore the importance of early smoking prevention that continues through high school. Ellickson, P.L., McGuigan, K.A., and Klein, D.J., Journal of Adolescent Health, 29(2), pp. 101-108, 2001.

High-Risk Behaviors Associated With Early Smoking

This study compared problem behaviors of 7th grade nonsmokers, experimenters, and smokers at baseline and at 5-yr follow-up. 4,327 7th grade students completed questionnaires concerning academic difficulties, substance use, and delinquent behavior at baseline and at 5-yr follow-up. Subjects were classified as nonsmokers, experimenters, or smokers. Results showed that, compared with nonsmokers, early smokers were 3+ times more likely by 12th grade to regularly use tobacco and marijuana, use hard drugs, sell drugs, have multiple drug problems, drop out of school, and experience early pregnancy and parenthood. These subjects were also at higher risk for low academic achievement and behavioral problems at school, stealing and other delinquent behaviors, and use of predatory and relational violence. Early experimenter subjects were at significantly greater risk for these problems as well, although to a lesser extent than smokers. The higher risk of many of these problems was evident for experimenters and smokers as early as 7th grade. It is concluded that early experimenters and smokers are more likely than nonsmokers to experience various problem behaviors by 12th grade, with many of these problems evident as early as 7th grade. Ellickson, P.L., Tucker, J.S., and Klein, D.J., Journal of Adolescent Health, 28(6), pp. 465-473, 2001.

Inflating GPA In Self-Report Related To Reports of Less Psychological Distress

The purpose of this study was to better understand the implications for using self-reported grade point average (GPA) versus school-record GPA in academic achievement research. The authors examined the degree of accuracy between self-reported and school-record GPA among 679 African American high school students (mean age 15.1 yrs) and studied how the discrepancy between GPA is related to psychological distress, academic beliefs, and problem behaviors. Structural equation modeling was used to examine how the 2 GPA measures are related differently to these outcomes, regardless of their discrepancy. Results show that nearly half the youths interviewed over reported their GPAs by at least 2 half grades. Youth who over reported their GPAs also reported less psychological distress, more successful academic beliefs, and fewer problem behaviors. Self-reported GPA was associated with all 3 sets of variables, but school-record GPA was associated with only problem behaviors. The findings suggest that it may be useful for researchers to consider how different measures of GPA may influence their results. Zimmerman, M.A., Caldwell, C.H., and Bernat, D.H., Journal of Applied Social Psychology, 32(1), pp. 86-109, 2002.

Primary Mental Disorders are Significant Predictors of First Onset of Subsequent Substance User Disorders

Kessler and colleagues present results of analyses of patterns of comorbidity between mental disorders and substance use disorders utilizing data from seven epidemiologic surveys carried out in six countries including the U.S., Canada, Brazil, Mexico, Germany and the Netherlands. Results are consistent across the surveys in showing that strong comorbidities exist between mental disorders and substance use disorders, that mental disorders are typically temporally primary and that primary mental disorders are significant predictors of the first subsequent onset of substance use disorders. Only active mental disorders, not remitted disorders, predict subsequent substance use, problems, and dependence. These findings suggest that there is something about the mental disorders themselves rather than about determinants of these disorders, that promotes substance disorders. Further analyses revealed that mental disorders are less powerful predictors of first drug use than of progressing from use to problem use and from problem use to dependence. Simulations suggest that primary mental disorders are associated with 54.7% of all drug dependence among men and 47.8% among women in these surveys. Conduct disorder and adult antisocial behavior are responsible for these cases among men, while anxiety disorders and mood disorders are also important among women. The authors conclude that the study results suggest that early interventions to treat mental disorders might be effective in reducing the number of people who would otherwise become dependent on drugs. Kessler, R.C., Aguilar-Gaxiola, S., Andrade, L., Bijl, R., Borges, G., Caraveo-Anduaga, J., DeWit, D., Kolody, B., Merikangas, K., Molnar, B., Vega, W., Walters, E., Wittchen, H. and Ustun, T. Mental-Substance Cormorbidities in the ICPE Surveys. Psychiatria Fennica, 32(supplement 2), pp. 62-79, 2001.

Exploring Why Heroin Epidemics Occur in Different Groups

As part of a project to explain heroin use trends, Agar and colleague develop and explore the concept of "open marginality" to highlight how different groups impacted by heroin epidemics have a common historical experience. Analysis of the literature on the history of drug epidemics in the U.S. together with the authors' work on two heroin epidemics in the Baltimore region demonstrate the diversity of groups who have been "at risk" over the years. Agar's approach is to integrate political, socioeconomic and cultural factors within an historical framework. Analysis of cases shows that such groups experience a rapid and unexpected change, such that a gap between expectations and reality opens up, a gap that is taken up in national public discourse. The paper presents the concept of "open marginality" as part of a broader working theory to explain drug trends that the authors hope will enhance our ability to forecast and thus anticipate (and potentially prevent) new drug use trends. Agar, M. and Reisinger, H.S. Open Marginality: Heroin

Epidemics in Different Groups. Journal of Drug Issues, 31(3), pp. 729-746, 2001.

Using Trend Theory to Explain Heroin Use Trends

Trend theory is developed by the authors in an effort to integrate histories of populations and distribution systems to explain the key epidemiological question: why do these people in this place at this time experience a rapid increase in heroin use? The theory grows out of work on heroin trends in the Baltimore metropolitan area, specifically on epidemics among urban African-Americans in the 1960s and among suburban white youth in the 1990s. The authors describe trend theory as an example of agent-based adaptive models characteristic of complexity theory and draw on the heroin epidemic studies to illustrate how the model works. Agar, M., and Reisinger, H.S. Using Trend Theory to Explain Heroin Use Trends. Journal of Psychoactive Drugs, 33(3), pp. 203-210, 2001.

Intergenerational Transmission of Risks for Problem Behavior

The intergenerational transmission of risk factors for problem behaviors was examined across three generations. Two hundred fifty-four 2-year-old toddlers, one or two of their parents, and one grandmother of each toddler were studied. Grandmothers and parents were individually interviewed. Data were analyzed for the male and female toddlers combined. Correlations and hierarchical multiple regression analyses were performed. Findings indicate that the grandmother-parent relationship, parental personality attributes, marital harmony, and drug use and the parent-toddler relationship, predict the toddlers' behavior. The investigation provides evidence for a longitudinal, intergenerational process whereby the grandmother-parent relationship and the parents' personality and behavioral attributes are transmitted across generations through their association with the parent-child relationship. Brook, J.S., Whiteman, M., and Zheng, L. Journal of Abnormal Child Psychology, 30(1), pp. 65-76, February 2002.

Childhood Adversities Associated with Risk for Eating Disorders or Weight Problems during Adolescence or Early Adulthood

This community-based prospective longitudinal study was conducted to investigate the association between childhood adversities and problems with eating or weight during adolescence and early adulthood. A sample of 782 mothers and their offspring were interviewed during the childhood, adolescence, and early adulthood of the offspring. Childhood maltreatment, eating problems, environmental risk factors, temperament, maladaptive parental behavior, and parental psychopathology were assessed during childhood and adolescence. Eating disorders and problems with eating or weight in the offspring were assessed during adolescence and early adulthood. A wide range of childhood adversities were associated with elevated risk for eating disorders and problems with eating or weight during adolescence and early adulthood after the effects of age, childhood eating problems, difficult childhood temperament, parental psychopathology, and co-occurring childhood adversities were controlled statistically. Numerous unique associations were found between specific childhood adversities and specific types of problems with eating or weight, and different patterns of association were obtained among the male and female subjects. Maladaptive paternal behavior was uniquely associated with risk for eating disorders in offspring after the effects of maladaptive maternal behavior, childhood maltreatment, and other co-occurring childhood adversities were controlled statistically. The authors conclude that childhood adversities may contribute to greater risk for the development of eating disorders and problems with eating and weight that persist into early adulthood. Maladaptive paternal behavior may play a particularly important role in the development of eating disorders in offspring. Johnson, J.G., Cohen, P., Kasen, S., and Brook, J.S. Am J Psychiatry, 159(3), pp. 394-400, March 2002.

Adolescent Life Events as Predictors of Adult Depression

Among adults, life events predict future episodes of major depression as well as a range of anxiety disorders. While studies have begun to examine this issue in adolescents, few studies rely upon prospective epidemiological designs to document relationships between adolescent life events and adult major depression. A sample of 776 young people living in Upstate New York received DSM-based psychiatric assessments and an assessment of life events in 1986. Psychopathology was again assessed in 1992. This study examined the predictive relationship between life events in 1986 and depression as well as anxiety in 1992, controlling for depression/anxiety in 1986. Results show that adolescent life events predicted an increased risk for major depression diagnosis in adulthood. When analyzed continuously, an association emerged with symptoms of major depression as well as with symptoms of generalized anxiety disorder. However, this association with generalized anxiety disorder was limited to females. Pine, D.S., Cohen, P., Johnson, J.G., and Brook, J.S. J Affect Disord, 68(1), pp. 49-57, February 2002.

Gender Differences in Juvenile Arrestees' Drug Use, Self-Reported Dependence, and Perceived Need for Treatment

The authors examined gender differences in drug use, self-reported dependence, and perceived need for treatment in a national sample of juvenile arrestees and detainees between the ages of nine and 18 years. A sample of 4,644 boys and girls, drawn from the Juvenile Drug Use Forecasting Survey from 1992 to 1995, was matched by sex within each of seven sites by survey year. In anonymous interviews, respondents were asked about their living arrangements, drug use, and need for drug treatment. Questions about drug use covered marijuana, cocaine, crack, heroin, crystal methamphetamine, amphetamines, and phencyclidine (PCP). Logistic regression was used to identify significant predictors of drug dependence and perceived need for treatment. Results showed that girls were significantly more likely than boys to report dependence but were no more likely to report a need for treatment. Among those who reported current, frequent drug use, girls were significantly less likely than boys to report a need for treatment. Girls who reported having more severe drug problems were more likely than their male counterparts to report dependence and a need for treatment. The authors conclude that clinicians should assess and reduce barriers to treatment perceived by girls in particular to engage them in services before their drug use escalates. Kim, J.Y., and Fendrich, M. Psychiatr Serv, 53(1), pp. 70-75, January 2002.

Sex-Specific Predictors of Suicidality Among Runaway Youth

This study examined predictors of suicidality (ideation and attempts) among 348 adolescent runways (197 boys; 56% African American; Mean age = 16) using sex-specific models that tested the impact of the three domains of the Social Action Model: individual characteristics, interpersonal influences, and life events. Twenty-five percent of the girls and 14% of the boys had attempted suicide at least once. Male suicidality was mainly predicted by individual characteristics: identifying as gay, emotional distress, fewer conduct problems, and avoidant reasons for drug use. The interpersonal influence of suicidal friends also predicted suicidality. Variables from all three domains influenced girls: individual characteristics of lower age, lower self-esteem, and emotional distress; interpersonal influence of suicidal friends; and life events of having lived on the streets and assaults. Findings suggest some sex-specific interventions, but decreasing emotional distress and lessening the influence of suicidal friends may be useful for both boys and girls. Leslie, M.B., Stein, J.A., and Rotheram-Borus, M.J. J Clin Child Psychol, 31(1), pp. 27-40, March 2002.

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Research Findings

Services Research

Integrating Primary Medical Care With Addiction Treatment: A Randomized Controlled Trial

The prevalence of medical disorders is high among substance abuse patients, yet medical services are seldom provided in coordination with substance abuse treatment. The objective of this study was to examine differences in treatment outcomes and costs between integrated and independent models of medical and substance abuse care as well as the effect of integrated care in a subgroup of patients with substance abuse-related medical conditions (SAMCs). A randomized controlled trial was conducted between April 1997 and December 1998. Subjects comprised adult men and women (n = 592) who were admitted to a large health maintenance organization chemical dependency program in Sacramento, CA. Patients were randomly assigned to receive treatment through an integrated model, in which primary health care was included within the addiction treatment program (n = 285), or an independent treatment-as-usual model, in which primary care and substance abuse treatment were provided separately (n = 307). Both programs were group based and lasted 8 weeks, with 10 months of aftercare available. Main outcome measures included: abstinence outcomes, treatment utilization, and costs 6 months after randomization. Both groups showed improvement on all drug and alcohol measures. Overall, there were no differences in total abstinence rates between the integrated care and independent care groups (68% vs. 63%, P = .18). For patients without SAMCs, there were also no differences in abstinence rates (integrated care, 66% vs. independent care, 73%; P = .23) and there was a slight but nonsignificant trend of higher costs for the integrated care group ($367.96 vs. $324.09, P = .19). However, patients with SAMCs (n = 341) were more likely to be abstinent in the integrated care group than the independent care group (69% vs. 55%, P =.006; odds ratio [OR], 1.90; 95% confidence interval [CI], 1.22-2.97). This was true for both those with medical (OR, 3.38; 95% CI, 1.68-6.80) and psychiatric (OR, 2.10 95% CI, 1.04-4.25) SAMCs. Patients with SAMCs had a slight but nonsignificant trend of higher costs in the integrated care group ($470.81 vs. $427.95, P =.14). The incremental cost-effectiveness ratio per additional abstinent patient with an SAMC in the integrated care group was $1581. Authors concluded that individuals with SAMCs benefit from integrated medical and substance abuse treatment, and such an approach can be cost-effective. These findings are relevant given the high prevalence and cost of medical conditions among substance abuse patients, new developments in medications for addiction, and recent legislation on parity of substance abuse with other medical benefits. Weisner, C., Mertens, J., Parthasarathy, S., Moore, C., and Lu, Y. JAMA. 286(14), pp. 1715-1723, 2001.

Testing the Effectiveness of Cognitive-Behavioral Treatment for Substance Abuse in a Community Setting: Within Treatment and Posttreatment Findings

The authors evaluated the short-term effectiveness of cognitive-behavioral treatment (CBT) for substance abuse delivered in a community setting. At entry into outpatient community substance abuse treatment, participants (N = 252) were randomly assigned to 3 conditions: high-standardization CBT, low-standardization CBT, and treatment as usual. Treatment consisted of 12 weekly individual therapy sessions. There was a significant decrease in substance use from baseline, with participants reporting being abstinent on 90% of within-treatment days and 85% of days during the 6 months posttreatment. However. there were no significant differences in outcomes across conditions. The hypothesis that disseminating CBT to community settings will improve outcomes was not supported. Standard substance abuse counseling may be more effective than previously thought or closer attention must be paid to implementing protocols. Morgenstern, J., Blanchard, K.A., Morgan, T.J., Labouvie, E., and Hayaki, J. Journal of

Consulting and Clinical Psychology, 69(6), pp. 1007-1017, Dec 2001.

The Role of Social Support following Short-term Inpatient Treatment

The intensive, time-limited, short-term inpatient modality treatment for substance abuse appears to have positive outcomes despite its brevity. The researchers examined patient characteristics and posttreatment experiences to understand who is likely to benefit from this treatment and under what circumstances. The sample included 748 patients in 12 short-term inpatient programs. Twenty-two percent of patients used cocaine at least weekly in the 1-year follow-up period, and an additional 9% drank frequently (compared with pretreatment rates of 69% and 15%, respectively). Overall, patients' social support networks following treatment were more important factors than the pre- or during-treatment variables examined. Broome, K.M., Simpson, D.D., and Joe, G.W. American Journal on Addictions, 11(1), pp. 57-65, 2002.

12-step Program Participation and Effectiveness: Do Gender and Ethnic Differences Exist?

Although 12-Step is increasingly utilized as a recovery resource and is viewed by many addiction specialists as an integral component of treatment and long-term recovery, questions regarding participation and effectiveness of 12-Step programs for women and ethnic minorities have been raised. Utilizing data from the Los Angeles Target Cites Evaluation Project (n = 356), participants in adult outpatient alcohol and drug treatment were followed for 24 months and rates of 12-Step participation and effectiveness were assessed for all gender and ethnic groups. Contrary to reports that 12-Step is more appropriate for European-American males, statistical analyses reveals that women and ethnic minorities are equally likely to attend 12-Step programs, and to recover in conjunction with such participation as European-American males. Although 12-Step may not appeal to all seeking to cease alcohol and drug use, the clinical implications for treatment providers and other addiction specialists points to the benefits of integrating 12-Step components into traditional treatment programs and recommending 12-Step participation for clients of all gender and ethnic groups. Hillhouse, M.P., and Fiorentine, R. J Drug Issues, 31(3), pp. 767-780, 2001.

Motivation as a Predictor of Therapeutic Engagement in Mandated Residential Substance Abuse Treatment

Motivation for treatment is critical for retaining clients in the committee based substance abuse treatment program and for their becoming therapeutically engaged in the recovery process. Nevertheless few have examined the effect of motivation on therapeutic engagement in criminal justice settings. Baseline and during-treatment data were collected prospectively from 419 probationers remanded to a 6-month modified therapeutic community. Desire for help and treatment readiness were associated with indicators of therapeutic engagement even after statistically controlling for additional factors that could have confounded these relationships. Targeted readiness and induction interventions are therefore recommended for offenders with low motivation who are remanded to treatment in correctional settings. Hiller, M.L., Knight, K., Leukefeld, C., and Simpson, D.D. Criminal Justice and Behavior, 29(1), pp. 56-75, Feb 2002.

Involuntary Treatment Within a Prison Setting - Impact on Psychosocial Change During Treatment

Given the high proportion of criminal justice treatment clients in the United States, a major policy and program issue in drug treatment is the appropriateness and effectiveness of coercing offenders to enter and remain in treatment. As part of a comprehensive evaluation of a large treatment facility in California, the authors conducted an analysis of during-treatment psychosocial changes of inmates admitted voluntarily and those admitted involuntarily. The main focus was on psychological functioning (self-esteem, depression, anxiety, decision making, and self-efficacy) and social functioning (hostility, risk taking, and social conformity). Regardless of voluntary or involuntary admission status, treatment participants exhibited significant during-treatment change on most measures of psychosocial functioning, although significant change was more likely on measures of psychological than on social functioning. In addition, similar percentages of both groups were paroled from treatment (as opposed to being discharged from the program prior to parole) and agreed to attend community treatment. Prendergast, M.L., Farabee, D., Cartier, J., and Henkin, S. Criminal Justice and Behavior, 29(1), pp. 5-26, Feb 2002.

Drug Problem Recognition, Desire for Help, and Treatment Readiness in a Soup Kitchen Population

Researchers determined hypothesized predictors of three components of motivation for change-drug problem recognition, desire for help, and treatment readiness-in a high-risk, drug-using population. The sample consisted of

190 guests at two inner-city soup kitchens in Brooklyn, NY who reported drug/alcohol use and were not participating in substance dependency treatment. Ever receiving addiction treatment, having no trade/job skills, and more severe symptoms of depression were associated with greater drug problem recognition. More recent days of drug/alcohol use, intensive pattern of drug use, and greater problem recognition were associated with greater desire for help. Caring for children, more recent days of drug; alcohol use, physical health problems, and desire for help were the direct predictors of treatment readiness. Problem recognition had a strong indirect effect on readiness mediated through desire for help. Knowledge of a drug user's motivational state and the factors leading to it can help guide the development of more effective interventions. Nwakeze, P.C., Magura, S., and Rosenblum, A. Substance Use & Misuse, 37(3), pp. 291-312, 2002.

Drug Court Effectiveness: A Review of California Evaluation Reports, 1995-1999

Over the past two decades, drug courts have emerged as a viable alternative for addressing drug cases within the criminal justice system. In California, the Drug Court Partnership Program (DCPP) was created in 1998 and has supported and funded the development of drug courts throughout the State. The authors report on a review of California drug court evaluations through January 2000 conducted as part of an evaluation of the California DCPP. A total of 23 evaluations were collected. Seventeen were reviewed in detail, and six were excluded because they were internal reports rather than evaluations. A standardized review process was initiated which led to a scored rating of the evaluation reports. This review supports previous findings that drug court participants may experience reduced rearrest rates by 11% to 14% compared to non-participants. The largest reduction in rearrest rates appears among graduates. The graduation rates were between 19% and 54%. Costs and savings associated with drug courts were discussed but no conclusions were possible based on the findings from these evaluations. The evaluation of the effectiveness of drug courts presents unique challenges. This review concludes with a discussion of evaluation methods (e.g. standardizing rate calculations, term definitions) that would strengthen drug court research. Guydish, J., Wolfe, E., Tajima, B., and Woods, W.J. Journal of Psychoactive Drugs, 33(4), pp. 369-378, Oct-Dec 2001.

Innovations in Treatment for Drug Abuse: Solutions to a Public Health Problem

Illicit drug use is an important public health problem with broad social costs. The low effectiveness of prevention efforts leaves treatment of drug dependence as one of the most powerful means of fighting illicit drug use. Treatment reduces drug use and crime and increases individuals' functioning. However, programs that treat drug dependence have high dropout rates and low completion rates. In addition, some individuals continue to use drugs while in treatment, and relapse is common. Furthermore, only a fraction of those who need treatment receive it. Recently, there have been important innovations that reduce barriers and increase effectiveness of treatment. These innovations include new pharmacological agents, novel counseling strategies, promising ways to motivate, and treatment in new settings. Researchers describe standard treatments and recent innovations designed to increase (a) effectiveness of treatment, (b) motivation to seek care, (c) access, (d) retention, and (e) cost-effectiveness. Researchers provide criteria on how these innovations should be evaluated in order to determine which should be adopted, funded, and transferred to existing and future treatment programs. Sindelar, J.L., Fiellin, D.A. Annual Review of Public Health, 22, pp. 249-272, 2001.

Correlates and 6-month Outcomes for Co-occurring Cannabis Use in Rural and Urban At-risk Drinkers

Little is known about the functional correlates of recent cannabis use when such use is additional to an "alcohol disorder" in non-treatment populations. Researchers report on data from a prospective study of a large probability community survey of 733 at-risk drinkers in six Southern U.S. states (Alabama, Arkansas, Georgia, Louisiana, Mississippi, and Tennessee) conducted from 1995 to 1996. Twenty-one percent reported cannabis use during the past six months at the baseline interview. These cannabis users were significantly less likely to be married, employed, or a high school graduate ($p < .05$). They were also more likely to have a diagnosis of "antisocial personality disorder" or "panic disorder. Recent cannabis users also reported more negative consequences of their alcohol use, including more frequent recent diagnoses of an "alcohol disorder," legal difficulties associated with their drinking, and more social consequences attributed to drinking. At the six-month follow-up interview, negative alcohol outcomes were associated with concurrent cannabis use, including higher frequency and quantity of alcohol consumption, greater frequency of recent "alcohol abuse" and "dependence," and greater social consequences of drinking. These results all point to substantially poorer functioning and experiences of individuals with concurrent at-risk alcohol and cannabis use. Authors suggest that cannabis use may be a marker for greater impairment associated with at-risk drinking. Booth, B.M., and Kirchner, J.A.E. Substance Use & Misuse, 36(6-7), pp. 717-733, 2001.

Engagement Models for Adolescents in DATOS-A

Considerable research conducted with adults in drug treatment has demonstrated that engaging patients is essential for maximizing treatment retention, completion, and posttreatment outcome. Based on the importance of during-treatment activities for improving outcomes, relationships between patient background, treatment readiness, and therapeutic engagement were examined in a national sample of adolescents admitted to 20 treatment programs representing three modalities. Adolescent patients with higher readiness for treatment at intake subsequently became more therapeutically involved, replicating previous findings on relationships between motivation and engagement in adult samples. One of the most influential background factors associated with higher treatment readiness was patient relationships with family and friends. Interventions that focus on treatment readiness appear to be appropriate strategies for improving treatment engagement. Broome, K.M., Joe, G.W., and Simpson, D.D. Journal of Adolescent Research, 16(6), pp. 608-623, 2001.

Treatment Service Patterns and Organizational Structures: An Analysis of Programs in DATOS-A

As a first step in examining drug abuse treatment typologies for adolescents, the researchers investigated the relationship between patient needs and program characteristics. They hypothesized that there may be systematic differences in the types of services provided that are a function of program characteristics as well as the needs of patients entering treatment. The availability of a variety of treatment services was examined within a national sample of programs treating adolescent drug abuse patients. Treatment service delivery profiles were created and examined in the context of organizational variables such as program modality, program directors' academic credentials, program capacity, staff composition, accreditation, and patient problems. Researchers found distinct profiles of services existed within residential and outpatient modalities and that these service profiles were related both to organizational factors and to patient problem profiles. Delany, P.J., Broome, K.M., Flynn, P.M., and Fletcher, B.W. Journal of Adolescent Research, 16(6), pp. 590-607, 2001.

Attrition Prevention with Individuals Awaiting Publicly Funded Drug Treatment

The aim of this study was to evaluate the effectiveness of a motivational intervention to reduce attrition from a waiting list for substance abusers seeking publicly funded treatment. Randomized clinical trial compared an "attrition prevention" condition to standard care while awaiting treatment admission. The study was conducted at a centralized substance abuse assessment and referral center in Seattle, Washington. Study participants comprised substance abusers (n = 654) eligible for publicly funded drug abuse treatment. Measurements collected were: alcohol and drug use, substance-related negative consequences, areas in need of help, perceived need for help, emotional status, readiness to change, reasons for seeking and perceived barriers to entering treatment. Overall, approximately 70% of clients entered treatment, and of these approximately 70% completed their assigned treatment. Those who entered treatment showed significant reductions in substance use and improved psychosocial function at a short-term 3-month follow-up. However, the attrition prevention intervention had no differential effect on treatment entry, completion, or outcome compared to the standard waiting list. Further, there were no differences across therapists on these outcome measures. Authors concluded that a motivational attrition prevention intervention did not enhance treatment entry, completion, or outcome among treatment-seeking substance abusers and suggested that alternative strategies, such as contingency management and case management, may help facilitate treatment entry for individuals seeking publicly funded treatment. Donovan, D.M., Rosengren, D.B., Downey, L., Cox, G.B., and Sloan, K.L. Addiction, 96(8), pp. 1149-1160, 2001.

Drug Abuse Treatment and Comprehensive Services for Adolescents

Data from two national studies of treatment spanning two decades-Treatment Outcome Prospective Study (TOPS), 1979 to 1981, and Drug Abuse Treatment Outcome Studies for Adolescents (DATOS-A), 1993 to 1995-provided a comparison of treatment and services provided to 261 TOPS and 1.519 DATOS-A in treatment adolescent patients in a cross-modality sample of 24 TOPS and 31 DATOS-A programs. The authors used patient self-reports of treatment needs and services received to compare unmet needs for six services. Findings showed a general decline over treatment eras in services received that was only partially offset by significant decreases in some self-reported service needs in DATOS-A. Unmet needs increased significantly over treatment eras for specific services, including psychological, family, employment, and financial services. The highest need in both studies was for family services. The DATOS-A appeared to be addressing family needs better than the TOPS program much of which was more adult focused. Across all DATOS modalities, from 40% to 50% patients reported unmet need for psychological services, considerably higher than the 7% to 10% of TOPS patients. Potential explanations for the increases in unmet needs include changes in treatment access and decreases in program resources for services. Etheridge, R.M., Smith, J.C., Rounds-Bryant, J.L., and Hubbard, R.L. Journal of Adolescent Research, 16(6), pp. 563-589, 2001.

The Effect of Drug Treatment on Criminal Behavior among Adolescents in DATOS-A

The authors examined the effects on criminal behavior among 1,167 adolescents who participated in a community-based substance abuse treatment study (Drug Abuse Treatment Outcome Studies for Adolescents) (DATOS-A). The primary goals of this study were to assess the effect of substance abuse treatment on adolescent crime and to identify the patient characteristics that were most closely associated with reductions in crime during the posttreatment period. Reductions in alcohol or marijuana use were independently associated with significant reductions in the likelihood of committing crimes during the 12-month follow-up period among adolescents who had engaged in criminal activity during the 12 months prior to entering DATOS-A treatment. The present study also provides further support for emphasizing dynamic rather than static patient characteristics to predict the likelihood of continued drug-related offending among substance-abusing adolescents. Farabee, D., Shen, H.K., Hser, Y.I., Grella,.E., and Anglin, M.D. Journal of Adolescent Research, 16(6), pp. 679-696, 2001.

Transportation and Retention in Outpatient Drug Abuse Treatment Programs

To determine whether certain types of transportation assistance improve outpatient treatment retention beyond thresholds shown to have therapeutic benefits, the researchers analyzed data from 1,144 clients in 22 outpatient methadone maintenance (OMM) programs and 2,031 clients in 22 outpatient drug-free (ODF) programs in the Drug Abuse Treatment Outcomes Study (DATOS), a national, 12-month, longitudinal study of drug abuse treatment programs. Directors' surveys provided information about provision of car, van, or contracted transportation services or individual vouchers/payment for public transportation. Chart-abstracted treatment retention was dichotomized at 365 days for OMM and 90 days for ODF. Provision of car, van, or contracted transportation services improved treatment retention beyond these thresholds for both OMM and ODF, but individual vouchers or payment for public transportation did not. Future research should validate whether car, van, or contracted transportation services improve retention and other treatment outcomes in outpatient drug abuse treatment. Friedmann, P.D., Lemon, S.C., and Stein, M.D. Journal of Substance Abuse Treatment, 21(2), pp. 97-103, 2001.

Prospective Risk Factors and Treatment Outcomes Among Adolescents in DATOS-A

The researchers applied a problem behavior approach to examining the relationship between pretreatment risk factors and posttreatment outcomes among 292 admissions to nine outpatient drug-free (ODF) and 418 admissions to eight residential (RES) adolescent programs. Assessments were administered at intake into treatment and 12 months following discharge. Using a structural modeling approach, the researchers found stability over time for alcohol use, criminal involvement, and psychological maladjustment. For adolescents treated in outpatient programs, (a) severity of drug use predicted lower rates of treatment retention, and (b) family drug involvement was related to higher posttreatment rates of alcohol use. Among those treated in residential programs, (a) family drug involvement and criminal involvement predicted lower rates of treatment retention, and (b) conduct disorders were related to more marijuana use at follow-up. The findings underscore the need for intervention strategies that address the intrapsychic and interpersonal functioning of drug-abusing adolescents to improve their behavioral outcomes. Galaif, E.R., Hser, Y.I., Grella, C.E., and Joshi, V. Journal of Adolescent Research, 16(6), pp. 661-678, 2001.

Effects of Program and Patient Characteristics on Retention of Drug Treatment Patients

The objective of this study was to examine effects of program and patient characteristics on patient retention in residential drug treatment programs, outpatient drug-free programs (ODF), and methadone maintenance (MM) programs. Patient data were based on admission and discharge records for individuals entering treatment programs in Los Angeles County during 1992 and 1993. Program data were collected from program directors via a mail survey. The study sample included 26,047 patients in 87 programs. The dependent variable was patient completion of a critical threshold of treatment (360 days for MM and 180 days for the other two modalities). Threshold retention rates were generally low in all three modalities (18.1% for residential programs, 22.9% for ODF, and 13.6% for MM). An articulated programmatic focus and low caseload increased patient retention in residential programs. A lower level of group therapy focus increased patient retention in ODF programs. A low programmatic focus and a low percentage of recovering staff were associated with high retention rates among MM patients. For ODF programs, none of the slopes showed random effects, while for residential and MM programs, some program factors contributed to the explanation of the random effects in several slopes (e.g., drug use severity). The authors concluded that program practice and service provision played important roles in determining patient retention in treatment. Service providers and planners should consider these key factors to improve retention of patients, which is likely to increase overall treatment effectiveness and efficiency. Hser, Y.I., Joshi, V., Maglione, M., Chou, C.P., and Anglin, M.D. Evaluation and Program Planning, 24(4), pp. 331-341, 2001.

Relationships Between Counseling Rapport and Drug Abuse Treatment Outcomes

Two cohorts of outpatients who were being treated with methadone in four cities were studied. Cohort 1 comprised 354 patients in community-based nonprofit programs, and cohort 2 comprised 223 patients from a private for-profit program. In both cohorts, ratings made by counselors, during treatment, of therapeutic involvement and relationships with patients provided a useful measure of counseling rapport. A lower level of rapport during treatment predicted worse post-index treatment outcomes, including more cocaine use and criminality, both by itself and after adjustment for treatment retention, satisfaction with treatment, and post-index treatment status. Counseling strategies were associated with the development of counseling rapport. Findings led authors to conclude that counseling rapport is a vital part of the therapeutic process and helps explain why and when treatment is effective. It contributes explicitly to the prediction of outcomes, apart from treatment retention, and accounts in part for the usual association between treatment retention and outcomes. Joe, G.W., Simpson, D.D., Dansereau, D.F., and Rowan-Szal, G.A. Psychiatr Serv, 52(9), pp. 1223-1229, 2001.

A Self-administered Instrument for Assessing Therapeutic Approaches of Drug-user Treatment Counselors

In this article the authors describe the development and psychometric properties of a self-administered instrument for assessing drug-user treatment counselors' therapeutic approaches such as psychodynamic or interpersonal, cognitive-behavioral, family systems or dynamics, 12-step, and case management. Authors generated an initial pool of items corresponding to these five approaches and modified them based on expert ratings. Three sets of items were developed. The first concerned the beliefs underlying each therapeutic approach. The second and third concerned the practices of each applicable approach within individual and group counseling, respectively. With the exception of case management, an approach that originated within social work and which is only applicable to individual counseling, the other four approaches are applicable, at least theoretically, to both individual and group counseling. Additionally, the authors included items that describe techniques used exclusively with groups (i.e.. group techniques). Finally, they included some items that are not associated with any of the traditional approaches but which reflect the practical approach that drug-user treatment programs often take to both individual and group counseling (i.e., practical counseling). The initial instrument consisted of 17 subscales with a total of 76 items. This instrument was administered to 226 counselors from 45 drug-user treatment programs in Los Angeles County. Based on this data, the researchers further refined these scales using confirmatory factor analysis to ensure both construct validity and discriminant validity. The final instrument consisted of 14 subscales with a total of 48 items. Kasarabada, N.D., Hser, Y.I., Parker, L., Hall, E., Anglin, M.D., and Chang, E. Substance Use & Misuse, 36(3), pp. 273-299, 2001.

Organizational and Financial Issues in the Delivery of Substance Abuse Treatment Services

Examination of organizational and financial characteristics of the specialty substance abuse treatment system allows an understanding of how to meet the needs of clients in the system. Further, this assessment may afford insights into how the specialty sector may adapt in the changing environment of managed care. Data from Phase I of the Alcohol and Drug Services Study (ADSS) describe the specialty substance abuse treatment system in terms of type of care, setting, level of affiliation, licensure/accreditation, ownership, revenue sources, client referral sources, client's primary substance of abuse, and managed care. Although the system is largely outpatient and remains substantially two tiered in terms of public/private funding mix, it varies along a number of organizational and financial dimensions which have implications for system structure and facility viability in the changing environment of substance abuse treatment service delivery. Horgan, C.M., Reif, S., Ritter, G.A., and Lee, M.T., Recent Dev Alcohol, 15, pp. 9-26, 2001.

Financing of Substance Abuse Treatment Services

The financing of treatment for substance abuse problems has differed from the rest of financing of health care in part because of the dominant role of the public sector as the payer of services. Nonetheless, the rise of managed care has affected substance abuse treatment services as well as the rest of the health care system. Alternative payment mechanisms are one important component of some managed care approaches. Behavioral health carve-outs are another managed care development that has affected substance abuse services. In this chapter, salient features of financing for substance abuse treatment are reviewed within the conceptual framework of payers (purchasers and intermediaries), providers, and consumers. Existing literature on substance abuse treatment financing is summarized, while recognizing that much remains to be researched. Horgan, C.M., and Merrick, E.L. Recent Dev Alcohol,15, pp. 229-252, 2001.

A Client-Treatment Matching Protocol For Therapeutic Communities: First Report

The present study is the first report on a client-treatment matching protocol (CMP) to guide admissions to residential

and outpatient substance abuse treatment settings. Two cohorts, a field test sample (n = 318) and cross-validation (n = 407) sample were drawn from consecutive admissions to nine geographically distributed multisetting therapeutic communities (TCs). A passive matching design was employed. Clients received the CMP on admission, but agencies were "blind" to the CMP treatment recommendation (i.e., match) and assigned clients to treatment by the usual intake procedures. Bivariate and logistical regression analyses show that positive treatment dispositions (treatment completion or longer retention in treatment)) were significantly higher among the CMP-matched clients. The present findings provide the empirical basis for studies assessing the validity and utility of the CMP with controlled designs. Though limited to TC-oriented agencies, the present research supports the use of objective matching criteria to improve treatment. Melnick, G., De Leon, G., Thomas, G. and Kressel, D., Journal of Substance Abuse Treatment, 21(3), pp. 119-128, 2001.

Selective Contracting in Managed Care: The Case of Substance Abuse Treatment

The authors address two critical questions concerning managed care and outpatient substance abuse treatment organizations. Specifically, they consider (1) to what extent selective contracting occurs between managed care firms and treatment providers and (2) what attributes of treatment providers and their operating environments are associated with selective contracting. Using data from a nationally representative sample of outpatient treatment organizations, the authors find evidence of systematic selection. Several indicators of providers' quality and costs, including accreditation status, private ownership, size, and prior experience with managed care, are positively associated with managed care contracting. By contrast, units providing methadone treatment are less likely to be involved in managed care. To a lesser extent, characteristics of treatment providers' operating environment, including extent of competition based on costs and attributes of the Medicaid managed care program, are also positively associated with managed care contracting. Lemak, C.H., Alexander, J.A., and D'Aunno, T.A. Medical Care Research and Review, 58(4), pp. 455-481, 2001.

A Comparison of Psychosocial Barriers Among Welfare Recipients: Implications For Drug Treatment

Implementation of Temporary Assistance for Needy Families (TANF) presents welfare recipients with time-limited benefits and work requirements. However, over 140,000 welfare recipients meet the DSM-IV criteria for "drug dependence." In this study, samples of chronic drug using and non-drug using female TANF recipients were compared with regard to: current employment, psychological functioning, self-perceived employment skills, barriers to employment, and need for help in seeking employment. Non-drug using study participants were significantly more likely to be employed and reported significantly higher self-perceived work skills than users. Chronic users reported significantly greater barriers to seeking employment. Montoya, I.D., Atkinson, J.S., and Struse, H.M. Substance Use & Misuse, 36(6-7), pp. 771-788, 2001.

Examining the Substance Use Patterns and Treatment Needs of Incarcerated Sex Offenders

Using data from a Bureau of Justice Statistics' National Prison Inmate Survey This paper analyzes alcohol and drug use and abuse patterns among men incarcerated in state prison for sex crimes. Of the 13,986 inmates in the sample, 11.5% were incarcerated for a sex offense. Two thirds were substance-involved, meaning that they were under the influence of alcohol or drugs at the time of their crime, had committed a crime to get money for drugs, had histories of regular illegal drug use, had received treatment for alcoholism, or shared some combination of these characteristics. The level and type of substance-involvement was related to age and race, to history of victimization, and to victim characteristics. Peugh, J., and Belenko, S. Sex Abuse. 13(3), pp. 179-195, 2001.

Patient Characteristics and Treatment Outcomes for African American, Hispanic, and White Adolescents in DATOS-A

The author attempted to extend what is known about adolescent substance abusers in adolescent-oriented substance abuse treatment by describing and comparing background and pretreatment characteristics and posttreatment outcomes of African American (n = 213), Hispanic (n = 108), and White adolescent (n = 773) substance abusers who participated in the Drug Abuse Treatment Outcome Studies for Adolescents (DATOS-A). The pretreatment data indicated that patients in each group were similar only with respect to basic demographics (gender, age and primary drug use) but differed in terms of referral source, involvement with the criminal justice system and prevalence of mental disorders. Posttreatment comparisons revealed significant racial/ethnic differences in serious posttreatment criminal behavior, only. Logistic regression results indicated that African American adolescents had a lower likelihood of engaging in serious illegal activity as compared to White adolescents during the posttreatment period. Rounds-Bryant, J.L., and Staab, J. Journal of Adolescent Research, 16(6), pp. 624-641, 2001.

The Organization of Substance Abuse Managed Care

Managed care came to dominate the delivery of substance abuse services during the 1990s. Substance abuse managed care typically is "carved out" of the general health care plan and treatment is coordinated by a behavioral health managed care company that manages treatment access, length, type, and intensity. This administrative agent is provided financial incentives to keep costs low and otherwise faces such mandates as to ensure timely access to treatment and to deliver reports. A typical agent has some interest in improving the quality of decision-making, but has few incentives for controlling the treatment technology. In contrast, agents tend to control treatment providers through relatively rigid rules that substitute outpatient for inpatient care, regulate the length and intensity of services, provide limited social services, mandate accreditation, allow limited clinician discretion, administer an entire "network" of providers as an only slightly differentiated mass, and rarely shape the details of the treatment process. These patterns are analyzed in terms of transaction cost economics and institutional and resource dependency theories. In general, managed care reflects an interest in controlling costs but also in ensuring access within an environment where there is uncertainty accompanying competing demands, varying conceptions of the client, and controversies over the efficacy of specific treatment technologies. Sosin, M.R., and D'Aunno, T. Recent Dev Alcohol, 15, pp. 27-49, 2001.

Effects of Managed Care on Programs and Practices for the Treatment of Alcohol and Drug Dependence

Managed care is affecting the organization and financing of treatment services for alcohol and drug dependence. The authors examine the effects of managed care on program operations including the use of clinical protocols, the administrative burden, information systems, staffing, and program consolidation. They also reviewed the effects of managed care on system performance related to employer-sponsored health plans, state employee health plans, and Medicaid and other public plans. In this review of managed care's influences on the alcohol and drug abuse treatment system, the author finds evidence of systemic reductions in access to inpatient care and increased reliance on outpatient services. Moreover, although analyses of behavioral health carve-outs often suggest increases in the use of outpatient care, evaluations of substance abuse claims report reductions in ambulatory utilization for the treatment of alcohol and drug dependence. Sosin, M.R., and D'Aunno, T. Recent Dev. Alcohol, 15, pp. 51-71, 2001.

Social Support Systems of Women Offenders who Use Drugs: A Focus on the Mother-daughter Relationship

Conceptually, social support among very heavily drug-involved women is complex and multidimensional. The authors examine the structure and function of the social support systems of women offenders (N = 100) who used drugs during the last 6 months before entering court-mandated drug-free treatment programs. These systems typically contain about nine supporters, almost equally divided between men and women, and about half of the women's supporters are family members. The women identify parents and partners as their major providers of practical help and advice. They look most to their partners for a sympathetic ear, and to their parents for affirmation of their self-worth. Overall, two-thirds of the women identify their mothers as among their supporters. These mothers are often anxious to do whatever they can to help their daughters stop using drugs. Paradoxically, the assistance many mothers give their daughters in providing money or basic life necessities often enables the daughter's drug use. Although many daughters appreciate their mother's help, there is an element of distrust and control in many of the mother-daughter relationships, and some daughters receive unwanted help from their mothers. Drug treatment providers can benefit from understanding their clients' social support systems, especially the dynamics of important relationships with main pretreatment supporters, such as parents. By gaining this understanding and helping their clients to effectively accept and use social support. Strauss, S.M., and Falkin, G.P. American Journal of Drug and Alcohol Abuse, 27(1), pp. 65-89, 2001.

Crack Cocaine, Alcohol, and Other Drug Use Patterns among Homeless Persons with Other Mental Disorders

Co-occurrence of cocaine, alcohol, marijuana, and other drug use among treatment seeking homeless persons to determine whether alcohol use predicted cocaine use differently than marijuana and other drugs predicted cocaine use. Participants were 141 homeless persons with substance use and other nonpsychotic mental disorders seeking drug treatment at a metropolitan health care agency for homeless persons. They were 72.3% male, 27.7% female, 82.7% African American, 17.3% Caucasian, with an average age of 37.7 (SD 7.1) years and had 13.1 (SD 2.4) average years of education. The assertion that cocaine use was strongly associated with extent of alcohol use was supported. The association between cocaine and alcohol was stronger than the association between cocaine and other drug use, including marijuana. Participants with cocaine plus alcohol disorders were retained longer in treatment than

disorders of cocaine only with no differences in abstinence outcome. The findings should drive further research into the use of alcohol as a trigger or predictor of cocaine use, the deleterious effects of the combined use of cocaine and alcohol, and specialized treatments for polysubstance users. Usdan, S.L., Schumacher, J.E., Milby, J.B, Wallace, D., McNamara, C., and Michael, M. Am J Drug Alcohol Abuse, 27(1), pp. 107-120, 2001.

Rural-Urban Differences In Substance Use And Treatment Utilization Among Prisoners

The authors examine differences between urban and rural drug use patterns and treatment utilization among chronic drug abusers to determine whether, and in what ways, rurality may affect substance abuse and treatment seeking. The authors examine these issues in a group of chronic drug users who were incarcerated at the time of the study. Significant differences in drug use and treatment utilization of urban and rural offenders. Chronic drug abusers from rural and very rural areas have significantly higher rates of lifetime drug use, as well as higher rates of drug use in the 30 days prior to their current incarceration than chronic drug abusers from urban areas. Nonetheless, being from a very rural area decreased the likelihood of having ever been in treatment after controlling for the number of years using and race. While problem recognition appears to explain much of the effect of very rural residence on treatment utilization for alcohol abuse, the effects of being from a very rural area on seeking treatment for drug abuse remain statistically significant even after controlling for several other variables. The importance of providing culturally appropriate education to very rural communities on the benefits of substance abuse treatment and of providing substance abuse treatment within the criminal justice system is examined. Warner, B.D., and Leukefeld, C.G. The American Journal of Drug and Alcohol Abuse, 27(2), pp. 265-280, 2001.

Social Support and Abstinence from Opiates and Cocaine during Opioid Maintenance Treatment

Social support may play an important role in helping drug users achieve abstinence; however these benefits may depend on the type of support experienced. The authors examined the extent to which general and abstinence-specific support, both structural and functional, predicted opiate and cocaine abstinence in 128 opioid maintenance patients receiving either methadone or LAAM. A new multidimensional self-report instrument assessing abstinence-specific functional support was developed for the study. Previously validated measures were used to assess the remaining types of support. With baseline abstinence and other statistically important covariates adjusted, hierarchical logistic regression analyses demonstrated that the associations between social support at study baseline and biochemically confirmed abstinence 3 months later varied by type of support and by drug. Greater abstinence-specific structural support (operationalized as fewer drug users in the social network) and decreases in three types of negative abstinence-specific functional support (Complaints about Drug Use, Drug Exposure, and Demoralization) predicted cocaine, but not opiate abstinence. There were no effects for general support, whether structural or functional, on abstinence from either drug. Interventions that focus on modifying patients' abstinence-specific support may be helpful in reducing the high rates of cocaine use disorders in this population. Wasserman, D.A., Stewart, A.L., and Delucchi, K.L. Drug and Alcohol Dependence, 65(1), pp. 75-85, 2001.

Drug Courts - A Bridge Between Criminal Justice and Health Services

There is striking overlap between the public health threats of drug abuse and crime. Crimes are often drug related, and drug abusers frequently encounter the criminal justice system. However, with few exceptions (e.g., Treatment Alternatives to Street Crime, TASC), the intersection of drug abusers with the courts has rarely addressed the defendants' drug problems. Drug courts represent an innovative approach to addressing both crime and drug abuse. Especially promising, and of great importance given that drug abuse is associated with a host of other health and social service needs, is the link that drug courts represent between the criminal justice and health services systems. Connections to health services are considered vital to drug courts but are poorly understood. The need for a bridge between criminal justice and health services is discussed, and a conceptual framework for its investigation is presented. Using data collected from site visits of 14 drug courts across the United States and Puerto Rico, the services available to drug court clients are described and linkages between drug courts and health services (including drug treatment providers) are explained. Wenzel, S.L., Longshore, D., Turner, S., and Ridgely, M.S. Journal of Criminal Justice, 29(3), pp. 241-253, 2001.

The Relationship Between Partner Abuse and Substance Use among Women Mandated to Drug Treatment

The authors investigates the relationship between substance use and partner abuse among women (N = 1,025) who entered drug-treatment programs through the criminal justice systems in New York City and Portland, Oregon. Self-report data on substance use and partner abuse indicate that although the rate of partner abuse in both cities is well

above the national average, the less substance-involved women in Portland reported more abuse than their New York counterparts. The relationship between partner abuse and substance use during conflicts varies within the population of women offenders who are heavily drug-involved, with women in Portland reporting a greater direct link between partner abuse and substance use. There is a need for drug-treatment providers to understand their clients' victimization histories and the relationship between partner abuse and substance use in order to engage clients in the treatment process and help them learn how to avoid being victimized in the future. Wilson-Cohn, C., Strauss, S.M., and Falkin, G.P. Journal of Family Violence, 17(1), pp. 91-105, March 2002.

Selecting Data Sources for Substance Abuse Services Research

In this article the authors discuss the strengths and weaknesses of using different types of data sources for alcohol and drug abuse services research. To do this, the author describes four types of data sources used in substance abuse services research: surveys of organizations, medical records, claim and encounter data and program-level administrative data. For each, the authors outline where to obtain data, how each type has been used, and the advantages and challenges. This overview should allow investigators to think more critically about the datasets they now use; providers to understand the types of data sources most appropriate for specific research questions so as to participate more fully in research; and policy makers to interpret correctly results based on different types of data. Moreover, it should foster better communication among these stakeholders in collaborative projects to improve the effectiveness of services for people with addictions. Garnick, D.W., Hodgkin, D., and Horgan, C.M. Journal of Substance Abuse Treatment, 22,(1), pp. 11-22, January 2002.

Correlates of Poverty and Partner Abuse Among Women on Methadone

The association between poverty and experiences of partner abuse among 204 women recruited from methadone maintenance treatment programs was explored. Research showed that extreme poverty was prevalent and associated with partner abuse. Providers of methadone maintenance programs need to incorporate poverty indicators in their assessment because extreme poverty seems to correlate with all forms of partner abuse. The impact of welfare reform on partner violence should be on the agendas of policy makers and researchers. Moreno, C.L., El-Bassel, N., Gilbert, L., and Wada, T. Violence Against Women, 8(4), pp. 455-475, April 2002.

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Research Findings

Intramural Research

Clinical Pharmacology Section, Clinical Pharmacology & Therapeutics Research Branch

Open-Label Pilot Study of Bupropion plus Bromocriptine for Treatment of Cocaine Dependence

Combinations of medications are often used in neuropsychiatry to enhance treatment efficacy. This 8-week, open-label study tested the combination of bupropion (< 300 mg) and bromocriptine (< 7.5 mg) daily in 34 cocaine-dependent (DSM-IIIR) outpatients also receiving weekly individual counseling. The first 18 subjects spent 1 week at maximum dose; the next 16 spent 3 weeks. Both groups showed significant reductions in self-reported cocaine use, with no significant change in proportion of urine toxicology tests positive for cocaine. There were no significant differences in outcome between groups. These results suggest that the combination of bupropion and bromocriptine is safe in cocaine addicts, but provide ambiguous evidence of its efficacy. Montoya, I.D., Preston, K.L., Rothman R., and Gorelick D.A. American Journal of Drug and Alcohol Abuse, 28, pp. 1-8, 2002.

Chemistry & Drug Metabolism Section, Clinical Pharmacology & Therapeutics Research Branch

Marijuana Craving Questionnaire: Reliability and Validity

The purpose of this study was to determine the reliability and validity of the Marijuana Craving Questionnaire (MCQ), using active imagery of auditorily presented scripts. Current marijuana users (n = 48) imaged scripts that varied in amount of descriptors of desire to smoke marijuana, from no-urge to high-urge content. Self-reported marijuana craving significantly increased as a function of script urge intensity on Factors 1, 3, and 4 of the MCQ. Homogeneity of items comprising each MCQ factor was examined, indicating no significant departures from unidimensionality. These results verify and extend the reliability and validity of the MCQ as a multidimensional measurement of marijuana craving. The data also suggest that drug craving is not an all-or-none phenomenon. Singleton, E.G., Trotman, A.J.-M., Zavahir, M., Taylor, R.C. and Heishman, S.J. Experimental and Clinical Psychopharmacology, 10, pp. 47-53, 2002.

Brain Imaging Section, Neuroimaging Research Branch

Cue-Induced Cocaine Craving Likely Activates Neural Systems that Process Memories and Emotions

NIDA IRP scientists have extended their pioneering work investigating the neural correlates of cue-induced cocaine craving through the use of positron emission tomography with greater spatial resolution (<4.6 mm), an evocative script, and a pixel-by-pixel analysis. Craving and cerebral glucose metabolism were measured after presentation of cocaine-related or neutral cues to 11 cocaine abusers. Cocaine cues, consisting of visual cues and an evocative script, elicited a higher degree of craving than has been previously reported and resulted in left hemispheric activation of lateral amygdala, lateral orbitofrontal cortex, and rhinal cortex and right hemispheric activation of dorsolateral prefrontal cortex and cerebellum. The intensity of activation representing increased brain metabolism in these areas

(except cerebellum), as well as in the left insula, was also correlated with craving. A remarkably consistent pattern of regional brain activation during the subjective state of cocaine craving has emerged from our original study, this, and other studies. The results suggest that induction of drug craving involves a neural network that assigns incentive motivational value to environmental stimuli through the coactivation of cortical and subcortical brain regions that process information about memories and emotions. Bonson, K.R., Grant, S.J., Contoreggi, C.S. Links, J.M., Metcalfe, Weyl, H.L, Kurian, V., Ernst, M., and London, E.D. Neuropsychopharmacology, 26, pp. 376-386, 2002.

Evaluation of Risk-Taking Using PET Identifies Unique Neural Networks Associated with Decision-making and Guessing

As decision-making is central to motivated behavior, understanding its neural substrates can help elucidate the deficits that characterize various maladaptive behaviors, including drug abuse. Twenty healthy, normal adults performed a risk-taking task during positron emission tomography with [O-15]-labeled water. The task, a computerized card game, tests the ability to weigh short-term rewards against long-term losses. A control task matched all components of the risk-taking task except for decision-making and the difference between responses to contingent and non-contingent reward and punishment. Decision-making (2 runs of the active task minus 2 runs of the control task) activated orbital and dorsolateral prefrontal cortex, anterior cingulate, insula, inferior parietal cortex and thalamus predominantly on the right side, and cerebellum predominantly on the left side. In an exploratory analysis, guessing (run 1 minus run 2 of the active task) accompanied activation of sensory-motor associative areas, and amygdala on the left side, whereas informed decision-making (run 2 minus run 1) activated areas that subserve memory (hippocampus, posterior cingulate) and motor control (striatum, cerebellum). The findings provide a framework for future investigations of decision-making in maladaptive behaviors based upon the apparent involvement of a right lateralized neural network for decision-making whereas guessing activated left-sided structures involved in sensory, motor and emotional coding and did not recruit structures subserving executive functions. Ernst, M., Bolla, K., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J-L., Kimes, A.S., and London, E.D. Neuropsychopharmacology, 26, pp. 682-691, 2002.

Effects of Triazolam on Brain Activity During Episodic Memory Encoding: A PET Study

It is well documented that acute administration of the benzodiazepine hypnotic drug triazolam (Halcion¨) impairs episodic memory encoding. We examined the neuroanatomical substrates of this effect in healthy adult volunteers using a double-blind, within-subject design. Following oral capsule administration (0.25 mg/70 kg triazolam or placebo), regional cerebral blood flow (rCBF) was measured using positron emission tomography (PET) with [O-15]-H2O during the performance of semantic categorization, orthographic categorization, and visual fixation (resting) tasks. rCBF associated with episodic memory encoding was measured by the difference in rCBF during the orthographic categorization task relative to that during the semantic categorization task. Results in the placebo condition (n = 9) replicated those of previous nonpharmacological encoding studies (activation in the left prefrontal cortex, cerebellum, anterior cingulate cortex, temporal cortex, and occipital cortex). Relative to placebo, results in the triazolam condition (n = 6) revealed significantly impaired memory performance, and deactivation during encoding in a subset of areas shown previously to be associated with encoding (anterior cingulate, cortex, cerebellum, and precuneus). Results are discussed in relation to triazolam's effects on mnemonic versus attentional processes. Mintzer, M.Z., Griffiths. R.R., Contoreggi, C., Kimes, A.S., London, E.D., and Ernst, M. Neuropsychopharmacology, 25, pp. 745-756, 2001.

Development of a Potential Single Photon Emission Computed Tomography (SPECT) Imaging Agent for the Corticotropin-Releasing Hormone Receptor Type-1

Corticotropin-releasing hormone (CRH) is secreted in response to stress and overstimulation of CRH type-1 receptors (CRHR-1) may be the underlying factor in the pathogenesis of a variety of mental disorders that include major depression, anxiety, and substance abuse. A high-affinity, nonpeptide radioligand for CRHR-1 has been prepared that can serve as a template for the development of SPECT imaging agents. 5-chloro-N-cyclopropylmethyl-N-(2,6-dichloro-4-iodophenyl)-2-methyl-N-propylpyrimidine-4,6-diamine (Ki=14 nM), and the corresponding 4-bromophenyl analogue (Ki=21 nM), were synthesized in four steps. The high binding affinity exhibited by the iodo analogue (Ki=14 nM), makes its I-125 analogue an intriguing template for further development of the SPECT imaging agent for the CRHR-1. In summary, IRP investigators have developed the synthesis of the first nonpeptide potential SPECT ligand for CRHR-1. This ligand holds great potential as a selective nonpeptide radioligand for the CRHR-1 binding assay, replacing the currently used peptide radioligands. The development a specific radioligand to label CRHR-1s *in vivo* would be a valuable diagnostic and prognostic tool for important illnesses, such as those cited above. Tian, X., Hsin, L-W. , Webster, E.L., Contoreggi, C., Chrousos, G.P., Gold, P.W., Habib, K., Ayala, A., Eckelman, W.C., Jacobson, A.E., and Rice, K.C. Bioorg. Med. Chem. Lett. 11, pp. 331-333, 2001.

PET Imaging of Nicotinic Acetylcholine Receptors: A Method to Test Hypotheses on the Role of Nicotinic Receptors in Facilitating Drug Abusing Behavior

Reduction of the demand for illicit drugs can be approached from different directions, such as interdiction or treatment. Our focus is on the potential role of nicotine-induced changes in the brain as a predisposing factor for drug abusing behavior and the development of a promising radiolabelled compound that, with positron emission tomography (PET), can be useful for non-invasively examining the role of nicotinic acetylcholine receptors (nAChRs) in drug abuse. Nicotine exposure may result in brain chemistry changes that lead to greater vulnerability to illicit, addicting drugs. Smokers exhibit greater densities of nAChRs than non-smokers and chronic nicotine upregulates alpha4beta2 nAChRs, the receptor subtype that appears responsible for nicotine addiction. Among four promising compounds that IRP investigators have developed for imaging and quantifying nicotinic receptors using PET, 2-[F-18]fluoro-A-85380 has been this group's primary focus. Its high affinity and selectivity for these receptors, the distribution of its radioactivity in the mouse and non-human primate brain in proportion to the known densities of alpha4beta2 nAChRs, a reasonably high binding potential (a measure describing the specificity of receptor binding for an *in vivo* ligand), and the absence of pharmacological activity at radiotracer doses indicate its suitability for quantitative analysis of receptor binding *in vivo*. These advances indicate that PET studies of alpha4beta2 receptors in the brains of human volunteers are imminent. This tool will allow us to examine the role of nicotinic receptors in the initiation and progression of drug dependence, and therefore, to find new, more effective ways of preventing and treating drug addiction. Kimes, A.S., Chefer, S.I, Vaupel, D.B., Pavlova, O., Koren, A.O., Contoreggi, C., London, E.D. and Mukhin, A. Proceedings of ONDCP Symposium, San Diego, California, June 25 - 28, 2001.

Neuroimaging and Substance Abuse Disorders in the Year 2000

Basic and clinical research have contributed to the fundamental principle that substance abuse is a brain disorder. Advances in the neurobiology of this disorder have evolved primarily from investigations in animals. Now with the development of neuroimaging tools, particularly functional imaging, findings from preclinical and clinical research can be integrated into testable hypotheses. Not only does neuroimaging provide a unique tool to bridge bench to bedside research, it also spurs new approaches, such as cognitive neuroscience, to study brain disorders in humans. The three critical aspects of substance abuse disorder that permeate all research questions and designs are: (1) cycle of addiction (intoxication, dependence, withdrawal, long-term abstinence, relapse), (2) direct pharmacological impact (long-term and short-term) of the addictive drugs not necessarily related to the addictive effects, and (3) polysubstance use by most substance abusers. Publications over the year of 2000 related to substance abuse research that have been targeted by neuroimaging techniques is reviewed in this paper. They include (1) brain morphometry, (2) neural connectivity and neural tracks, (3) integrated brain activity at rest (i.e., regional cerebral blood flow [rCBF] or regional cerebral metabolic rates of glucose [rCMRglc]), (4) cognitive activation, and (5) neurochemical systems. These domains of investigation converge to address the questions of (1) neural mechanisms of addiction (i.e., neural circuits, neurochemical substrates), (2) neural substrates of influential factors (e.g., sex, age, comorbidity, genetics), (3) therapeutic mechanisms (e.g., treatment development, predictors of therapeutic response), and (4) identification of risk and protective factors underlying substance abuse disorder. Ernst, M., and Chefer S.I. Current Opinion in Psychiatry, 14, pp. 179-185, 2001.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Bone Morphorgenetic Protein-6 Reduces Ischemia-induced Brain Damage In Rats

Bone morphogenetic protein-6 (BMP6) and its receptors are expressed in adult and fetal brain. Receptors for BMP6 are upregulated in adult brain after injury, leading to the suggestion that BMP6 is involved in the physiological response to neuronal injury. The purpose of this study was to determine if there was a neuroprotective effect of BMP6 *in vivo* and *in vitro*. Lactate dehydrogenase (LDH) and microtubule-associated protein-2 (MAP-2) activities were used to determine the protective effect of BMP6 against H2O2 in primary cortical cultures. The neuroprotective effects of BMP6 were also studied in chloral hydrate-anesthetized rats. BMP6 or vehicle was injected into right cerebral cortex before transient right middle cerebral artery (MCA) ligation. Animals were sacrificed for tri-phenyl-tetrazolium chloride staining, caspase-3 immunoreactivity and enzymatic assays, and TUNEL assay. A subgroup of animals was used for locomotor behavioral assays. Application of H2O2 increased LDH activity and decreased the density of MAP-2(+) neurons in culture. Both responses were attenuated by BMP6 pretreatment. Complementary *in vivo* studies showed that pretreatment with BMP6 increased motor performance, and generated less cerebral infarction, induced by MCA ligation/reperfusion in rats. Pretreatment with BMP6 did not alter cerebral blood flow or physiological parameters. There was decreased ischemia-induced caspase-3 immunoreactivity, caspase-3 enzymatic activity, and density of TUNEL(+) cells in ischemic cortex in BMP6 -treated animals. BMP6 reduces ischemia/reperfusion injury, perhaps by attenuating molecular events underlying apoptosis. Wang, Y., Chang, C.F., Morales, M., Chou, J., Chen,

H.L., Chiang, Y.H., Lin, S.Z., Cadet, J., Deng, X., Wang, J.Y., Chen, S.Y., Kaplan, P.L., and Hoffer, B.J., Stroke, 32, pp. 2170-2178, 2001.

Behavioral Neuroscience Section, Behavioral Neuroscience Research Laboratory

Brain Hyperthermia and Arousal

Stress and drugs of abuse cause brain and body hyperthermia, and hyperthermia plays an important role in the neurotoxicity associated with drugs of abuse. To determine the degree of brain hyperthermia associated with stress and other aspects of behavioral testing, we recorded brain temperature from the dorsal and ventral striatum and compared it with that of neck muscle. Animals were subjected to the stress of cage transfer, mild tail-pinch, exposure to another male rat, a female rat, and a mouse, and presentation of a novel light-tone combination. Each challenge elevated brain temperature, with cage transfer, tail pinch, and social interactions causing 1-2¡C elevations in brain and muscle temperature. Brain temperature was generally higher and increased more quickly than muscle temperature, suggesting neuronal activation as a source of the hyperthermia. These findings suggest that brain hyperthermia is not restricted to conditions of stress and that it may offer an alternative for fMRI for assessing general brain activation in small unanesthetized animals. Kiyatkin, E.A. and Wise, R.A., Brain Research, 918, pp. 141-152, 2001.

Brain Hyperthermia During Heroin Self-administration

Self-administered intravenous heroin caused and maintained elevations of brain temperature to approximate 39¡C in the dorsal striatum, dorsomedial thalamus, and temporalis muscle and to 39.6¡C in the nucleus accumbens. Temperature began to rise during the period of activation prior to the first injection, rose to peak levels with the first 2-3 injections, and remained at peak levels until drug availability was terminated. The initial rise was more closely time-locked to the initial lever-press than to the light-tone stimulus that signaled initial drug availability. Temperatures returned to normal in about 2 hours when drug availability was simply terminated and returned in about 20 minutes when heroin action was terminated by the opiate antagonist naloxone. This action of self-administered doses of heroin could exacerbate methamphetamine neurotoxicity when methamphetamine and heroin are taken concurrently. Kiyatkin, E.A. and Wise, R.A., Journal of Neuroscience, 22, pp. 1072-1080, 2002.

Contribution of the Norepinephrine Transporter in the Clearance of Brain Dopamine

While dopaminergic, noradrenergic, and serotonergic neurons each express unique transporters that clear their respective transmitter from the extracellular space, and while drugs selective for the different transporters are available, the transporters are rather promiscuous in that each can clear the other monoamines. Which transporter clears a given monoamine depends on both the selectivity of the transporter for the substrate and the relative density of the three transporters. IRP investigators confirmed this by assessing synaptosomal uptake of dopamine in dopamine and norepinephrine transporter knockout mice. Dopamine uptake into frontal cortex synaptosomes was normal in dopamine transporter knockout mice and minimal in norepinephrine transporter knockout mice. Conversely, dopamine uptake into striatal synaptosomes was normal in NET knockout mice and nil in DAT knockout mice. These findings confirm pharmacological studies that implicate NET in dopamine clearance from frontal cortex and suggest that NET may be involved in dopamine clearance from other structures, like the shell of nucleus accumbens, where DAT density is low. Mor—n, J.A., Brockington, A., Wise, R.A., Rocha, B.A. and Hope, B.T. Journal of Neuroscience, 22, pp. 389-395, 2002.

A Cannabinoid Mechanism in Relapse to Cocaine Seeking

Treatment of cocaine addiction is hampered by high rates of relapse even after prolonged drug abstinence. This relapse to compulsive cocaine use can be triggered by re-exposure to cocaine, by re-exposure to stimuli previously associated with cocaine or by exposure to stress. In laboratory rats, similar events reinstate cocaine seeking after prolonged withdrawal periods, thus providing a model to study neuronal mechanisms underlying the relapse to cocaine. The endocannabinoid system has been implicated in a number of neuropsychiatric conditions, including drug addiction. The active ingredient of marijuana, Delta9- tetrahydrocannabinol, activates the mesolimbic dopamine (DA) reward system and has rewarding effects in preclinical models of drug abuse. IRP investigators report here that the synthetic cannabinoid agonist, HU210, provokes relapse to cocaine seeking after prolonged withdrawal periods. Furthermore, the selective CB1 receptor antagonist, SR141716A, attenuates relapse induced by re-exposure to cocaine-associated cues or cocaine itself, but not relapse induced by exposure to stress. These data reveal an important role of the cannabinoid system in the neuronal processes underlying relapse to cocaine seeking, and provide a rationale for the use of cannabinoid receptor antagonists for the prevention of relapse to cocaine use. De Vries, T.J., Shaham, Y., Homberg, J.R., Crombag, H., Schuurman, K., Dieben, J., Vanderschuren, L.J. and

Schoffelmeer, A.N., Nature Medicine, 7, pp. 1151-1154, 2001.

Renewal of Speedball Seeking after Prolonged Extinction by Reexposure to Drug-Associated Contextual Cues

Contextual stimuli associated with drug exposure can modulate the behavioral effects of drugs, but little is known about the role of these stimuli in relapse to drug seeking in laboratory animals. Using a renewal procedure we report here that drug-associated contextual stimuli play a critical role in relapse to drug-seeking behavior previously maintained by a heroin-cocaine mixture (speedball). Rats were trained for 10 days to self-administer speedball after which drug-reinforced behavior was extinguished over 20 days, either in the self-administration context or in a different context. On the test day rats exposed to the drug-associated context, following extinction in a different context, renewed drug seeking to levels observed prior to extinction training. Authors suggest that the present renewal procedure can be used to study mechanisms underlying relapse to drug seeking induced by exposure to drug-associated contextual stimuli. Crombag, H.S. and Shaham, Y. Behavioral Neuroscience, 116, pp. 169-173, 2002.

Neurobiology of Relapse to Heroin and Cocaine: A Review

The objective of this article was to review data from studies that used a reinstatement model in rats to elucidate the neural mechanisms underlying relapse to heroin and cocaine seeking induced by exposure to the self-administered drug (drug priming), conditioned drug cues, and stressors. These factors were reported to contribute to relapse to drug use in humans following prolonged abstinence periods. In the reinstatement model, the ability of acute exposure to drug or nondrug stimuli to reinstate drug seeking is determined following training for drug self-administration and subsequent extinction of the drug-reinforced behavior. Authors reviewed studies in which pharmacological agents were injected systemically or intracranially to block (or mimic) reinstatement by drug priming, drug cues, and stressors. They also reviewed studies in which brain lesions, *in vivo* microdialysis and electrochemistry, and gene expression methods were used to map brain sites involved in relapse to drug seeking. Subsequently, they discussed theoretical issues related to the processes underlying relapse to drugs and address methodological issues in studies on reinstatement of drug seeking. Finally, the implications of the findings from the studies reviewed for addiction theories and treatment were discussed. The main conclusion of this review is that the neuronal mechanisms involved in relapse to heroin and cocaine seeking induced by drug priming, drug cues, and stressors are to a large degree dissociable. The data reviewed also suggest that the neuronal events mediating drug-induced reinstatement are to some degree dissociable from those mediating drug reinforcement. Shalev, U., Grimm, J.W. and Shaham, Y., Pharmacological Review, 54, pp. 1-42, 2002.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Laboratory

Lack of Persistent Changes in the Dopaminergic System of Rats Withdrawn from Methamphetamine Self-Administration

IRP investigators previously reported that rats that had actively self-administered methamphetamine for 5 weeks and were then withdrawn from methamphetamine for 24 h showed marked decreases in somatodendritic dopamine D2 autoreceptor levels in the ventral tegmental area and median and dorsal part of the substantia nigra zona compacta with a corresponding down-regulation of dopamine D1 receptors in the shell of the nucleus accumbens. The purpose of the present study was to determine whether neuroadaptive changes in dopamine receptors or transporters in the brains of of rats withdrawn for 24 h from chronic methamphetamine self-administration are persistent changes that can be demonstrated long after withdrawal. A "yoked" procedure was used in which rats were tested simultaneously in groups of three, with only one rat actively self-administering methamphetamine while the other two received yoked injections of either methamphetamine or saline. *in vitro* quantitative autoradiography was used to determine densities of dopamine uptake sites and dopamine D1 and D2 receptors in different brain regions following 7- and 30-day periods of withdrawal from chronic methamphetamine self-administration. No changes in dopamine transporter and dopamine receptor numbers were detected in any brain region examined in rats self-administering methamphetamine compared with littermates receiving yoked infusions of either methamphetamine or saline. Thus, neuroadaptive changes in densities of dopamine receptors or transporters in certain brain areas may contribute to the reinforcing effects of methamphetamine during the acquisition and maintenance phases of self-administration, but do not appear to contribute to the long-lasting neuroadaptive effects of chronic methamphetamine self-administration which may trigger craving and relapse. Stefanski, R., Hee, S-H., Yasar, S., Cadet, J.L., and Goldberg, S.R. European Journal of Pharmacology, 439, pp. 59-68, 2002.

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Director's Report to the National Advisory Council on Drug Abuse
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Program Activities

New NIDA PAs and RFAs

On February 5, 2002, **NIDA issued a Notice entitled NIDA National Prevention Research Initiative (NNPRI): Community Multi-Site Prevention Trials (CMPT), RFA-DA-02-004 and Transdisciplinary Prevention Research Centers, RFA-DA-02-005 and Using Basic Science to Develop New Directions in Drug Abuse Prevention Research, RFA-DA-02-010 (NOT-DA-02-002).** The Notice amends these three RFAs to specifically invite not only drug abuse prevention applications but also drug use-related HIV/AIDS prevention applications that focus on interventions for children, adolescents, and young adults at different levels of drug use and risk. Special populations of interest include youth with co-morbid mental health problems, homeless youth, youth experiencing academic failure or who have dropped out of school, youth diagnosed as HIV positive, and youth in foster care. Applications may include interventions delivered in diverse contexts, such as schools, primary health care, juvenile justice facilities, mental health facilities, religious organizations, community organizations, etc.

On February 6, 2002, NIDA issued a Notice entitled **Availability of Administrative Supplements to Support International Collaborative Research on Drug Abuse (NOT-DA-02-003).** Funding for international administrative supplements to existing NIDA-supported research projects will take advantage of unique opportunities to support research in all areas of drug-abuse science. Preference will be given to projects that are collaboratively funded by an agency of the host country. Only existing R01 and R21 grants supported by NIDA with at least one year of funding remaining at the time of the supplemental award are eligible for support under this program. Supplements may be requested for up to 2 years of support, but extend no longer than the parent grant, with funding beginning no later than September 30, 2002.

On February 5, 2002, NIDA issued a Program Announcement entitled **Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Gender Differences (PA-02-055).** The purpose of this PA is to announce the availability of small grants (R03) to support drug abuse doctoral dissertation research in epidemiology, prevention, treatment, services and women and gender differences where there is a significant need for new investigators. Grant support is designed to aid the research of new investigators and to encourage doctoral candidates from a variety of academic disciplines and programs to conduct research in these areas of interest to NIDA. It is hoped that this program will ultimately facilitate the entry of promising new investigators into the field of drug abuse research. This PA supercedes PA-98-109, published September 24, 1998.

On February 6, 2002, NIDA issued a Program Announcement entitled **Imaging - Science Track Award for Research Transition (I/START) (PAR-02-058).** This PA invites applications for the I/START program, a new program developed by NIDA to foster new investigators in areas of brain imaging and drug abuse research. The application of brain imaging has become widespread. However, it is sometimes difficult for new investigators to obtain independent funding in this area. This award will allow for the design and collection of "proof of concept" brain imaging data that can then be used in the transition to more extensive research proposals. The I/START program uses a brief application form and a rapid review process to ensure expedited funding decisions. Funding is limited to direct costs for one year of up to $150,000 and is non-renewable.

On March 4, 2002, NIDA issued a Program Announcement entitled **Science Education Drug Abuse Partnership Award (PA-02-070).** This PA replaces, in its entirety, the Science Education Drug Abuse Partnership Award (SEDAPA), PAR-99-076, published in the NIH Guide on March 23, 1999. The purpose of the SEDAPA Program is to fund the development and evaluation of innovative model programs and materials for enhancing knowledge and

understanding of neuroscience and the biology of drug abuse and addiction among K-12 students, the general public, health care practitioners, and other groups. The award provides support for the formation of partnerships between scientists and educators, media experts, community leaders, and other interested organizations for the development and evaluation of programs and materials that will enhance knowledge and understanding of science related to drug abuse. The intended focus is on topics not well addressed in existing efforts by educational, community or media activities.

On March 18, 2002, NIDA issued a Program Announcement entitled **Neuroscience Research on Drug Addiction (PA-02-085).** The intent of this program announcement is to continue to encourage investigator interest in the wide range of neuroscience research relevant to drug abuse, drug dependence, and drug addiction. Of particular interest are new areas of neuroscience that may be applied to questions of drug abuse and addiction. This PA replaces PA-99-033 published December 23, 1998.

On April 3, 2002, NIDA issued a Program Announcement entitled **Chemistry, Pharmacology, and Toxicology of Smoked Drugs of Abuse (PA-02-095).** The purpose of this PA is to encourage research that will further the understanding of the chemical composition of smoked drugs of abuse, and the resulting pharmacological and toxicological effects associated with such exposure.

On February 4, 2002, NIDA issued an RFA entitled **National Criminal Justice Drug Abuse Treatment Services Research System (RFA-02-011).** Through this RFA, NIDA invites cooperative agreement applications to participate in the National Criminal Justice Drug Abuse Treatment Research System (CJ-DATS). Awardees will participate in coordinated multisite studies to conduct rigorous scientific research with offender populations across multiple settings including jails, prisons and in the community. The goal of this cooperative research program is to establish and utilize a research infrastructure to develop and test research-based systems-level models that integrate public health and public safety approaches for criminal justice-involved individuals with addictive disorders. Letter of Intent Receipt Date for this RFA is April 12, 2002; Application Receipt Date is May 13, 2002.

PAs and RFAs Issued With Other NIH Components/Agencies

On February 21, 2002, NIDA issued a Notice entitled **Structural Biology of Membrane Proteins (PA-02-060) - Addendum (NOT-DA-02-004).** This addendum is to program announcement (PA) PA-02-060, which was released in the NIH Guide for Grants and Contracts on February 11, 2002. This PA is intended to support research on the structure of membrane proteins at atomic resolution. This addendum adds the National Institute on Drug Abuse (NIDA) as a participating institute in this program announcement.

On March 21, 2002, NIDA issued a Notice entitled **Innovative Technologies for Enhancing Function for Individuals with Disabilities - PA-02-071 - Addendum (NOT-DA-02-006).** The purpose of this notice is to add the National Institute on Drug Abuse (NIDA) as a participating institute in this program announcement. PA-02-071 was released on March 4, 2002. The goal of this program announcement is to encourage basic research on the structures of membrane proteins at atomic resolution.

On January 16, 2002, NIDA, and several other NIH components issued a Program Announcement entitled **Identifying Functional Links between the Immune System and Brain Function Including Behavior (PA-02-045).** The purpose of this PA is to request research grant applications to study neuroimmune molecules and mechanisms involved in regulating normal and pathological central nervous system (CNS) function. This PA was developed as a response to recommendations produced at two workshops: "Strategies for Identifying Functional Links Between the Immune System, Brain Function, and Behavior" and "Research Roundtable on Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS)". This PA supercedes PA-93-009 published October 23, 1992.

On January 22, 2002, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement entitled **Dissertation Research Grants for Underrepresented Minorities in the Ethical, Legal, and Social Implications (ELSI) of Genetics Research (PA-02-048).** The purpose of this PA is to stimulate and encourage underrepresented minority doctoral candidates from a variety of academic disciplines and programs to conduct research related to the ethical, legal, and social implications (ELSI) of genetics, genomics, and gene-environment interaction research. It is hoped that this program will facilitate the entry of promising new minority investigators into the field of ELSI research.

On February 12, 2002, NIDA with NIMH, issued a Program Announcement entitled **Translational Research Grants in Behavioral Science (PA-02-061).** The purpose of this program announcement is to encourage the development of collaborative partnerships between scientists who study basic behavioral processes and those who study the

etiology, diagnosis, treatment, and prevention of mental and behavioral disorders (including drug abuse and addiction) and the delivery of services to those suffering from these disorders.

On February 12, 2002, NIDA with NIMH, issued a Program Announcement entitled **Building Translational Research in Behavioral Science (PAR-02-062).** The National Institute of Mental Health (NIMH) and the National Institute on Drub Abuse (NIDA) seek to encourage the development of collaborative partnerships between scientists who study basic behavioral processes and those who study the etiology, diagnosis, treatment, and prevention of mental and behavioral disorders (including drug abuse and addiction) and the delivery of services to those suffering from those disorders.

On March 7, 2002, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Methodology and Measurement in the Behavioral and Social Sciences (PA-02-072).** The goal of this PA is to encourage research that will improve the quality and scientific power of data collected in the behavioral and social sciences, relevant to the mission of the NIH Institutes and Centers. Research that addresses methodology and measurement issues in diverse populations; issues in studying sensitive behaviors; issues of ethics in research; issues related to confidential data and the protection of research subjects; and issues in developing multidisciplinary, multimethod and multilevel approaches to behavioral and social science research is particularly encouraged.

On March 12, 2002, NIDA, in collaboration with several other NIH components, issued a Program Announcement entitled **Innovative Toxicology Models: SBIR/STTR (PA-02-075).** This PA encourages the development, standardization, and validation of new and innovative assays that determine or predict specific organ toxicities (e.g., hematotoxicity, cardiotoxicity, gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, ototoxicity, bladder toxicity, neurotoxicity, pulmonary toxicity and endocrine toxicity, including pancreatic beta cell toxicity) as well as new methodology for high throughput toxicity screening that involves the use of molecular endpoints, computer modeling, proteomics and genomics. The development of these toxicity assays and their incorporation early in the development process would assist in the evaluation and prediction of human sensitivity and allow for more cost efficient evaluations of numerous analogs prior to the selection of the ultimate drug development candidate.

On March 11, 2002, NIDA, in collaboration with the National Institute on Aging, issued a Program Announcement entitled **Mentored Clinical Scientists Development Program Award (K12 AWARD) (PAR-02-076).** This PA replaces, in its entirety, the Mentored Clinical Scientist Development Program Award (MCSDPA) (PA-95-054), published in the NIH Guide on April 28, 1995. This MCSDPA is an award to an educational institution or professional organization to support career development experiences for clinicians leading to research independence. Under this award, newly trained clinicians are to be selected and appointed to this program by the grantee institution. In other respects, the research experience of the research candidates selected for support under this award should resemble those supported by the individual Mentored Clinical Scientist Development Award (K08) or the Mentored Patient-Oriented Career Development Award (K23).

On March 5, 2002, NIDA, in conjuction with numerous other NIH components, issued an RFA entitled **Human Subjects Research Enhancements Program (OD-02-003).** The purpose of this initiative is to provide short-term interim support for institutional activities that will strengthen oversight of human subjects research at institutions that will receive significant NIH support for clinical research. This is a one-time solicitation. Application Receipt Date for this RFA is May 7, 2002.

On March 26, 2002, NIDA, along with a number of other NIH components, issued an RFA entitled **Large-Scale Genotyping for the Haplotype Map of the Human Genome (RFA-HG-02-005).** The purpose of this RFA is to develop a haplotype map of the human genome. This RFA solicits cooperative agreement applications for the large-scale genotyping across the genome of samples from three populations. The data will be used to develop a map of the haplotype patterns and of the genetic variants that are most informative for detecting these patterns. Letter of Intent Receipt Date for this RFA is April 25, 2002; Application Receipt Date is May 29, 2002.

On March 29, 2002, NIDA, along with NIMH and NINDS, issued an RFA entitled **Viral Genetics in HIV/CNS Disease: Implications for Pathogenesis (RFA-MH-02-012).** The purpose of this RFA is to solicit applications for grants to support studies focused on understanding the molecular and viral genetic factors controlling HIV-1 neuropathogenesis in the setting of highly active anti-retroviral therapy (HAART). The objective of this cooperative effort is to foster investigations utilizing genetic approaches to study mechanisms of HIV-1 induced nervous system disease with emphasis on trafficking, cell type specific and regional compartmentalization, viral evolution, functional diversity, establishment of latent reservoirs and the emergence of drug resistance in the central nervous system (CNS) versus other body compartments. Letter of Intent Receipt Date for this RFA is May 15, 2002; Application Receipt Date is June 12, 2002.

Other Program Activities

CTN Update

For protocols CTN 0001 - 0007, over 1,000 patients have been enrolled in these studies. A Spanish version of protocol CTN 0004 is being developed for Spanish only studies throughout the CTN. Five community treatment programs in five nodes have signed up for this study. Protocols CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) and CTN 0011 (A Feasibility Study of a Telephone Enhancement Procedure - TELE - to Improve Participation in Continuing Care Activities) have received approval and will begin enrollment this summer. Three new protocols are in the final stages of approval before being launched in the CTN. These are CTN 0008 (Baseline Survey), CTN 0009 (Smoking Cessation Treatment in Substance Abuse Programs), and CTN 0012 (Infections Screening in Substance Abuse Treatment Programs). The third wave of protocols has been submitted. These protocols are in various stages of development and review and should be launched in the fall or winter of 2002. By the end of 2002, it is projected that twenty protocols will be actively enrolling patients throughout the CTN.

NIDA's New and Competing Grants Awarded Since February 2002

Amara, Susan G. -- Oregon Health and Science University
Molecular Studies of Catecholamine Transporters

Augustine, George J. -- Duke University
Dynamic Imaging of Synaptic Inhibition

Barr, Gordon A. -- New York State Psychiatric Institute
Opiate Withdrawal & Tolerance: Development & Plasticity

Bolshakov, Vadim -- Mc Lean Hospital, Belmont, MA
Synaptic Mechanisms of Cocaine Addiction

Bonci, Antonello -- Ernest Gallo Clinic and Research Center
Mechanisms of Cocaine Induced Long-Term Potentiation

Bowen, Scott E. -- Wayne State University
Self-Administration of Abused Inhalants In Mice

Caton, Carol L. -- New York State Psychiatric Institute
Service Needs In Early Psychosis and Drug Use

Cervone, Daniel -- University of Illinois at Chicago
A Social Cognitive Theory of Personality and Smoking

Chang, Sulie L. -- Seton Hall University
Morphine Actions on the Immune System

Commons, Kathryn G. -- Children's Hospital of Philadelphia
Emotion, Pain and Pain Control Circuits

Coviello, Donna M. -- University of Pennsylvania
Comprenhensive Employment Program for Methadone Patients

Cravatt, Benjamin F. -- Scripps Research Institute
Enzymes That Regulate Fatty Acid Amide Function *in vivo*

Cronmiller, Claire R. -- University of Virginia, Charlottesville
A New Experiment Model for Cocaine's Effects on Cells

Dalton, Madeline A. -- Dartmouth College
Bupropion To Prevent Postpartum Smoking Relapse

Davies, Huw M. -- State University of New York at Buffalo
Methylphenidate Analogs as Medications for Cocaine Abuse

Devi, Lakshmi A. -- New York University School of Medicine
Posttranslational Regulation of Opioid Receptors

Dewey, William L. -- Virginia Commonwealth University
Enkephalins: Neuropharmacology and Abuse Potential

Donahoe, Robert M. -- Emory University
AIDS and Opiates: A Monkey Model

Dow-Edwards, Diana L. -- Suny Downstate Medical Center
Gender-Specific Ontogenic Cocaine Effects: Neuroanatomy

Dunlap, Eloise E. -- National Development and Research Institutes
Marijuana/Blunts: Use, Subcultures and Markers

Ehrman, Ronald N. -- University of Pennsylvania
Demand Free Cognitive Measures of Smoking Status

Eissenberg, Thomas E. -- Virginia Commonwealth University
Drug Craving: Pharmacologic and Associative Influences

Eyler, Fonda D. -- University of Florida
Project Care (Cocaine Abuse In The Rural Environment)

Farb, David H. -- Boston University
Neuroactive Steroids, Dopamine and Cocaine Sensitization

Forrester, Janet E. -- Tufts University
Micronutrient Metabolism In HIV+ and HIV-Drug Users

France, Charles P. -- University of Texas Health Sciences Center, San Antonio
Discriminative Effects of Benzodiazepine Withdrawal

French, Michael T. -- University of Miami
Utilization and Cost of Health Services By CDUs

Freudenberg, Nicholas -- Hunter College
Impact/HIV Intervention/Adolescent Males Leaving Jail

Froimowitz, Mark I. -- Massachusetts College of Pharmacy and Allied Sciences
Can Maintence Therapy Work For Cocaine Abuse?

Ghasemzadeh, M.B. -- Medical University of South Carolina
Glutamate Signaling and Drug Abuse

Hallfors, Denise D. -- University of North Carolina, Chapel Hill
HIV In Young Adulthood: Pathways and Prevention

Johnson, Bruce D. -- National Development and Research Institutes
Hard Drug Users and Operatives: Lifestyles and Consequences

Kaiyala, Karl J. -- University of Washington
Determinants of Tolerance To Nitrous Oxide Hypothermia

Kaminski, Norbert E. -- Michigan State University
CB1/CB2-Dependent and -Independent T Cell Modulation

Klein, Robert S. -- Montefiore Medical Center, Bronx, NY
Artherosclerosis/Bone Loss/Drug Use/HIV In Older Men

Koch, James E. -- University of Wisconsin, Oshkosh
Cannabinoid Antagonist Influences on Ingestive Behavior

Kuhar, Michael J. -- Emory University
Promoter Characterization of the CART Gene

Kusnecov, Alexander W. -- Rutgers, The State University of New Jersey, New Brunswick
Reinforcing Efficacy of Cocaine In Genetically Altered

Lavin, Antonieta -- Medical University of South Carolina
Dopaminergic Modulation of Thalamocortical Circuits

Li, Shi-Jiang W. -- Medical College of Wisconsin
Roles of Orbitofrontal Cortex In Cocaine Abuse By fMRI

Lidow, Michael S. -- University of Maryland Baltimore Professional School
Effect of Cocaine on Cortical Development

Loh, Horace H. -- University of Minnesota Twin Cities
Structural and Functional Studies of Mu Opioid Receptor

Luthar, Suniya S. -- Columbia University Teachers College
Maternal Drug Abuse Psychopathology and Child Adaptation

Makriyannis, Alexandros -- University of Connecticut, Storrs
Molecular Basis of Cannabinoid Acitivity

Margiotta, Joseph F. -- Medical College of Ohio at Toledo
Neuronal Acetylcholine Receptor Mechanisms

Marks, Michael J. -- University of Colorado at Boulder
Alpha Conotoxin Mii--Selective Nicotinic Receptor Probe

Marmor, Michael -- New York University School of Medicine
Drug Abuse, Depression and Responses to HIV Counseling

Marshall, John F. -- University of California Irvine
Methamphetamine Abuse and Cortical Cell Injury

Mehler, Ernest L. -- Mount Sinai School of Medicine of New York
Functional Properties of Protein Segments In Receptors

Melikian, Haley E. -- University of Massachusetts Medical School, Worcester
Trafficking and Regulation of Monoamine Transporters

Mello, Nancy K. -- McLean Hospital, Belmont, MA
Cocaine and Polydrug Abuse: New Medication Strategies

Mierke, Dale F. -- Brown University
Drug Design: Glutamate Receptor Signaling

Nikulina, Ella M. -- New England Medical Center Hospitals
Mechanisms of Social Stress-Induced Drug Sensitization

O'Leary, Michael E. -- Thomas Jefferson University
Effects of Cocaine on Cardiac Ion Channels

Oswald, Robert E. -- Cornell University, Ithaca
Cocaine & Nicotine Action on CNS Acetylcholine Receptors

Price, David A. -- University of Florida
Modulation of Acid-Sensing Pain Receptors By Peptides

Quang, Lawrence S. -- Massachusetts College of Pharmacy and Allied Sciences
Enzyme & Receptor Antagonists of GHB, GBL and 1, 4-BD

Ramaswami, Mani -- University of Arizona
Identification of Drosophila Proteins Modified By Neural Activity

Ricaurte, George A. -- Johns Hopkins University
MDMA Neurotoxicity In Humans: Occurence and Consequences

Roth, Robert H. -- Yale University
Prenatal Cocaine Alters Cortical Dopamine Function

Simons, Jeffrey S. -- University of South Dakota
Mood and Substance Use Among College Students

Sim-Selley, Laura J. -- Virginia Commonwealth University
Brain Cannabinoid Signaling: Selectivity and Adaptation

Smith, Desmond J. -- University of California Los Angeles
Voxelation: A New Method For 3d Gene Expression Analysis

Soderstrom, Kenneth M. -- East Carolina University
Cannabinoid Effects on Development of a Learned Behavior

Steiner, Heinz -- Finch University of Health Sciences/Chicago Medical School
Behavior/Drug Interactions In Striatal Gene Regulation

Stinchcomb, Audra L. -- University of Kentucky
Naltrexone Prodrugs for Transdermal Delivery

Stolerman, Ian P. -- University of London King's College, London
Comprehensive Database of Drug Discrimination Research

Teti, Laureen -- Pacific Institute for Research and Evaluation
Emotion Regulation of Children Exposed To Cocaine

Uz, Tolga -- University of Illinois at Chicago
5-HT N-Acetyltransferase and Cocaine-Induced Behaviors

Vanderah, Todd W. -- University of Arizona
RVM, CCK, Pain, and Opioid Tolerance

Vijayaraghavan, Sukumar -- University of Colorado Health Sciences Center
Calcium Signaling By Hippocampal Nicotinic Receptors

Vlahov, David -- Johns Hopkins University
Natural History of HIV Infection in Injection Drug Users

Wenger, Galen R. -- University of Arkansas Medical Sciences, Little Rock
Strain Differences In Response To Opioids

West, Mark O. -- Rutgers, The State University of NJ, New Brunswick
Cocaine Self-Administration: Incentive Motivation Firing

Williams, John T. -- Oregon Health & Science University
Chronic Morphine: Regulation of Ion Conductances

Wilson, Ira B. -- New England Medical Center Hospitals
Understanding and Improving Adherence in HIV Disease

Wilson, Mary A. -- Kennedy Krieger Research Institute, Inc.
Abused NMDA Antagonists: Effects on Cortical Development

Woodward, John J. -- Medical University of South Carolina
Neural Actions of Toluene

Wynne, Clive D. -- University of Florida
Long-Term Effects of Amphetamine on Interval Timing

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Director's Report to the National Advisory Council on Drug Abuse
May, 2002

Extramural Policy and Review Activities

Reviews

For this Council cycle, the Office of Extramural Affairs (OEA) arranged and managed 14 review meetings for grant applications including those in standing review committees, applications in conflict-of-interest with standing committees, and submissions to special initiatives. In addition, OEA arranged and managed fourteen contract proposal review meetings.

The reviews for NIDA's chartered committees were held. These consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). Five Special Emphasis Panels were held to review applications in conflict with the chartered committees. Three Special Emphasis panels were constituted for reviews of specific mechanisms: centers, program projects, and conference grant applications. In addition, OEA staff managed the reviews for B/START and Cutting Edge Basic Research Award (CEBRA) mechanisms.

The Contracts Review Branch managed the following proposal reviews:

N01DA-2-8821	Purity Specifications, Storage and Distribution for Medication Development
N43DA-2-5508	Develop Prevention Services Analytic Tools for Improved Substance Abuse Prevention Delivery.
N43DA-2-5513	Develop and Maintain Substance Abuse Prevention Methodological Software
N43DA-2-5518	Prevention Training (Fast Track: Phase I and Phase II proposals)
N43DA-2-7709	Virtual Reality for the Treatment of Pain (Fast Track)
N43DA-2-7730	High-Throughput Screening of Functional Activity Proteins Using Biosensor-based Technology
N43DA-2-7727	Analytical Techniques Program (Fast Track)
N43DA-2-7714	Technologies for Localizing Gene Expression and Proteins in the Nervous System
N01DA-2-2202	Administrative and Meeting Support for the CTN
N43DA-2-7726	Functional Imaging Agents
N43DA-2-8819	Medicinal Chemistry-Design and Synthesis (Fast Track)
N43DA-2-5517	Develop New Technologies for Drug Abuse Prevention Delivery
N43DA-2-8820	Dosage Form Development

N43DA-2-1109 Development of Science Education

Staff Training, Policy Development, and Extramural Activities

The OEA Symposium Series continued its monthly meetings for staff development, under the direction of Dr. Mark Swieter, SRA, Basic Sciences Review Branch. These sessions included a question and answer session with Dr. Glen Hanson, Acting Director, NIDA and Ms. Laura Rosenthal, Executive Officer and Associate Director, NIDA. Other sessions presented updates on and discussion of NIH extramural policies.

On March 1, 2002, Dr. Swieter gave a talk on the NIH Grants Enterprise to the NIDA INVEST and Humphrey fellows.

In anticipation of broader use of technology in peer review, Dr. Marina Volkov, SRA, Clinical, Epidemiological, and Applied Sciences Review Branch (CEASRB) and Ms. Marilyn Thomas, GTA, CEASRB, pilot tested a WEB based module for peer review for their February study section meeting.

Mr. Richard Harrison, Chief, Contracts Review Branch, has served as a reviewer for a number of minority-related initiatives, including: Administrative Supplement Applications for the NIDA Health Disparities Committee; Minority Supplement Applications for NIDA's Consortium on Minority Affairs, and Administrative Supplements for NIDA's Southern Africa Initiative.

Mr. Eric Zatman, Contracts Review Branch, continues to serve on the NIH committee revising the Contract manual "Initiation, Review, Evaluation and Award of Research & Development Contract Projects." This manual chapter guides policy for the review of contract proposals.

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Congressional Affairs

The President's Budget For FY 2003

The President released his proposed FY 2003 budget on February 4, 2002. The budget reflects the Administration's three main objectives of protecting the homeland, winning the war on terrorism abroad, and returning to economic vitality. The President's FY 2003 budget request of $27.3 billion for the NIH, completes the five-year doubling of the agency's budget by FY 2003. This sum provides an increase of $3.7 billion, or 15.7 percent, over the FY 2002 funding level. It is the largest dollar increase ever for NIH. For NIDA, the President's FY 2003 budget request is $968 million, an increase of 8.6 percent over FY 2002.

NIH Appeears Before Appropriators

On March 13, 2002, Acting NIH Director, Dr. Ruth Kirschstein appeared before the House Labor, HHS, and Related Agencies Appropriations Subcommittee (L-HHS) and its Chairman, Rep. Ralph Regula (R-OH).

The Subcommittee, continuing the format of "theme hearings" developed last year, heard from a panel of NIH directors the following day on the theme "From Bench to Bedside and Beyond," to highlight translational research and progress from basic discovery to the patient's bedside. On March 19, 2002, the second in the series of theme hearings was held before the subcommittee addressing "Fundamental Research: Biomedical Science in the Future." NIH witnesses included Dr. Kirschstein, Dr. Glen Hanson, Acting Director, NIDA, and the Directors of NIGMS, NIMH, NCRR, and CSR.

Dr. Hanson testified that new discoveries of significant promise are transforming our understanding of the brain and body and providing us with the knowledge we need to confront problems of the day. NIDA employs new science technology to elucidate the underlying mechanisms of drug addiction. NIDA's National Drug Abuse Treatment Clinical Trials Network, an infrastructure consisting of 14 nodes spread across the country, is testing science-based protocols and identifying how to adapt these therapeutic strategies for community use. NIDA anticipates expanding this network to reach underserved populations such as diverse minority groups and rural communities. Coupled with strong research is NIDA's ability to expand its dissemination to clinicians. Through coordinated dissemination and translational research efforts, NIDA ensures that even the most basic neurobiology discoveries systematically influence community prevention and treatment providers across the country so that our citizens can live healthier and more productive lives.

Dr. Hanson also testified about the role stress plays in drug abuse and addiction, particularly in light of the events of September 11. NIDA is expanding its research to better understand the role of stress in the initiation, escalation and relapse to drug use. Dr. Hanson concluded by noting that continued progress can be expected in curtailing drug abuse and addiction if we continue to capitalize on the strong research foundation that NIDA has established. Research is critical to all of our Nation's endeavors and there is hope in knowing that new and growing public health needs such as addiction, AIDS, bioterrorism, cancer and diabetes are being tackled head on with the formidable force of science.

Additional theme hearings before the House Appropriations L-HHS Subcommittee were on "Collaborations in Research", "Disease Prevention and Health Promotion", and "Bioterrorism."

The Senate Appropriations Subcommittee on Labor, Health and Human Services, Senator Tom Harkin (D-IA)

Chairman, held its hearing on the President's FY 2003 budget on March 21, 2002. Subcommittee Chairman Tom Harkin asked how NIH is preparing to adjust to lower annual increases projected by the Administration starting in FY 2004. Dr. Kirschstein testified that "science is not going to stop evolving and expanding because the [budget] doubling has ended." Other areas of concern by the Subcommittee included post-doubling continuation of funding of more and better quality grant applications; embryonic stem cell research; and centralization of the HHS legislative affairs, public affairs, and human resources offices.

NIDA Provides Statement for the Record to the Senate Help Committee

The Senate Health, Education, Labor and Pensions (HELP) Committee requested a statement for the record from NIDA for a hearing on February 12, 2002, on "OxyContin: Balancing Risks and Benefits." Dr. Hanson, Acting Director, NIDA, submitted a statement discussing what we have learned about psychoactive prescription drugs, their potential for abuse, and how we can prevent and treat individuals who may abuse or become addicted to them. Dr. Hanson provided information about the opiate OxyContin, and then broadened the discussion to talk about how research on a specific drug like this fits into NIDA's overall research portfolio. His statement noted that while OxyContin may be of great concern at this time, the overall picture of drug abuse in the U.S. is constantly changing. Both regional and national drug abuse patterns are constantly reshaping and rarely remain static. By monitoring these constantly changing drug trends and by having a comprehensive research portfolio that covers all substances of abuse, NIDA is positioned to use the power of scientific research to avert emerging drug problems before they become national epidemics.

NIDA Acting Director Briefs Senate Staff

On April 11, 2002, NIDA Acting Director, Dr. Glen Hanson, briefed Senate Special Committee on Aging staff at the request of Cecil Swamidoss and Phil Thevenet, staff to Senator John Breaux (D-LA), Chairman. The briefing addressed prescription drug abuse and the elderly.

Bills of Interest

H.R. 3793 - "The Health Professionals Substance Abuse Education Act" was introduced February 26, 2002, by Rep. Kennedy (D-RI). The bill was referred to the House Committee on Energy and Commerce. A companion measure, S.1966, was introduced February 26, 2002, in the Senate by Sen. Biden (D-DE). The Senate bill was referred to the Committee on Health, Education, Labor and Pensions. The bills would promote education of health professionals concerning substance abuse and addiction, authorize $3.5 million for FY 2002 through 2006, and would create an oversight committee to include the Director of the Office of National Drug Control Policy, and representatives of NIDA, NIAAA, SAMHSA, HRSA, as well as non-governmental organizations.

H.R. 3814 - "The National Center for Social Work Research Act" was introduced February 27, 2002, by Rep. Rodriguez (D-TX) for himself and Rep. Upton (R-MI). The bill was referred to the Committee on Energy and Commerce. The bill would establish a National Center for Social Work Research as part of the National Institutes of Health to conduct, support, and disseminate targeted research on social work methods and outcomes related to problems of significant social concern.

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Director's Report to the National Advisory Council on Drug Abuse
May, 2002

International Activities

At the invitation of the Thai government, NIDA officials and grantees visited Thailand in February 2002, to plan with Thai researchers to conduct clinical trials of treatments for methamphetamine-dependence. Clinical investigators will be trained in behavioral therapies that will serve as a platform for future pharmacotherapy trials. Additionally, discussions were held regarding potential clinical studies for the treatment of methamphetamine psychosis. Dr. Frank Vocci, DTR&D, and Dr. Steven Gust, International Program, joined grantee Dr. Walter Ling, UCLA, in meetings with representatives from the Thai Royal Family, the Ministry of Public Health, and multiple sites that provide both inpatient and outpatient treatment for drug abuse and psychosis. H.R.H. Princess Ubolratana, who holds a Master's Degree in Public Health from UCLA, will serve as honorary co-investigator for the project. Because the incidence of methamphetamine psychosis is thought to be higher throughout Southeast Asia than in the United States and appears to follow a different course than that documented in the literature, NIDA hopes to learn more about the nature of psychosis while assisting the Thai government in learning more about the situation in that country and providing advanced training for Thai clinical investigators. The first training is scheduled for May 7-12, 2002; additional training will be conducted throughout the next year and will include a number of short-term exchanges by experts from both countries. The project builds upon relationships forged through NIDA-supported research activities and conferences such as the Pacific Regional Conference on Methamphetamine and Other Amphetamine-Type Stimulants organized by the International Program in November 2000.

Dr. Minda Lynch, DNBR, represented NIDA at the **EuroConference on Modeling Addiction,** held during April 2002, in Austria. The conference addressed the ability of genetic, neurochemical, electrophysiological, and behavioral experimental models to predict human patterns of drug abuse and dependence. It was supported by the European Commission and was organized by former NIDA INVEST Fellow Dr. Gerald Zernig (1993-1994) and Dr. Alois Saria, both of the University of Innsbruck Medical School. NIDA travel support was also awarded to Dr. Sherie L. Kendall, University of Kentucky; Drs. Edie Seldon Sears and Eric C. Donny, Johns Hopkins University; and Dr. Norma Alonzo, Georgetown University. Keynote speakers included Dr. James Woods, University of Michigan; Dr. Harriet DeWit, University of Chicago; and Dr. Michael J. Kuhar, Emory University.

On May 13, 2002, NIDA staff presented at the **United States-European Union "Demand Reduction Seminar: Developing Evidence-Based Demand Reduction Policies"**, in Washington, D.C. Mr. Richard A. Millstein, NIDA Deputy Director, spoke on "Advances in the Science of Addiction Through Neuroscience and Behavioral Research," Dr. Frank Vocci, Director, DTR&D, on "Medications Development," and Dr. Betty Tai, Director, CCTN, on "Treatment Clinical Trials: Blending Clinical Practice and Research".

NIDA grantee Dr. Marilyn McDonald, University of Wisconsin-Madison, and her Russian colleague, Dr. Tatiana Grechanaia, International Association Against Drug Abuse and Drug Trafficking, began work in April 2002, on a collaboration supported by the **International Competitive Design Awards for Innovative Drug Abuse and HIV/AIDS Prevention Efforts** awarded by NIDA for participants in the 1999 *U.S. - Russia Binational Workshop: Drug Abuse and Infectious Disease Prevention Strategies.* The team will develop a Russian version of the drug abuse prevention program, Families and Schools Together (FAST). Three other binational teams and an individual Russian researcher have already begun working on projects funded by the awards.

NIDA welcomed the 2001-2002 **INVEST Research Fellows** with an orientation program at the Division of Intramural Research in Baltimore on February 28, 2002, and a grant-writing seminar at the Neuroscience Center on March 1, 2002. Dr. Zhao Min, China; Dr. Tatiana Tsarouk, Russia; and Dr. Debasish Basu, India, met with the following DIR staff: Drs. David Epstein, David Gorelick, Marilyn Huestis, Eric Moolchan, and Kenzie Preston, Clinical Pharmacology

and Therapeutics Research Branch; and Dr. Alane Kimes, Neuroimaging Research Branch. At NIDA headquarters, Dr. Tsarouk met with Dr. Eve Reider, DESPR; Dr. Zhao met with Dr. Melissa Racioppo, DTRD; and Dr. Basu met with Dr. Harold Gordon, DTRD. The INVEST Fellows are working with the following NIDA grantees: Dr. Howard Liddle, University of Miami (Dr. Zhao); Dr. Elaine Thompson, University of Washington (Dr. Tsarouk); and Dr. Joel Gelernter, Yale University (Dr. Basu). The **Hubert H. Humphrey Drug Abuse Research Fellows** joined the INVEST Fellows for the grant writing seminar to discuss the NIH grant process and international research and training opportunities. Presenters included: Dr. Steven W. Gust, International Program; Dr. Mark Swieter, Office of Extramural Affairs; Dr. Cindy Miner, OSPC; and Natalie Tomitch, Fogarty International Center. Four Humphrey Fellows are supported by NIDA: Dr. Monica Beg, Bangladesh; Dr. Petra Exnerova, Czech Republic; Ms. Olga Toussova, Russia; and Dr. Svitlana Pkhidenko, Ukraine.

The **2001-2002 NIDA Hubert H. Humphrey Drug Abuse Research Fellows** have established their professional affiliations. Part of their 10-month Fellowship includes an approximate 6-week professional affiliation to put into practice the academic learning phase of their fellowships and gain practical hands-on experience to bring back to their home countries. Dr. Monica Beg, Bangladesh, will be working with Dr. Steffanie Strathdee, Department of Epidemiology, Johns Hopkins University. Dr. Beg will work on study design, instruments, staff training, and quality assurance aspects of intervention programs. Dr. Petra Exnerova, Czech Republic, will be working with Mike Townsend at the Partnership for a Drug Free America. During her affiliation Dr. Exnerova will work on a drug prevention media campaign. Dr. Svitlana Pkhidenko, Ukraine, will be working with Dr. George Bigelow, Director of Behavioral Pharmacology Research Unit, Johns Hopkins University. Dr. Pkhidenko will be working on the design of innovative behavioral and pharmacological substance abuse treatment interventions and their potential for implementation in Ukraine. Dr. Olga Toussova, Russia, will be working with Dr. David Metzger, University of Pennsylvania. Dr. Toussova will be working on data analysis, literature searches, effectiveness evaluations and the development of skills to analyze and interpret data.

Dr. Feng Wei, a 2001-2002 **Hubert H. Humphrey Research Fellow** studying at Johns Hopkins University, will be working at NIDA's Center for Clinical Trials Network for his professional affiliation. The professional affiliation is an opportunity for the research fellows to put into practice the academic learning phase of their fellowships and gain practical hands-on experience to bring back to their home countries. Dr. Wei is the Director of the Center of Treatment and Rehabilitation on Drug Dependence of Shunyi District, the largest private treatment and rehabilitation hospital in Beijing.

Four researchers have been selected as the **2002-2003 NIDA Hubert H. Humphrey Drug Abuse Research Fellows**: Dr. Amit Chakrabarti, India; Dr. Winston De La Haye, Jamaica; Mr. Alisher Latypov, Tajikistan; and Dr. Ye Swe Htoon, Myanmar. A clinical pharmacologist, Dr. Chakrabarti chairs the Department of Pharmacology at Sikkim Manipal Institute of Medical Sciences where he teaches undergraduate medical and postgraduate students, treats patients at the De-Addiction Clinic, conducts research in psychopharmacology, and serves on the animal ethics committee. During his Fellowship, Dr. Chakrabarti will focus on expanding his knowledge of epidemiology, treatment, and prevention research. A psychiatrist, Dr. De La Haye is chief resident at University Hospital of the West Indies in Jamaica, where he treats patients with psychiatric and addiction disorders. As a Medical Officer for the Ministry of Health and the Jamaica Defense Force, Dr. De La Haye assisted in drug interdiction efforts, which fostered his interest in demand reduction efforts and the correlation between drug abuse and violence. During his Fellowship, Dr. De La Haye will study U.S. models for drug abuse education, prevention, and treatment. An economist and public information specialist, Mr. Latypov works at his country's Drug Control Agency, where he works with local and foreign media organizations, writes the agency's monthly bulletin, and translates both written and oral material. He helps coordinate training courses, workshops, and conferences on drug abuse issues organized by UNDCP and nongovernmental organizations. Mr. Latypov will spend his Fellowship year concentrating on the development of comprehensive, research-based national drug control policies, prevention interventions, and treatment strategies. Dr. Ye Swe Htoon is a field officer for the Border Area Development Association, where he organizes health, sanitation, and education projects in Northern Myanmar. He was a founder of the Border Area Development Association and the Myanmar Anti-Narcotics Association, which conducts drug education and prevention programs. He has also worked with the International Red Cross and UNDCP, launched programs for the nongovernmental organizations MŽdecins sans Fronti rs and Maltesa, and developed collaborations with the Myanmar Ministries of Health and Home Affairs. During his Fellowship, Dr. Ye Swe Htoon will focus on the integration of drug abuse policy, prevention, and treatment programs with public health policy on the national, regional, and international stage. NIDA sponsors the competitive, 10-month Fellowships in cooperation with the U.S. Department of State, the Institute of International Education, and The Johns Hopkins University. Through a combination of academic courses and professional experience, Fellows learn about NIDA-supported drug abuse research and the application of research to the development of prevention programs, treatment protocols, and government policy.

The **2002 WHO/NIDA/CPDD International Traveling Fellows** have been selected. They are: (1) Yehuda D.

Neumark, Ph.D., Dr. Neumark is a lecturer in epidemiology in the department of social medicine at the School of Public Health and Community Medicine, Hebrew University of Jerusalem in Israel. Following the Annual CPDD Meeting and the NIDA International Forum, Dr. Neumark will travel to Richmond, Virginia to visit with Dr. Robert Balster and his colleagues at Virginia Commonwealth Institute to consider directions for future collaboration in the research of inhalant drug use; (2) Arun Kumar Sharma, M.D., Dr. Sharma is a lecturer in the department of community medicine at the University College of Medical Sciences in Sahadara, Delhi, India. Following the Annual CPDD Meeting and the NIDA International Forum, Dr. Sharma will work with Dr. Samuel Friedman and his colleagues at the National Development and Research Institutes in New York to 1) develop a draft of a research plan that will study the drug-using and sexual networks of drug injectors in New Delhi and 2) to study the relationships between network variables and levels of drug-related and sexual risk behaviors and prevalences of HIV and selected STIs.

Jonathan Pollock, Ph.D., DNBR, Joe Frascella, Ph.D., DTR&D, and Jag H. Khalsa, Ph.D., CAMCODA, organized a mini-symposium on **Drug Abuse and Neuropsychiatric Issues** at the *"International Workshop on Brain Banking"*, that was organized by Dr. Piotr Kozlowski of NINDS, NIH (Bethesda Marriott Pooks Hill), March 11-12, 2002. Over sixty neuropathologists, neurologists, and other neuroscientists from nine countries including the United States participated in a two-day workshop that was co-sponsored by NINDS, NIDA, and NIA. They discussed issues related to brain tissue banking and recommended that the NIH give a serious thought to the establishment of brain tissue repositories to conduct innovative research on causes and consequences of brain diseases. A summary of the workshop will appear on the websites of NIDA, NIA and NINDS. The abstracts will be published in a special supplement to the Journal of Pathology.

Jag Khalsa, Ph.D., CAMCODA, Frank Vocci, Ph.D., Director, DTR&D, and Steven Gust, Ph.D., Acting Director, International Program, organized for the first time, a mini-symposium on **Drug-Drug Interactions** at the *3rd International Workshop on Clinical Pharmacology of HIV Therapy,* Washington, DC, April 11-13, 2002. This was a follow-up to Dr. Khalsa's short note in JAMA , and a presentation at the 2nd International Workshop on Clinical Pharmacology, Amsterdam, April 2001, where it was felt that drug-drug interactions relevant to NIDA's interest should be further discussed in this international forum. At this meeting, a group of clinical pharmacologists pointed out a further need for NIDA to support research on underlying mechanisms of interactions between drugs of abuse, drug addiction treatment medications such as methadone, LAAM, buprenorphine, and antiretroviral drugs.

Drs. Elizabeth Robertson and Eve Reider, DESPR and Dr. Steven Gust met with Dr. Jairo Werner, President of the Helosia Matomho Research Institute, Niteroi, Brazil. Discussions included an overview of the NIDA and recent advances in the prevention and treatment of addiction.

Ana Anders and Pam Goodlow, Special Populations, OD, Beverly Jackson, OSPC and Dr. Eve Reider, DESPR met with the Western Hemisphere, "Drug Demand Reduction Efforts" group. The group included representatives from seven different countries in Central and South America including: Mr. Carlos Acosta, Argentina, Mr. Alvaro Gomez, Chile, Ms. Lizu Lee-Chacon, Costa Rica, Ms. Sandra Juarez Lopez De Temaj, Guatemala, Ms. Maria Elena Ramos Rodriguez and Ms. Maria Christina Santoscoy Gutierrez, Mexico, Mr. Jesus Rodriguez, Venezuela and Mr. Elexis Ruiz, Dominican Republic. Discussion areas included media and public awareness campaigns and treatment and prevention programs.

Drs. Timothy Condon, Associate Director, NIDA, and Steven Gust met with Dr. Shen Jie, Deputy Director, Chinese Center for Disease Control and Prevention and Director, National Center for AIDS/STD Control and Prevention, Mr. Qiang Zhengfu, Director, Department of International Cooperation, Chinese Center for Disease Control and Prevention and Dr. Zunyou Wu, Director, Department of Health Education and Behavioral Intervention, National Center for AIDS/STD Control and Prevention. Discussions centered on ways to form collaborations between these Departments and NIDA, particularly in the area of drug abuse and HIV/AIDS.

Drs. Jerry Flanzer and Pete Delaney, both of DESPR, met with Mr. Liu Huiming, Deputy Chief, Drug Prohibition Section, Jilin Province. Topics discussed included prevention and treatment programs and drug treatment centers, and economics of treatment and prevention.

Dr. Thomas Hilton presented a paper co-authored with Drs. Flanzer, Cartwright, and Fletcher, all of DESPR, entitled "Resistance to Innovation Among US Drug Abuse Treatment Providers: When Organizational Knowledge Interferes With Organizational Learning" at the 3rd International Conference on Organizational Knowledge, Learning and Capabilities - Athens, Greece, April 5-7, 2002.

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Meetings/Conferences

NIDA sponsored **Blending Clinical Practice & Research** at the Grand Hyatt, New York, March 14-15, 2002. Attended by 800 participants, this conference provided an opportunity for clinicians and researchers to examine the latest findings about drug abuse and addiction and their application to clinical practice. Conference participants also had the opportunity to help determine additional areas related to drug addiction treatment. In addition to the conference, NIDA also held a science writer's seminar the afternoon of March 14, 2002 at the Grand Hyatt. The seminar offered members of the media the opportunity to meet some of the experts that presented at the Blending meeting, and to get first-hand information about the latest in substance abuse research and other related topics.

The Entertainment Industries Council, Inc. (EIC), the Robert Wood Johnson Foundation, and the National Institute on Drug Abuse annually partner up to present the syndicated television show, **PRISM Awards™**, for outstanding efforts in the accurate depiction of drug, alcohol and tobacco use and addiction in film, television, interactive media, and comic book entertainment. Established in 1997, the PRISM Awards honor creative contributions that are not only powerfully entertaining, but also proactively address substance abuse and addiction. This year the event took place on May 9, 2002. Dr. Glen Hanson, Acting Director, NIDA, presented one of the awards. Also in attendance were Dr. Timothy P. Condon, Associate Director, NIDA, Dr. Jack Stein, Deputy Director, OSPC, and Ms. Beverly Jackson, Branch Chief, Public Information and Liaison Branch, OSPC. The event will be broadcast over 100 stations nationwide in August 2002.

In Chapel Hill, NC on May 21, 2002, NIDA sponsored the **North Carolina Parent Corps Pilot Program Evaluation Meeting.** Co-hosted by the North Carolina Division of Mental Health, Developmental Disabilities, and Substance Abuse Services, this meeting provided consultation with prevention scientists to develop an evaluation strategy for the National Parent Corps. The Parent Corps is a new Presidential initiative to recruit, train, and support parent leaders to mobilize parents to become involved in drug prevention efforts in their local communities. The program will begin pilot testing in North Carolina soon.

NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA) held a Working Meeting on **Strategies to Improve the Replicability, Sustainability, and Durability of HIV Prevention Interventions for Drug Users**, on May 6-7, 2002, in Chevy Chase, Maryland. The meeting brought together experts in the field of HIV prevention to exchange information on their current research on interventions to prevent HIV and other infectious diseases among drug users, their sexual partners, and other at- risk populations. Its focus was on strategies to improve the replicability, sustainability, and durability of interventions, and to address gaps and future directions in HIV prevention research in drug users and other populations at risk. Helen Cesari and Elizabeth Lambert of CAMCODA organized the Working Meeting, which was chaired by Wendee Wechsberg, Ph.D., of the Research Triangle Institute. Mr. Richard Millstein and Dr. Henry Francis presented remarks.

NIDA sponsored a **Special Events Program at the Society for Research on Adolescence Biennial Meeting** in New Orleans, LA, April 11 - 14, 2002. This program included two components. The first is the "Career Opportunities Program," which featured a Mentoring Program, a poster and discussion hour focusing on child and adolescent research support at NIDA, and a NIDA Exhibit Booth. The second component, a scientific symposium titled "Building Bridges Between Adolescent Research and Substance Abuse Research: Challenges and Opportunities," included five speakers. Members of the Child and Adolescent Workgroup that participated in the planning of the events and/or represented NIDA at the conference include Drs. Jessica Campbell, Kevin Conway, Aria Crump, Kathleen Etz, Teresa Levitin, Rachel Schiffman, and Vince Smeriglio.

On April 27, 2002 at the American Society of Addiction Medicine's (ASAM) 33rd Medical Scientific Conference in Atlanta, Georgia, a day-long Symposium entitled **"HIV/AIDS, Viral Hepatitis, and Addiction: Perspectives on Treatment and Prevention"**, was jointly sponsored by the NIDA, the Centers for Disease Control and Prevention, and ASAM. The Symposium organizers were Drs. Dorynne Czechowicz, Henry Francis, Jag Khalsa (NIDA), Dr. T. Stephen Jones (CDC), and Drs. Lawrence Brown, Marc Gourevitch, David Ostrow, and Mel Pohl (ASAM). The Symposium addressed the latest science-based information on effective approaches for the treatment of drug and alcohol users with these infectious diseases. Patients living with HIV and hepatitis C discussed clinical issues from their own experiences. A panel discussion followed the presentations, with attention focused on integrating screening, prevention, and treatment for hepatitis and HIV with addiction treatment.

On February 27, 2002, NIDA Acting Director, Dr. Glen R. Hanson and other NIDA senior staff briefed White House Office of National Drug Control Policy (ONDCP) Director, John P. Walters and several of his senior staff members on NIDA's research programs. Following introductory remarks and an overview of NIDA by Dr. Hanson, NIDA Office and Center Directors, Dr. David Shurtleff (DNBR), Dr. Frank Vocci (DTR&D), Dr. Betty Tai (CCTN), Mr. Richard A. Millstein (DESPR), Dr. Henry "Skip" Francis (CAMCODA), and Dr. Barry Hoffer (IRP) described highlights of ongoing and planned reseach from their respective programs.

NIDA's Behavioral Sciences Working Group is continuing efforts to recruit and retain new investigators into the fold of drug abuse investigation in basic, epidemiological, prevention and treatment research. As part of these ongoing outreach efforts, the workgroup sponsored three pilgrimages to regional meetings that are well attended by behavioral and social scientists from smaller universities and colleges in the U.S. Workgroup members conducted grants writing workshops and discussed research interests relevant to NIDA's programmatic mission at the following venues: Western Psychological Association Annual Meeting, Irvine, CA, April 12-14 (Drs. Melissa Racioppo, DTR&D and Marina Volkov, OEA), 14th Annual Indian Health Service Research Conference, Albuquerque, NM, April 29-May 1 (Drs. Kathy Etz, DESPR and Joe Frascella, DTR&D), and Midwestern Psychological Association Annual Meeting, May 1-4 (Drs. Paul Schnur, DNBR, Kathy Etz, DESPR and Mark Green, OEA).

On February 25-26, 2002, NIDA sponsored a workshop on **"Lapse and Relapse: The Chronic Recurring Nature of Drug Addiction"** in Rockville, MD. This workshop brought together leading researchers from various areas of drug abuse research and researchers studying other chronic, relapsing disorders or conditions, to identify common scientific challenges and opportunities for better understanding the neurobiological, behavioral, emotional and cognitive dimensions of relapse to addiction. The goal of the workshop was to identify gaps and opportunities in drug abuse relapse that need to be explored in order to better understand and prevent drug abuse relapse. Each participant had the opportunity to summarize their major research findings and to share their current thinking on the issue of relapse. Subsequent workshop discussion focused on the nature of lapse and relapse across neuropsychiatric disorders, clinical findings in relapse, as well as data from preclinical models of drug abuse relapse. The workshop format allowed for an extensive discussion about the current state of the field and a lively exchange of ideas on future research directions. Participants included: G. Alan Marlatt, Ph.D., University of Washington; Michael S. Robbins, Ph.D., University of Miami; James C. Coyne, Ph.D., University of Pennsylvania; Nora D. Volkow, M.D., Brookhaven National Laboratory; Wayne Drevets, M.D., National Institute of Mental Health; Jeffery N. Wilkins, M.D., UCLA School of Medicine; Timothy B. Baker, Ph.D., University of Wisconsin; Janet Polivy, Ph.D., University of Toronto; Katie Witkiewitz, M.A., University of Washington; Scott Lukas, Ph.D., McLean Hospital/Harvard Medical School; Peter Kalivas, Ph.D., Medical University of South Carolina; Yavin Shaham, Ph.D., National Institute on Drug Abuse; Michael Sayette, Ph.D., University of Pittsburgh; and Varda Shoham, Ph.D., University of Arizona.

NIDA was a co-sponsor of the American Psychological Association conference, **Enhancing Outcomes in Women's Health**, February 21-23, 2002, in Washington, DC. NIDA's Women and Gender Research Group organized and chaired three symposia: "The convergence of Drug Abuse, Sex, and Violence," "Gender Issues in Drug Abuse Prevention and Treatment Interventions," (chaired by Dr. Cora Lee Wetherington, DNBR and NIDA's Women and Gender Research Coordinator, and organized by Adele Roman, DNBR and NIDA's Deputy Women and Gender Research Coordinator), and "Intervention Approaches with Women in Diverse Populations at Risk for Drug Abuse."

Staff of the Division of Treatment Research and Development hosted Dr. Arvid Carlsson, 2001 Nobel Laureate in Medicine, on April 5, 2002 to discuss pharmacological approaches to the treatment of stimulant dependence.

Jag Khalsa, Ph.D., CAMCODA, and Joseph Frascella, Ph.D., DTR&D, of NIDA collaborated with David Stoff, Ph.D. of the National Institute of Mental Health (NIMH), and Andrew Monjan, Ph.D. of the National Institute on Aging (NIA) in organizing a workshop entitled **Mental Health Research Issues in HIV Infection and Aging**, held April 22-23, 2002. A group of NIMH, NIA and NIDA-funded (e.g., Drs. Jeanne Bell, Thomas Ernst, Igor Grant, and Charles Hinkin) clinicians/scientists presented outstanding research findings on issues of HIV, and co-morbid conditions such as neurocognitive and neurobehavioral impairment, mental disorders, Parkinson's and Alzheimer and other neurodegenerative diseases, and drug abuse-and HIV-related complications among older (50+) adults. Due to the

fact that by the year 2030, there might be about 70 million older people in the US, it was recommended that the NIH consider supporting basic, epidemiologic, clinical, and interventions research in this rapidly growing population. A summary will appear on the NIDA/NIMH/NIA websites soon. A publication in a professional journal is being considered.

On May 2-3, 2002, Lan-Hsiang Wang, Ph.D. of the NHLBI and Jag H. Khalsa, Ph.D., of CAMCODA, NIDA conducted a meeting on **Cardiovascular Complications of HIV (and substance abuse [cocaine, alcohol])**. A group of well-recognized clinicians/scientists (funded by NHLBI and NIDA co-sponsored RFAs) presented data from their ongoing studies on etiology and underlying pathophysiology of cardiovascular complications of HIV/AIDS, and substance abuse (cocaine, alcohol). This was a follow-up to an earlier meeting /Meetings/CardioMtg.html that appeared on NIDA website. The participants of this follow-up meeting also made a number of recommendations for future research. A brief summary, agenda and a list of participants will appear on the NIDA website.

A **National CTN Steering Committee Meeting** was held January 28-30, 2002, in Charleston, South Carolina. Dr. Glen Hanson, Acting Director of NIDA, presented at the meeting. The Police Chief of Charleston, SC, also addressed the group. The meeting focused on: Lead Investigator updates on protocol progress, the Gender Group Snapshot, and the presentation of health services research grantee proposals for using the CTN as a platform for research.

A **National CTN Steering Committee Meeting** was held March 13, 2002, in New York City. During this meeting, the reorganization of the CTN infrastructure was approved and protocol progress was reviewed.

The **CTN Data and Safety Monitoring Board** met February 13-14, 2002 and April 15, 2002 in Bethesda, MD. The Board reviewed the current trials for safety and scientific integrity. The meetings addressed: 1) reports on all Serious Adverse Events; 2) the trials' progress; 3) review of a new protocol; and 4) discussion of current issues.

The **CTN Criminal Justice System Interest Group** conducted a meeting on February 27-28, 2002, in Bethesda, MD. The meeting focused on: reviewing current treatment research status, exploring opportunities/needs for court involved patients, identifying possible research concepts, and detecting protocol implementation barriers and solutions.

Mr. Richard A. Millstein, NIDA Deputy Director, met with Dr. Ford Kuromoto, National Director, Ms. Emilie Dearing, Vice Chairperson, and Dr. Frank Wong, Member of the Board of Directors, National Asian Pacific American Families Against Substance Abuse, on NIDA's Asian/Pacific Islander Work Group recommendations, April 10, 2002, Bethesda, MD.

Mr. Millstein presented to the Okura Mental Health Leadership Fellows on drug abuse research and career opportunities, April 16, 2002, Bethesda MD.

Dr. Timothy P. Condon, Associate Director, NIDA, presented "Drug Abuse and Addiction: What's New on the Research Scene" at the American Academy of Child and Adolescent Psychiatry K-12 Annual Retreat on Seabrook Island, SC on March 8, 2002.

Dr. Timothy P. Condon presented "Advances in Drug Abuse and Addiction Research: Implications for Prevention and Treatment" at the California Association of Alcohol & Drug Program Executive (CAADPE) Conference: "Forging Partnership Celebrating 13 Years" in Sacramento, CA on March 12, 2002.

Dr. Timothy P. Condon presented "National Institute on Drug Abuse (NIDA) Update: Recent Advances in Drug Addiction and Co-occurring Disorders Research", at the Plenary Session of the Co-occurring Disorders Conference in Yakima, WA on April 4, 2002.

Drs. Timothy P. Condon, Associate Director, NIDA, and Jack Stein, Deputy Director, OSPC, presented "Blending Research and Practice: Opportunities for Collaboration" at the Addiction Technology Transfer Centers Strategic Planning Meeting in Silver Spring, MD on April 15, 2002.

On April 25, 2002, Dr. Timothy P. Condon provided a National Overview of Drug Abuse at the invitation of the Milton Marks "Little Hoover" Commission on California State Government Organization and Economy, in Sacramento, CA. The Commission, an independent oversight agency that holds hearings on various topics of concern to the State, invited Dr. Condon to testify on the scope of drug abuse throughout the country and on what recent advances in science tell us about drug abuse and addiction. This testimony will contribute to the Commission's analysis of how the State administers its drug abuse treatment programs.

Dr. Timothy P. Condon presented the Keynote Address at the Chief Resident Immersion Training (CRIT) Program of Clinical Addiction Research and Education in Cape Cod, MA, on May 15, 2002.

Dr. Jack Stein, Deputy Director, OSPC, provided an update on NIDA activities at the Fourth Annual Targeted Capacity Expansion Grantee Meeting in Washington, DC on January 24, 2002.

Dr. Jack Stein conducted a workshop entitled "Raves, Risks, and Research: Update on Club Drugs" at the 13th Annual Maryland Student Assistance Program Professionals Association Conference in Ellicott City, MD on February 4, 2002.

Dr. Cathrine Sasek, Science Policy Branch, OSPC, gave a presentation on prescription drug abuse on March 11, 2002, to an audience of senior citizens. The presentation was part of the Brain Awareness Week activities.

Dr. Donald Vereen, Acting Chief, Special Populations Office, made a presentation entitled, "The Science of Addiction" at Southern University's 8th Annual Career day in Baton Rouge, Louisiana on March 6, 2002.

Dr. Donald Vereen moderated a panel entitled, "New Developments in Drug Abuse Research with Ethnic Minorities at the Lonnie Mitchell National HBCU Substance Abuse Conference in Baltimore, Maryland on April 3, 2002.

Dr. Donald Vereen made a presentation entitled, "Research Issues on Prescription Drug Abuse" at the Lonnie Mitchell National HBCU Substance Abuse Conference in Baltimore, Maryland on April 4, 2002.

Dr. Donald Vereen made a presentation entitled, "Update on Research for HIV Prevention and Care Among Intravenous Drug Using Populations", to the Population Council's Horizons Program in Washington, DC on April 10, 2002.

In March 2002, Ana Anders, Senior Advisor on Special Populations, co-chaired a planning meeting in Los Angeles for the Latino Behavioral Health Institute annual conference, which will take place in September 2002.

Ana Anders, along with staff from NIMH, participated in the National Hispanic Science Network steering committee meeting at the University of Miami in March 2002.

Ana Anders participated in the 8th National Conference of the National Asian Pacific American Families Against Substance Abuse (NAPAFASA) in Washington, DC on March 10 -12, 2002.

On March 7, 2002, Dr. Betty Tai, Director, CCTN, participated in an Institute of Medicine Clinical Research Roundtable. The workshop consisted of two panel discussions: 1) implementation of clinical research results into practice, and 2) opportunities and challenges in conducting clinical research.

On March 14, 2002, Dr. Betty Tai, Director, CCTN, gave a presentation on the Clinical Trials Network at the NIDA Blending Conference in New York City, NY. Nearly 1,000 attendees were at that conference.

Drs. Joe Frascella, Steven Grant, and Frank Vocci attended two briefings at ONDCP on March 8 and 13, 2002 on the applications of neuroimaging to further understand the treatment of substance abuse.

Drs. Ahmed Elkashef and Frank Vocci spoke at the 4TH Annual Hawaii Conference on Addictions on May 9, 2002. The conference was titled: Methamphetamine: All about Ice. Their presentations were related to clinical and neurobiological approaches to the treatment of methamphetamine dependence, respectively.

Dr. Cece McNamara, DTR&D, presented a talk entitled "Minority Drug Abuse Treatment" at the Lonnie E. Mitchell HBCU National Substance Abuse Conference.

Dr. Steven Grant, DTR&D, gave a talk entitled "Cognitive Neuroscience of Craving" at the NIDA conference on "Blending Clinical Practice and Research in New York City, March 14-15, 2002. Dr. Grant spoke during the symposium on "Craving, Addiction and the Brain".

Drs. Steven Grant, of DTR&D, and David Shurtleff of DNBR represented NIDA at the annual meeting of the Cognitive Neuroscience Society in San Francisco, CA on April 13 - 16, 2002.

Dr. Joseph Frascella, DTR&D, attended the NSATTC Systems Change and Technology Transfer Symposium held in Albany, New York and gave a talk entitled "The Clinical Neurobiology of Addiction: How What We're Learning Will Impact the Field", April 7-8, 2002.

Drs. Joseph Frascella, DTR&D, and Paul Schnur, DNBR attended the 9th Annual Undergraduate and Graduate Science Research Symposium as participants and scientific judges on the campus of Morgan State University. This research symposium is a forum for the presentation of research by students from area HBCUs and was held in Baltimore, MD, April 18, 2002.

Dr. Joseph Frascella along with Dr. Kathleen Etz, DESPR, attended the Indian Health Service's 14th Annual Research

Conference, where they conducted a workshop on grant writing and research opportunities for Native American researchers. The conference was held in Albuquerque, New Mexico, April 29-May 1, 2002.

Dr. Jerry Frankenheim, DNBR, presented "MDMA (Ecstasy) and Methamphetamine: What the Research Is Telling Us," at the American Academy of Pediatrics Committee on Substance Abuse, in Baltimore, April 8, 2002.

Dr. Dave Thomas, DNBR, presented "Funding Opportunities at the National Institute of Drug Abuse and the National Institutes of Health for Virtual Reality-Based Treatment Research" at the Medicine Meets Virtual Reality meeting held January 23-26, 2002 in Newport Beach, California.

Drs. Dave Thomas, DNBR, Marina Volkov, OEA, Cindy Miner, OSPC, Charles DesBordes, OEA, Angela Martinelli, OSPC, and Cathrine Sasek, OSPC, participated in **Brain Awareness Week** activities for middle school students at the National Museum of Health and Medicine on March 13 and 14, 2002. Several hundred students participated in the NIDA game "Who Wants to Be a NIDA Neuroscientist." Each student received a packet of NIDA publications, bookmarks, art cards, and key chains.

Dr. Cora Lee Wetherington, DNBR and NIDA's Women & Gender Research Coordinator, gave an invited talk "Gender-Related Issues in Drug Abuse" in the Gender Issues Workshop held at the NIDA conference Blending Clinical Practice & Research: Forging Partnerships to Enhance Drug Addiction Treatment, New York City, NY, March 14-15, 2002.

Dr. Cora Lee Wetherington, DNBR and NIDA's Women & Gender Research Coordinator, gave an invited talk, "Gender Differences Issues in Drug Abuse." 24th Annual Substance Abuse Librarians and Information Specialists Conference. Washington, DC, April 16-20, 2002.

Dr. Cora Lee Wetherington, DNBR and NIDA's Women & Gender Research Coordinator, gave an invited talk, "Gender Differences in Vulnerability to Addiction" in the symposium, "The Clinical Implications of Gender for Addiction" at the Annual Medical-Scientific Conference of the American Society of Addiction Medicine. Atlanta, GA, April 25, 2002.

Dr. Minda Lynch, DNBR, addressed the Neurochemistry Club International Neurochemistry Winter Conference on April 6, 2002, in Solden, Austria, where she described NIDA's efforts to stimulate and support drug abuse research worldwide and highlighted programs of support for training and encouraging collaborations involving European investigators.

At the 17th biennial meeting of the Conference on Human Development, which was held in Charlotte, NC in April 2002, Dr. Teresa Levitin, Director, OEA, and a colleague from the NICHD led an invited discussion on "Research Grants Programs in Developmental Psychology".

Dr. Levitin, OEA, joined with other members of the Child and Adolescent Workgroup to plan a number of events at the ninth biennial meeting in April of the Society for Research on Adolescence, including a poster session, discussion hour, and symposium.

Dr. Mark Green, Chief, Clinical, Epidemiological, and Applied Sciences Review Branch, OEA, has been collaborating with the NIH National Center for Minority Health and Health Disparities (NCMHD) to provide guidance on NIH extramural support. He participated in technical assistance workshops hosted by the NCMHD on Feb 11-12, 2002, in Dallas, TX and on March 4-5, 2002, in Seattle, WA.

Dr. Teresa Levitin, Director, OEA, served as an evaluator of projects for the INTEL High School Science Talent Search for the 2002 awards.

NIDA Deputy Director, Richard A. Millstein and members of the Prevention Research Branch at NIDA, including Drs. Elizabeth Robertson, Jackie Kaftarian, and Eve Reider, met with members of the Center for Substance Abuse Prevention (CSAP), including Ruth Sanchez-Way, Elaine Parry, Paul Brounstein, and Alvira Stern. The meeting was held on February 22, 2002 at CSAP in Bethesda and the purpose of the meeting was to discuss the possibility of NIDA/CSAP collaboration in joint activities and projects in order to accelerate research and improve practice of substance abuse prevention services and systems.

Dr. Shakeh J. Kaftarian, PRB, DESPR, was invited to serve on CDC's expert panel for Evaluation of Prevention Projects Conducted by Community-based Organizations convened in Atlanta, Georgia on April 15-16, 2002.

Dr. Shakeh J. Kaftarian, PRB, DESPR, presented the three components of NIDA's National Prevention Research Initiative and their research translation goals to the Prevention Research Coordinating Committee of NIH and to the representatives of the Office of Extramural Prevention Research of CDC on February 12, 2002.

Dr. Shakeh J. Kaftarian, PRB, DESPR, presented the three components of NIDA's National Prevention Research

Initiative to the State Incentive Grantees of the Substance Abuse and Mental Health Services Administration at the Needs Assessment Conference in Baltimore on February 5, 2002.

Drs. Elizabeth Robertson and Shakeh J. Kaftarian of PRB, DESPR represented NIDA at the inaugural Translational Research Committee meeting of NIH, convened by NIH's Office of Behavioral and Social Science Research on March 20, 2002.

Drs. Peter Delany, Elizabeth Robertson and Shakeh J. Kaftarian, DESPR, met with representatives of the Casey Family Programs Foundation on March 6, 2002 for the purpose of establishing a partnership and collaborative research activities between NIDA and Casey.

Drs. Aria Crump and Eve Reider, DESPR, prepared and presented a paper at the Lonnie E. Mitchell HBCU Conference in Baltimore, Maryland on April 3, 2002. The paper was entitled "Drug Abuse Prevention with Ethnic Minorities."

Ms. Moira O'Brien, DESPR, represented NIDA at the NIH Office of AIDS Research Fiscal Year 2004 Planning Workshop for Natural History and Epidemiology, Bethesda, MD, February 5, 2002.

Arnold Mills, DESPR, participated in the Dr. Lonnie E. Mitchell National Historically Black Colleges and Universities Substance Abuse Conference held in Baltimore, MD April 1-5, 2002. As part of a panel on new developments in drug abuse research with ethnic minorities, he made a presentation on the influence of social and cultural factors on drug use.

Dr. Thomas Hilton, DESPR, presented an overview of health services research projects in the NIDA Clinical Trials Network to the CTN steering committee at their meeting in Charleston, SC, January 30, 2002.

Dr. Thomas Hilton chaired and presented a panel with Dr. Karen Sirocco (CSR) on NIDA's SBIR program at the annual meeting of the Association of Small Business and Entrepreneurship- St. Louis, MO, March 5-9, 2002.

Dr. Jerry Flanzer, DESPR, was a featured speaker (adolescent drug abuse treatment and services) at the Society of Adolescent Medicine's annual conference. He also co-led a workshop on grant writing at this same conference with Dr. James Hill of the University of Iowa. Boston, March 2002.

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Media and Education Activities

Press Releases

February 4, 2002 - **NIDA Hosts Conference in New York to Facilitate Closing the Gap Between Research and Clinical Practice**. The National Institute on Drug Abuse (NIDA), one of the National Institutes of Health, held the meeting, Blending Clinical Practice and Research: Forging Partnerships to Enhance Drug Treatment, in New York. The conference provided an important opportunity for clinicians and researchers to examine cutting-edge scientific findings about drug abuse and addiction and their application to clinical practice. Coverage of this release appeared in, *Newsday*.

February 11, 2002 - **Public Service Announcements and In The Mix Show Highlight the Dangers of Anabolic Steroids**. Part of the angst of adolescence is concern about body image. In the quest for physical perfection and athletic performance America's young adults increasingly have turned to anabolic steroids, despite the serious side effects of these drugs. The National Institute on Drug Abuse (NIDA), which began a public education program about abuse of anabolic steroids in April 2000, is now distributing public service announcements entitled "Game Plan" in English and Spanish to television stations across the country. The announcements are designed to educate teens, parents and others about the dangers of anabolic steroid abuse. The Institute also participated in the development of "Steroids: The Hard Truth," a special on anabolic steroid abuse among young people that aired on In the Mix, a national television show for teens on PBS.

March 13, 2002 - **NIDA Takes Part in National Inhalants and Poison Awareness Week**. The National Institute on Drug Abuse (NIDA), National Institutes of Health, participated in a press conference to kick-off the 10th Annual National Inhalants and Poisons Awareness Week (NIPAW), March 17 - 23, 2002. Dr. David Shurtleff, Acting Director, Division of Neuroscience and Behavioral Research, joined ONDCP Director John Walters; SAMHSA Administrator Charles Curie; CSAT Director Westley Clark; CSAP Acting Director Elaine Parry; Partnership for a Drug Free America's President and CEO Stephen J. Pasierb; and Harvey Weiss, Executive Director of the National Inhalant Prevention Coalition (NIPC), the driving force behind NIPAW. Dr. Shurtleff spoke about NIDA's new research initiative, Inhalant Abuse: Supporting Broad-Based Research Approaches, designed to intensify its research efforts on the epidemiology, social, behavioral, cognitive, and neurobiological consequences of inhalant abuse, as well as treatment and prevention. To coincide with the 2002 NIPAW, NIDA has produced two informational post cards featuring graphics from the National Inhalant Prevention Coalition website, courtesy of GSD&M, and is distributing 12,500 copies of these free in surf, ski, and skate shops nationwide. These shops reach younger teen audiences. Coverage of this release appeared in, *ABC News, Alive and Free, Healthscout.com, Join Together Online* and *USA Today.*

March 27, 2002 - **Adolescent Depression and High Receptivity to Tobacco Ads May Lead to Teen Smoking**. A NIDA-funded study by researchers at the Georgetown University School of Medicine and the University of Pennsylvania School of Medicine reports that adolescent depression, combined with high receptivity to tobacco advertising, plays a powerful role in whether a teen smokes cigarettes. While research has demonstrated the effects of a number of factors on adolescent smoking behavior (including exposure to smoking by family and friends, high receptivity to tobacco advertising, and positive attitudes and beliefs about smoking), this is one of the first studies to examine how depression combines with these factors to influence the likelihood of smoking. Coverage of this release appeared in, *Ascribe Newswire* and *Join Together Online*.

March 27, 2002 - Study Assesses Impact of September 11th Events on Manhattan Residents. In the aftermath of the events of September 11th, researchers funded in part by the National Institute on Drug Abuse assessed post

traumatic stress disorder (PTSD) and depression among Manhattan residents five to eight weeks after the attacks. The researchers, from the New York Academy of Medicine, found that 7.5 percent of the study's 1,008 participants reported symptoms of PTSD and 9.7 percent reported symptoms of depression. More than three percent of participants reported symptoms of both PTSD and depression. The New York findings are two to three times higher than the PTSD and depression rates reported by participants in a national mental health study conducted in the early 1990s. Coverage of this release appeared in, *Newsday, Join Together Online, Post and Courier, American Health Line* and *Washington Times*.

Articles of Interest

January 9-15, 2002, *The Village Voice* - "Prescription: Euphoria" - Interview with Alan I. Leshner, Ph.D., and Jerry Frankenheim, Ph.D.

January 20, 2002, *USA Today* - "Date Rape Drug GHB Making Inroads in Nation's Club Scene" - Interview with Alan I. Leshner, Ph.D.

January 29, 2002, *The New York Times* - "Marijuana's Effects: More Than Munchies" - Interview with Alan I. Leshner, Ph.D.

February 10, 2002, *The New York Times Magazine* - "Drug Fix-Does Rehab Actually Work?" - Interview with Alan I. Leshner, Ph.D.

February 11, 2002, *USA Today* - "Ecstasy Grows as Danger to Teens" - Interview with Glen R. Hanson, Ph.D., D.D.S.

February 12, 2002, *USA Today* - "Teen Steroid Abuse Prompts New Round of TV Warnings" - Interview with Glen R. Hanson, Ph.D., D.D.S.

March 25, 2002, *Workplace Substance Abuse Advisor* - "NIDA Director Cool to Proposed Merger Being Studied in Congress" - Interview with Glen R. Hanson, Ph.D., D.D.S.

March 26, 2002, *Newsday* - "Post-9/11, Manhattanites are Drinking and Smoking More" - NIDA conference article.

March 28, 2002, *Desert News (UT)* - "Faith Healing: Spirituality Offers Help on Addictions" - Interview with Glen R. Hanson, Ph.D., D.D.S.

April 1, 2002, *USA Today* - "Scientific Accuracy, Entertainment Value" - PRISM Awards article, NIDA mentioned.

April 1, 2002, *Popular Science* - "Who's an Addict" - Interview with Roy Wise.

NIDA Exhibits Program

Meetings where NIDA exhibited publications and program announcements over the past several months are as follows:

January 24-26, 2002	NADCP 3rd Annual Juvenile Justice and Family Court Training Conference
February 14-19, 2002	American Association for the Advancement of Science
February 20-23, 2002	Society for Research on Nicotine and Tobacco
February 22, 2002	Women's Heart Day Health Fair
February 24-27, 2002	Council on Social Work Education
March 11-15, 2002	Brain Awareness Week
March 14-15, 2002	NIDA Blending Clinical Practice and Research
March 26-30, 2002	National Science Teachers Association
April 3-6, 2002	Lonnie E. Mitchell National HBCU Substance Abuse Conference
April 11-14, 2002	Society for Research on Adolescence Biennial Meeting
April 11-14, 2002	National Student Assistance Conference
April 20-24, 2002	Experimental Biology 2002
April 25-28, 2002	American Society of Addiction Medicine
May 18-23, 2002	American Psychiatric Association

EDUCATIONAL ACTIVITIES

NIDA's new high school science education curriculum "The Brain: Understanding Neurobiology Through the Study of Addiction" is now available. Developed in collaboration with the NIH Office of Science Education, the curriculum provides accurate research-based information on various aspects of drug abuse, including neurobiology, behavioral components, and treatment. The curriculum is designed as lessons for use in the science classroom. It consists of print materials, and an interactive CD-ROM.

OTHER MEDIA ACTIVITIES

Dr. Frank Vocci, Director, DTR&D, was interviewed by Mr. John Schultz of the Kansas City Star regarding recruitment of drug dependent subjects in clinical trials.

Dr. Frank Vocci was interviewed by Ms. Kitta McPherson of the New Jersey Star Ledger on two occasions. The first was to discuss the development of buprenorphine and the second was to discuss the neurobiology of addiction and potential interventions.

Dr. Frank Vocci was interviewed by Ms. Susan Seibel of the Pittsburgh Post Gazette regarding new treatments for heroin addiction.

Dr. Frank Vocci was interviewed by the BBC on the development of treatments for addiction. He covered behavioral, pharmacological, and immunological treatment approaches.

Dr. Frank Vocci presented on future trends in pharmacotherapies for substance abuse disorders at an Addiction Studies Workshop for Journalists in Atlanta.

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Planned Meetings

Drs. Kathy Etz from DESPR, Minda Lynch and Cora Lee Wetherington from DNBR, and Suman Rao from OSPC are organizing a meeting on **Proximal Processes in the Decision to Abuse Drugs** for July 19, 2002 at the Bethesda Marriott. The participants will focus their discussion on: the cognition/emotion interface in adolescent development; neurobiological processes in cortical and subcortical emotional areas that are important for this interface; contextual factors at the time of decisions to abuse drugs; the adolescent's perception of risk; and role of risk calculation and value estimation as proximal processes in these decisions. Recommendations for future field and laboratory-based investigation on proximal processes will be entertained, and attention will be given to methodological considerations and behavioral assessment strategies.

A meeting entitled **Nonconscious Processes in Self-regulation: Application to Drug Abuse and Addiction** is planned for July 22-23, 2002. The meeting, to be held at NIDA, will bring together experts on automaticity in self-regulation with drug abuse researchers who have explored automaticity as a paradigm for compulsive drug use. Participants include Timothy Baker, Roy Baumeister, Tanya Chartrand, Stephen Woods among others. The meeting is designed to assist in the development of the social cognition research portfolio at NIDA.

Drs. Steven Grant and Joseph Frascella, DTR&D, are members of the organizing committee for a NIDA-sponsored meeting on **Youth, Internet, and Drugs**, to be held June 6, 2002 in Bethesda, MD.

CAMCODA staff, working with NIDA grantees and other individuals and organizations, developed seven proposals for **satellite sessions for the XIV International AIDS Conference**, to be held in July 2002, in Barcelona, Spain. All of the sessions were approved, and include: 1) Youth Drug Abuse and HIV Infection in Cultural Context; 2) Impact of Health Disparities on HIV Interventions in Drug-Using Populations; 3) Drug Abuse Treatment as HIV Prevention; 4) Effects of Drug Abuse and Sex Work on HIV Prevention Across National Borders; 5) HIV Risk Among Transgenders: The Social and Cultural Context of Substance Abuse; 6) Clarifying the Controversy About Whether Drug Abuse Influences AIDS Progression; and 7) the Global Research Network on HIV Prevention in Drug-Using Populations. An eighth session, on Psychostimulant Abuse and HIV Risk, was submitted by Dr. Frank Vocci, Director of NIDA's Division of Treatment Research and Development, and was approved.

National CTN Steering Committee Meetings are planned for the follow dates and locations: August 12-14, 2002, in Seattle, Washington; and October 21-24, 2002, in Bethesda, Maryland.

The CTN Data and Safety Monitoring Board will meet, July 22-23, 2002, and October 10-11, 2002, in Bethesda, Maryland.

The CTN Protocol Review Board will meet August 20, 2002, and November 5, 2002, in Bethesda, Maryland.

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Publications

NIDA Publications

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group,
Volume I - December 2002
NIH Pub. No. 02-5109
This report provides an ongoing assessment of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policymakers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse - Community Epidemiology Work Group,
Volume II - December 2002
NIH Pub. No. 02-5110
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.

Problems of Drug Dependence 2001: Proceedings from the 63rd Annual Scientific Meeting of the College on Problems of Drug Dependence
NIH Pub. No. 02-5097
This publication documents plenary symposia and reports from the annual meeting of the College on Problems of Drug Dependence, Inc., including comprehensive, up-to-date reviews of research in progress from many disciplines in drug abuse and dependence.

Serie De Reportes De Investigación Esteroides Anabolicos Abuso
NIH Pub. No. 02-3721(S)
This Spanish language translation provides an overview of anabolic steroid use and effects.

NIDA INVEST Letter, Winter/Spring 2002
The lead stories in this issue reported on a contract with Thai researchers to conduct clinical trials of methamphetamine-dependence treatments and the U.S. - Netherlands Workshop on Bi-National Research Collaboration on Drug Abuse and Drug Addiction, held September 6 and 7, 2001, in Cumberland, Maryland. The 2002 WHO/NIDA/CPDD International Traveling Fellowships and the 2002-2003 NIDA Hubert H. Humphrey Drug Abuse Research Fellows were announced.

NIDA NOTES

NIDA NOTES, Volume 16, Issue No. 5
NIH Pub. No. 02-3478

The front-page story for this issue of NIDA NOTES describes the international NIDA-sponsored conference on MDMA/Ecstasy. The article summarizes a number of the presentations at the meeting relating to the epidemiology for the drug, its acute effects and its long-term effects. A companion story describes the many different types of individuals who abuse this drug. A research story describes cocaine's effects on dopamine cells in mice brains, indicating that cocaine causes alterations in the way the brain works. Another story reports on the different patterns

of drug abuse by cocaine and methamphetamine users.

NIDA NOTES, Volume 16, Issue No. 6
NIH Pub. No. 02-3478

The front-page story for this issue of NIDA NOTES describes the Second National Conference on Drug Abuse Prevention held in August 2001 in Washington, D.C. The article describes the components of NIDA's new National Drug Abuse Prevention Research Initiative and summarizes a number of presentations relating to risk and protective factors for drug use, elements of effective prevention programs, and the number and type of prevention programs used by junior high and middle schools. In the Director's Column, Dr. Glen Hanson describes NIDA's past and current prevention efforts and indicates a number of areas for new research efforts.

Another story reports on research using a blood pressure medication to reduce the withdrawal symptoms of cocaine addiction. An update on the activities of NIDA's Clinical Trials Network is the focus of another story, and two related stories detail the first groups of research protocols underway in the network and the activities of special interest groups.

Another article announces the appointment of Dr. Glen Hanson as NIDA Acting Director, following the departure of Dr. Alan I. Leshner. The Tearoff highlights the results of the annual Monitoring the Future study, which surveys alcohol, tobacco, and drug use among 8th-, 10th-, and 12th-graders in more than 400 schools across the country.

The annual index of topics, publications, events, and people is included in this issue of NIDA NOTES.

NIDA Science and Practice Perspectives, Vol. 1
The National Institute on Drug Abuse has developed a new publication directed towards a combined specialized audience of drug abuse researchers and practitioners. This bi-annual publication aims to enhance the practical use of research and the rapid adaptation of research-based practices in drug abuse treatment. The first issue of this publication will be available in May 2002.

Principles of HIV Prevention in Drug-Using Populations: A Research-Based Guide In March 2002, NIDA released a research-based guide on the principles of HIV prevention in drug-using populations. The *Guide*, prepared by staff in NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse and Office of Science Policy and Communications, contains information reflecting more than 15 years of NIDA-sponsored research on the co-occurring epidemics of drug abuse and HIV/AIDS. This research has yielded a set of scientifically-based principles that should prove useful to community planners, policymakers, service providers, and medical practitioners as they develop and implement programs to prevent the spread of HIV and other infections among injecting and non-injecting drug users and their sexual partners. The Guide summarizes the basic overarching principles that characterize effective HIV/AIDS prevention in drug-using populations; provides answers to frequently asked questions; and describes the epidemiology of HIV/AIDS risk behaviors. It also provides an overview of major research programs that NIDA has supported since the mid-1980s to gauge the effectiveness of outreach-based interventions in preventing the spread of HIV/AIDS and other diseases among drug users and their sex partners. Although research has shown clearly that HIV/AIDS can be prevented in drug-using populations, the epidemic continues to spread. This Guide, as an important contribution to the ever-expanding prevention toolbox, helps to ensure that research-based findings on HIV/AIDS prevention are adapted for use within diverse drug-using groups and their communities. NIDA. *Principles of HIV Prevention in Drug-Using Populations: A Research-Based Guide.* NIH Publication No. 02-4733, March 2002.

The Challenging Interactions Between Antiretroviral Agents and Addiction Drugs: Khalsa et al. of CAMCODA, NIDA note that while advances in antiretroviral treatment have provided significant benefit for persons infected with HIV, the population of drug users continues to have limited access to and poor utilization of available therapies. They also point out that it is important to further define the drug interactions of significance to the treatment of the substance abuser with HIV disease. Khalsa, J.H., Genser, S., Vocci, F., Francis, H.F., and Bean, P. HIV Forum, Am. Clin. Lab, 21(3), pp. 10-13, 2002.

Eight editions of the CTN Bulletin Board were distributed this period. The Bulletin Board is an electronic report on the activities of the various protocol teams and subcommittees of the CTN. The Fall/Winter 2001 edition of the CTN Report, a quarterly newsletter on the CTN, was distributed in January 2002. A poster on good clinical practice strategies entitled "Be on Target with Your Protocols!" was approved and will be distributed to all clinical trial sites within the CTN.

Other Publications

Crombag, H.S., and Shaham, Y. Renewal of Drug Seeking by Contextual Cues after Prolonged Extinction in Rats. Behav Neurosci., 116(1), pp. 169-173, February 2002.

Shalev, U., Grimm, J.W., and Shaham, Y. Neurobiology of Relapse to Heroin and Cocaine Seeking: A Review. Pharmacol Rev. 54(1), pp. 1-42, March 2002.

De Vries, T.J., Shaham, Y., Homberg, J.R., Crombag, H., Schuurman, K., Dieben, J., Vanderschuren, L.J., and Schoffelmeer, A.N. A Cannabinoid Mechanism in Relapse to Cocaine Seeking. Nat Med., 7(10), pp. 1151-1154, October 2001.

Borlongan, C.V., Su,T.P., and Wang, Y. Delta Opioid Peptide Augments Functional Effects and Intrastriatal Graft Survival of the Fetal Rat Ventral Mesencephalic Cells. Cell Transplantation, 10, pp. 53-58, 2001.

Borlongan, C.V., Zhou, F.C., Hayashi,T., Su, T.P., Hoffer, B.J., and Wang,Y. Involvement of GDNF in Neuronal Protection against 6-OHDA-induced Parkinsonism Following Intracerebral Transplantation of Fetal Kidney Tissues in Adult Rats. Neurobiol. Dis., 8, pp. 636-646, 2001.

Chiang,Y.H., Morales, M., Zhou, F.C., Borlongan, C.V., Hoffer, B.J., and Wang, Y. Fetal Intranigral Ventral Mesencephalon and Kidney Tissue Bridge Transplantation Restores the Nigrostriatal Dopamine Pathway in Hemiparkinsonian Rats. Brain Res., 889, pp. 200-207, 2001.

Deng, X., Wang,Y., Chou, J., and Cadet, J.L. Methamphetamine Causes Widespread Apoptosis in the Mouse Brain: Evidence from Using an Improved TUNEL Histochemical Method. Mol. Brain. Res., 93, pp. 64-69, 2001.

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Wang, J.Y., Wu, J.N., Cherng, T.L., Hoffer, B.J., Chen, H.H., Borlongan, C.V., and Wang, Y. Vitamin D3 Attenuates 6-hydroxydopamine-induced Neurotoxicity in Rats. Brain Res., 904, pp. 67-75, 2001.

Wang,Y., Chang, C.F., Morales, M., Chou, J., Chen, H.L., Chiang, Y.H., Lin, S.Z., Cadet, J., Deng, X., Wang, J.Y., Chen, S.Y., Kaplan, P.L., and Hoffer, B.J. Bone Morphorgenetic Protein-6 Reduces Ischemia-induced Brain Damage in Rats. Stroke, 32, pp. 2170-2178, 2001.

Wang, Y., Hayashi, T., Chang, C.F., Chiang, Y.H., Tsao, L.I., Su, T.P., Borlongan, C.V., and Lin, S.Z. Methamphetamine Potentiates Ischemia/Reperfusion Insults after Transient Middle Cerebral Artery Ligation in Mice. Stroke, 32, pp. 775-782, 2001.

Wu, W.C., Wang, Y., Su, C.K., and Chai, C.Y. The nNOS/cGMP Signal Transducing System is Involved in the Cardiovascular Responses Induced by Activation of NMDA Receptors in the Rostral Ventrolateral Medulla of Cats. Neurosci. Lett., 310, pp. 121-124, 2001.

Heishman, S. J. Tobacco - The Once and Future Addiction. Addiction, 96, pp. 1389-1390, 2001.

Singleton, E.G., Trotman, A.J.-M., Zavahir, M., Taylor, R.C., and Heishman, S.J. Determination of the Reliability and Validity of the Marijuana Craving Questionnaire Using Imagery Scripts. Experimental and Clinical Psychopharmacology, 10, pp. 47-53, 2002.

Conway, K.P., Swendsen, J.D., Rounsaville, B.R., and Merikangas, K.R. Personality, Drug of Choice, and Psychiatric Comorbidity among Substance Abusers. Drug and Alcohol Dependence, 65, pp. 225-234, 2002.

Conway, K.P., and McCord, J. A Longitudinal Examination of the Relation between Co-offending with Violent Accomplices and Violent Crime. Aggressive Behavior, 28, pp. 97-108, 2002.

McCord, J. and Conway, KP. Patterns of Juvenile Delinquency and Co-offending. In Waring, E. & Weisburd, D. (Eds.), Crime & Social Organization: Advances in Criminological Theory, Vol. 10 (pp. 15-30). Transaction: New Brunswick, 2002.

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Staff Highlights

Staff Honors and Awards

Dr. Ahmed Elkashef, Chief, Clinical Medical Branch, DTR&D, has received the **Physician Researcher of the Year Award** from the U.S. Public Health Service Commissioned Corps. The award recognizes his significant accomplishments in clinical trials research and administration. In a little more than two years since joining NIDA, Dr. Elkashef has fashioned both clinical pharmacology sites and a clinical trials group in the continental U.S. and Hawaii capable of performing studies of potential pharmacotherapies for the treatment of methamphetamine dependence. Dr. Elkashef has also provided substantial technical assistance to the Kingdom of Thailand in furtherance of their efforts to deal with a burgeoning epidemic of methamphetamine abuse and addiction.

On April 16, 2002, the following **staff of OPRM's Grants Management Branch** were honored by NIH at an Awards Ceremony held at the Natcher Building:

Deborah Wertz - Special Recognition Award - for her work on the development of an NIH Grants Management Training Seminar and for her other significant contributions to the work of the Grants Management Advisory Committee's (GMAC) Subcommittee on Training.

Daisey Parker - Letter of Appreciation - for her significant contributions in promoting the grants management profession as an active member of the Grants Management Professional Advocacy Committee.

Diana Haikalis - Letter of Appreciation - for her significant contributions in promoting the grants management profession as an active member of the Grants Management Professional Advocacy Committee.

Diana Haikalis - Letter of Appreciation - for significant contributions to the NIH Grants Guidance Subcommittee's activities.

Debra Battle-Dudley - Letter of Appreciation - for significant contributions to the IMPAC 2 Grants Management Lead Users Committee's activities.

Staff Changes

Charlotte Annan joined the Special Populations Office as a Secretary in April 2002. Prior to this position she served as Secretary to the Clinical Trials Network and to Dr. Frank Vocci, Division Director, DTR&D.

William Corrigall, Ph.D. joined the Division of Neuroscience and Behavioral Research (DNBR) as Chief of the Translational Research Branch on May 6, 2002. Dr. Corrigall will also serve as the Director, Nicotine and Tobacco Addiction Program for NIDA. Before coming to NIDA, Dr. Corrigall was the Director of Smoking and Nicotine Dependence Research at the Centre for Addiction and Mental Health at the University of Toronto, Canada, and has been a long-time NIDA-funded researcher. Dr. Corrigall obtained his Doctorate in Biophysics from the University of Western Ontario and did a Fellowship in Neuroscience at Albert Einstein College of Medicine. Since joining the Addiction Research Foundation at the University of Toronto (now the Centre for Addiction and Mental Health) he has also served, among other positions, as Head of the Behavioural Pharmacology Section, Chief, Preclinical Treatment Research Unit, and Director of the Biobehavioural Research Department.

Dave Daubert joined OPRM's Management Analysis and Services Branch (MASB) as the Deputy in March 2002. Before coming to NIDA, Mr. Daubert was a Budget Analyst with the Division of Intramural Research of the National Institute of Mental Health (NIMH), and has also held other administrative positions at NIMH. Dave has a degree in Management Technology from Montgomery College. As the Deputy of the MASB, he will assist the Chief in carrying out the many administrative functions of the Branch.

Ron A. Dobbins joined the CCTN as a program analyst in February 2002. Ron earned his Bachelor's Degree from Southern Illinois University in Health Care Management and is actively enrolled in the M.B.A. program at Mount Saint Mary's College. Prior to his arrival at the CCTN, he served as a Quality Assurance Representative and Maintenance Manager within the Clinical Engineering Division of Walter Reed Army Medical Center.

Susan E. Martin, Ph.D. joined NIDA's Division of Epidemiology, Prevention and Services Research as a health scientist administrator in February 2002. Previously she was a program director in the National Institute on Alcohol Abuse and Alcoholism (NIAAA) where she managed that Institute's research programs on prevention of alcohol-related violence, unintentional injury and public policy; prevention of worksite alcohol-related problems; and alcohol and advertising. Prior to coming to NIH, she was a Study Director at the Police Foundation in Washington, DC and Director of the Committee on Law Enforcement and the Administration of Justice at the National Research Council. She holds a B.A. from Swarthmore College and Ph.D. in Sociology from American University. At NIDA she will manage the evaluation contract for the White House Office of National Drug Control Policy's National Youth Anti-Drug Media Campaign and grants focused on persuasive communications.

Dawn Rabunsky came to NIDA's Contract Management Branch as a Contract Specialist in February 2002. Prior to this time, she was a Contract Specialist in the Office of Research Services in the Office of the Director, NIH. At NIDA, as a senior contracting official, Dawn will handle a wide range of contracts and serve as a resource person for junior contracting staff.

Carol Cowell retired from her position in the Services Research Branch, DESPR, after more than 30 years of dedicated government service.

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Director's Report to the National Advisory Council on Drug Abuse
May, 2002

Grantee Honors

Dr. Regina M. Carelli, University of North Carolina, has received the Presidential Early Career Award for Scientists and Engineers (PECASE). This is the highest honor bestowed by the United States Government on outstanding scientists and engineers at the outset of their independent research careers.

Dr. Allan C. Collins, of the University of Colorado, has been selected to receive the Society for Research on Nicotine and Tobacco's 2003 Langley Award for "excellence in a research career devoted to the study of nicotine addiction." This is only the second time that the Society has awarded the Langley (J-P Chaneux was the first). Dr. Collins will give the Langley Award lecture in New Orleans, LA in February 2003.

Dr. Renee M. Cunningham-Williams, Washington University School of Medicine, was recognized by the Institute for Research on Pathological Gambling and Related Disorders for presenting the "Best Poster" at the 2001 annual conference held in Las Vegas, Nevada. Along with her co-authors, Linda B. Cottler and Samantha J. Books, Dr. Cunningham-Williams presented her work on the development of a diagnostic module for assessing problem gambling.

Dr. Thomas Dishion of the University of Oregon, received the 2002 Society for Research on Adolescence Social Policy Award for the journal article Dishion, T., McCord, J. & Poulin, F. When Interventions Harm: Peer Groups and Problem Behavior. American Psychologist, 54, pp. 755-764, 1999.

Dr. Brian Flay of the University of Illinois at Chicago, received the American Academy of Health Behavior 2002 Research Laureate Award.

Dr. Joanna S. Fowler of the Brookhaven National Laboratory was awarded the Glenn T. Seaborg Award for Nuclear Chemistry from the American Chemical Society. Dr. Fowler was honored for her work in the synthesis of organic compounds labeled with radioactive isotopes and their use in radiotracer research. Her work was recognized for its significant impact in chemistry, biology, and medicine. Among her many accomplishments were measurement of the pharmacokinetics of cocaine in the human brain; demonstrating that the binding site for cocaine in humans is the basal ganglia; and studies of the role of MAO B in smoking. Dr. Fowler is a member of the NIDA Board of Scientific Counselors and a member of the Board of Directors for the Society for Nuclear Imaging in Drug Research.

Dr. Victor J. Hruby, Regents Professor and professor of chemistry and biochemistry at the University of Arizona, was awarded the Ralph F. Hirschmann Award in Peptide Chemistry, sponsored by Merck Research Laboratories. Dr. Hruby was recognized for his use of nuclear magnetic resonance and other physical methods for performing conformational analysis of peptide hormones and analogs and neurotransmitters. Dr. Hruby has utilized these methods to design analogs of enkephelin with delta opioid receptor specificity.

Dr. Andrei Kozlov, Director of the St. Petersburg Biomedical Center and head of the Russian HIV Vaccine Program, was awarded, together with Librarian of Congress James Billington (a Russian scholar) and U.S. Senator Ted Stevens, Rotary International's highest award, the Paul Harris Fellowship. The award was presented to Dr. Kozlov, in recognition of his major contributions in AIDS research which have benefited the international community, at the Rotary International conference, "Cold War Healing: Health Assistance for Russia," Washington, D.C. Feb. 7 through 9, 2002. Dr. Kozlov was also honored recently by a visit from Russian First Lady Ludmilla Putin on April 16, 2002. An express purpose of Mrs. Putin's visit was to learn more about the research which NIDA is funding Dr. Kozlov to do on drug abuse and AIDS.

Dr. Jonathan Sweedler of the University of Illinois, Urbana-Champaign, received the 2002 Heinrich-Emanuel-Merck-Prize for Analytical Chemistry. The award is intended for chemists up to the age of 45, working in particular on developing new methods of chemical analysis and their applications in areas of human interest.

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