RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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Court-Mandated Treatment Works as Well as Voluntary

Regardless of their impetus for participating in drug treatment—internal drive or external pressure—men had similar outcomes in the long term.

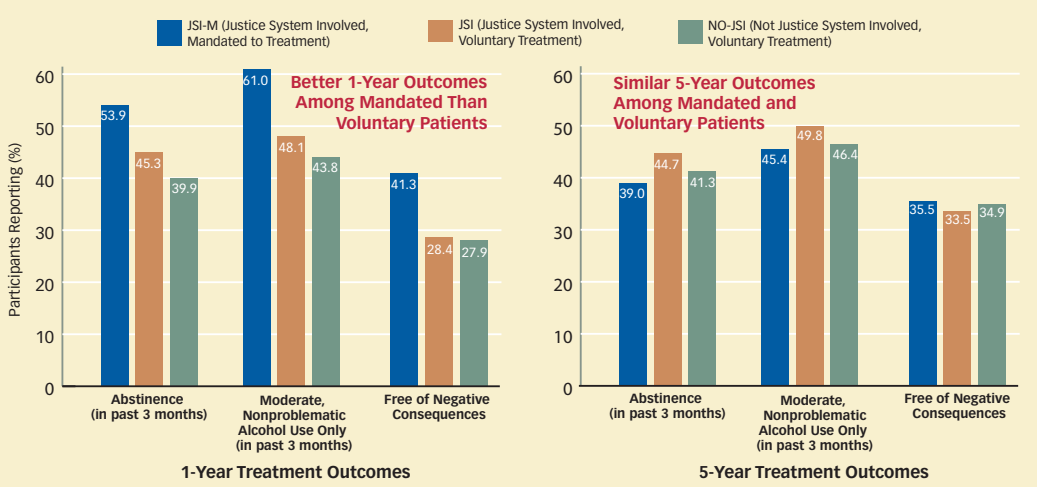
BY LORI WHITTEN,
NIDA Notes Staff Writer

A group of men who completed court-ordered treatment for alcohol and drug problems reported lower intrinsic motivation at the beginning of treatment, but, 5 years later, reported the same rates of abstinence, employment, and rearrest as peers who sought help on their own. The findings from a NIDA- and Department of Veterans Affairs (VA) Health Services Research and Development Service-supported analysis of data on treatment outcomes affirm the results of shorter term studies that have shown similar therapeutic outcomes for voluntary and legally mandated patients. The new study also included an important, but largely unstudied, comparison group: people who had been in court, but were not mandated to enter treatment.

"Once in a therapeutic environment, mandated patients seem to reflect on their situation and accept the need for treatment," says Dr. John Kelly, lead investigator of the study, conducted at the VA Palo Alto Healthcare System and Stanford University School of Medicine. "Our findings suggest that people can learn from the 'teachable moment' offered by a judicial mandate, even though the initial motivation for treatment is external. Judicial mandates may provide an opportunity for offenders to gain access to and benefit from needed treatment."

[*Continued on page 6*]

MANDATED TREATMENT WORKS Patients legally mandated to treatment reported better outcomes than nonmandated offenders and nonoffenders 1 year after residential treatment for alcohol and drug problems. Five-year outcomes were similar among the three groups.



ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*

Challenges in HIV/AIDS Research

The HIV/AIDS epidemic has always been a moving target for health and prevention planners, with infection rates rising in some population groups as they level off or fall in others. Recently, the disease has spread most rapidly among women, minorities, lower income groups, and young men who have sex with men (MSM). Of particular concern to NIDA are the heavy burden of HIV among African-Americans and the growing importance of heterosexual activity associated with drug use as a source of viral transmission. To elucidate the current dynamics, NIDA has developed two new initiatives: Health Disparities in HIV/AIDS: Focus on African Americans (PA-06-069) and Non-injection Drug Abuse and HIV/AIDS (PAS-06-054).

AFRICAN-AMERICANS: HIGHER PREVALENCE, WORSE PROGNOSIS

People from all racial and cultural backgrounds contract HIV/AIDS, but in the United States, African-Americans carry a disproportionate burden of the disease. Although they make up only 12 percent of the U.S. population, African-Americans accounted for half of the new AIDS cases diagnosed in 2003. Of persons diagnosed with AIDS since 1995, a smaller percentage of African-Americans (60 percent) than Whites (70 percent) were alive 9 years after diagnosis. NIDA-supported investigators have identified some contributing factors:

- A higher likelihood that a particular episode of sexual activity or injection drug abuse will result in HIV transmission among African-Americans than other ethnic groups: The elevated prevalence of HIV in the African-American community raises the chances that a sexual or needle-sharing partner will have the virus.
- Lack of awareness of HIV status: African-Americans account for more than half of those receiving an AIDS diagnosis within 1 year of testing positive for HIV, an indication that the infection went undiagnosed for a long time. A related finding suggests that as many as 90 percent of African-American HIV-positive MSM do not know they are infected.

NIDA's African-American initiative will support research to further illuminate the causes of the HIV disparities affecting African-Americans, as well as research on:

- Access to HIV treatment and services available to drug-abusing African-Americans;
- Connections between HIV/AIDS and criminal justice involvement;
- Mental health issues that influence HIV high-risk behaviors; and
- Sociocultural factors that enhance, sustain, or perpetuate health disparities.

NONINJECTION DRUG USE AND HIV/AIDS

Since the early years of the epidemic, NIDA-supported research contributed to a decline in the proportion of HIV/AIDS cases attributable to injection drug use. Now, NIDA is also focusing attention on ways that noninjection drug use—more prevalent by far—may contribute to new HIV infections. We know that drug abuse affects judgment and may lead to high-risk sexual encounters that increase transmission rates. There also is evidence that, regardless of the route of exposure, drugs have immunological effects that may increase the risk of HIV transmission and disease sequelae. To further advance scientific understanding of the relationships, we support studies that help explain how, where, why, and among whom HIV/AIDS is spreading through noninjection drug use and associated high-risk sexual behavior; and studies that develop effective prevention and treatment interventions. ■

NIDA Notes

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"Light" Cigarettes Deliver Heavy Carcinogen Load

New research confirms that smokers who switch to low-tar and low-nicotine brands of cigarettes modify the way they smoke to compensate for the lower nicotine yield, thereby exposing themselves to the same levels of carcinogens they incur smoking higher yield brands. In a comprehensive assessment of biomarkers for tobacco smoke exposure, Dr. Neal Benowitz and colleagues measured carbon monoxide as well as tobacco alkaloids and chemicals representative of two classes of known carcinogens (tobacco-specific nitrosamines and PAHs). This work significantly extends earlier research, which evaluated only levels of carbon monoxide, nicotine, or cotinine. The investigators found that the compensations smokers make to obtain desired nicotine concentrations in their blood, such as smoking more cigarettes per day, or taking deeper puffs, result in no significant reduction in measured carcinogens. Thus, the researchers say, there is no evidence that reduced-yield tobacco should lead to any reduction in the health risks of smoking.

> Cancer Epidemiology, Biomarkers, and Prevention 14(6):1376-1383, 2005.

African-Americans Metabolize Nicotine Slowly

African-Americans who smoke consume fewer cigarettes than their White counterparts. A new study suggests a biological basis for this difference: reduced activity of a liver enzyme cytochrome P450, (2A6) that metabolizes nicotine. As a result, active nicotine metabolites continue to circulate in the blood longer, delaying the smoker's feeling that he or she needs another "hit" on the cigarette.

Dr. Eric Moolchan and colleagues at the NIDA Intramural Research Program measured the byproducts of nicotine breakdown in 92 adolescent smokers (69 percent female, 31 percent African-American, average age 15). The African-Americans consumed fewer cigarettes per day than Whites (15 versus 20). They had higher blood levels of the nicotine byproduct cotinine for each cigarette consumed and lower levels of the cotinine breakdown product *trans*-3'-hydroxycotinine (3HC). After breaking nicotine down to form cotinine, their bodies evidently took longer with the next step in nicotine metabolism, which is the breakdown of cotinine.

> Ethnicity and Disease 16(1):239-243, 2006.

The Brain in Pain

The blood-brain barrier (BBB) is a thin layer of tightly packed cells that line the brain's blood vessels, shielding the organ from harmful chemical intruders while ushering in needed substances such as glucose, the molecular fuel used by all cells. A new study has shown that pain with inflammation alters the proteins that seal the BBB cells together, "loosening" the barrier so that circulating chemicals—including toxins and medications—may more readily enter the brain.

Dr. Tracy Brooks—a postdoctoral fellow in the laboratory of Dr. Thomas P. Davis, professor of medical pharmacology at the University of Arizona—and colleagues demonstrated that rats with swelling and pain in their hindpaws had a 60 percent reduction in the level of key protein components of the BBB, called occludins. These proteins also shifted location, moving from an even distribution along the membrane into a spotty pattern. In contrast, levels of two other key proteins, claudin-3 and claudin-5, dramatically increased. A rise in the level of claudin-3 increases BBB permeability, and the proliferation of claudin-5 is thought to be a compensatory response to "tighten" the barrier. "Our results demonstrate the complexity of the protein makeup of the BBB and that an intricate balance of protein levels and interactions is critical for maintaining the barrier's integrity," says Dr. Brooks.

> American Journal of Physiology–Heart and Circulatory Physiology 289(2):H738-H743, 2005.

Parents' Actions, More Than Their Words, Influence Kids' Smoking

Researchers looking for family influences on children's smoking have found that actions speak louder than words. As part of a large long-term study of factors that may increase or lower the risk of drug abuse, Dr. Karl Hill and colleagues at the University of Washington surveyed 808 children and their parents annually from age 10 to age 21. Of those who became daily smokers by age 21, the strongest predictive characteristic was having a parent who smoked at the time of the original interview, regardless of the parent's expressed attitude about smoking. The most protective parental characteristics were nonsmoking, clear family rules and monitoring, and strong family bonding.

> Journal of Adolescent Health 37(3):202-210, 2005.

NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse

Medications Development Division Nurtures the Creation of New Addiction Treatments

BY LORI WHITTEN,
NIDA Notes Staff Writer

In the Anti-Drug Abuse Act of 1988, Congress mandated NIDA to promote the development of medications "to treat the symptoms and disease of drug abuse." Research by NIDA-supported scientists and others had by then made clear that drug abuse is a neurological disorder treatable by pharmacotherapy, but only three anti-addiction medications were available (disulfiram, methadone, and naltrexone), all developed in the 1960s and early 1970s. Congress recognized the need for Federal leadership and, because of NIDA's resources and expertise, entrusted the Institute with facilitating the development of pharmacotherapies to treat addiction.

With an initial appropriation of $8 million, NIDA launched a Medications Development Program that same year and formally established the Medications Development Division in 1990. From its beginning, the Division has supported and coordinated academic and private sector scientists engaged in every stage of medications development—from the creation of new compounds in the laboratory to the testing of products in clinical trials. The Division's efforts have been instrumental in bringing buprenorphine and buprenorphine-naloxone—safe and effective treatments for opiate addiction, the latter suitable for office-based therapy—to the Nation's clinics and pharmacy shelves. Among other current priorities, the Division supports work to establish the safety and efficacy of the smoking-cessation aids nicotine replacement and bupropion for people with psychiatric conditions, pregnant women, and adolescents.

Under the leadership of Division Director Dr. Frank Vocci, Dr. Nora Chiang, Chief of the Chemistry and Pharmaceutics Branch, manages laboratory research grants designed to develop new compounds with therapeutic potential; Dr. Jane Acri, Director of the Addiction Treatment Discovery Program, leads a multidisciplinary team that screens compounds and advances those with therapeutic potential into testing for safety and efficacy; and Dr. Ahmed Elkashef, Chief of the Clinical/Medical Branch, coordinates the evaluation of data from clinical trials.

The Division pursues a dual strategy that balances the need to advance scientific discovery and the need to find safe and effective treatments as rapidly as possible. On one track, NIDA intramural and funded scientists seek new medications. Researchers in the Cocaine Treatment Discovery Program have identified and evaluated more than 3,000 compounds whose molecular characteristics or performance in animal studies suggested they might reduce cocaine craving and prevent relapse. This process has, for example, identified a new compound called JDTic, which has anti-stress and antidepressant characteristics and prevents relapse in ani-

DUAL STRATEGY GUIDES NIDA's DRUG ABUSE MEDICATION DEVELOPMENT

Test Existing Medications
Researchers evaluate marketed medications whose chemical properties suggest they might reduce drug abuse.

Characteristics	Examples
Medications are already approved for marketing for other conditions.	Methadone and buprenorphine, widely used for opiate addiction treatment, were first used as analgesics.
Known safety profile.	Bupropion, prescribed for nicotine addiction, was first used for depression.
Less expensive to develop than new compounds.	Currently being evaluated for cocaine abuse: modafinil (narcolepsy), topiramate (seizures), disulfiram (alcohol dependence), bupropion.
Short time to gain approval for marketing.	Currently being evaluated for cocaine and methamphetamine abuse: selegiline (Parkinson's disease), baclofen (muscle spasms), ondansetron (prevents chemotherapy-related nausea).

Develop New Medications
Researchers investigate the therapeutic potential of new compounds.

Characteristics	Examples
Lengthy process of discovery. Relies on behavioral, biochemical, and neuroimaging experiments with ultimate translation of laboratory findings to clinical studies.	Two compounds (GBR 12909, NS2359) that generate modest and long-lasting increases in dopamine have reached human safety evaluation. NIDA stopped testing of GBR 12909 because of cardiovascular concerns, but continues to evaluate NS2359.
Takes advantage of breakthrough discoveries in neuroscience. Potential for discovering medications that affect multiple addictions.	A compound (CP-154,526) that blocks the neurochemical corticotropin-releasing factor 1 attenuates stress-induced relapse to cocaine and heroin in animals.

mals, and is developing the agent for potential clinical testing. Under the second approach, NIDA has established a network of clinical investigators to screen marketed medications with neurochemical effects that suggest a potential for reducing drug abuse (see chart, page 4). Among 65 medications examined so far, eight potential treatments for cocaine abuse—including topiramate, disulfiram, and modafinil—have advanced to the confirmatory stage of clinical trials in cocaine-dependent patients.

Throughout the 1990s, as well, the Division advanced research on vaccines that prevent drugs from reaching the brain. A vaccine to prevent cocaine addiction and another for nicotine abuse are now being tested for safety and efficacy.

Because medication development is an enormously complex and costly enterprise, the Division collaborates with other Government agencies, particularly the U.S. Food and Drug Administration (FDA), and the pharmaceutical industry. The relationship with FDA has been vital to overcoming scientific and regulatory barriers to evaluating new medications for opiate addiction and shepherding buprenorphine through the necessary approvals. The Division's relationships with industry frequently have been formalized as Cooperative Research and Development Agreements (CRADAs). In this type of arrangement, NIDA provides expertise, equipment, and facilities to test a corporate-owned compound as a potential pharmacotherapy; if the results are as hoped and a marketable medication results, the company maintains the commercial rights and NIDA retains a license to perform further research. Under a current CRADA, NIDA is working with Teva (formerly IVAX Corporation) to determine whether talampanel, a compound in clinical testing for treatment of epilepsy, may help cocaine abusers overcome their addiction.

Dr. Vocci says, "Our first 15 years have taught us the importance of developing treatments that patients will accept and readily use, and that medications are most effective in combination with psychotherapy or counseling. We now apply these lessons to all efforts." Looking ahead, Dr. Vocci lists Division goals for the next 5 years:

- Validate the effectiveness of promising medications for cocaine addiction;
- Advance compounds that have shown promise in animal research to clinical testing in people who are addicted to methamphetamine and marijuana;
- Advance a new smoking cessation aid into clinical trials (possibly selegiline, which has shown promise in preliminary studies);
- Determine optimal immunization schedules for nicotine and cocaine vaccines and obtain FDA approval;
- Identify medications to curb cognitive problems that limit patients' ability to benefit from behavioral therapies;
- Continue preliminary clinical studies of interactions between HIV infection, antiviral therapies, and anti-addiction pharmacotherapies and identify interventions that slow the progress of the infection in drug abusers; and
- Collaborate with other branches of NIH and industry partners to test a vaccine for hepatitis C among drug-abusing populations.

"Bringing a new medication to market is a lengthy and expensive endeavor, but physicians and patients need a choice of many treatment options. The progress in anti-addiction pharmacotherapies shows the strength of the dual strategy of medications development, which will continue to provide us with the best hope for novel approaches to treating addiction," says Dr. Vocci. ■

MANDATED TREATMENT

[*Continued from page 1*]

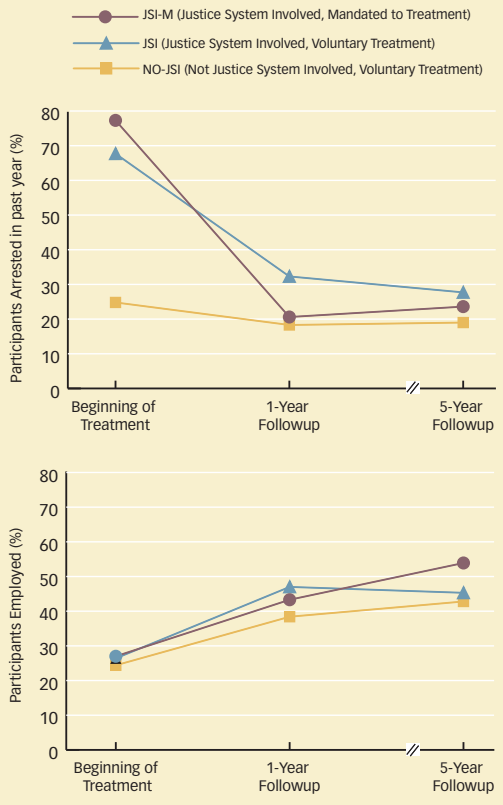
Drs. Kelly, Rudolf Moos, and John Finney analyzed data, gathered by Drs. Moos and Finney and Dr. Paige Ouimette, on 2,095 men who were treated for alcohol and drug problems in 15 VA programs and followed for 5 years. About half the men (54 percent) were addicted to drugs; 80 percent were dependent on alcohol. Most (82 percent) had no criminal justice system involvement and entered treatment voluntarily (No-JSI); 7 percent were on probation or parole and were required to participate in treatment by order of a court or criminal justice official (JSI-M); 11 percent had been before a court, but not mandated to treatment (JSI). About half (49 percent) of the participants were African-American; 45 percent were White; and the remaining 6 percent were Hispanic, Native American, or Asian. Most (74 percent) were unemployed when they started treatment.

The men completed 21 or 28 days of residential treatment, which took one of three therapeutic approaches: group psychotherapy and individual activities based on the 12-step approach, cognitive-behavioral therapy, or a mix of both. When they completed treatment, the men were urged to participate in outpatient programs and self-help activities.

At the beginning of treatment, each man completed a questionnaire that assessed characteristics considered important to recovery: motivation, self-efficacy, coping skills, 12-step participation, psychiatric symptoms, history of negative consequences of alcohol and drug problems, number of previous treatment episodes, and whether they considered themselves to be addicted. They also reported any prior year arrests and any judicial mandate for treatment. At the end of the treatment program, participants repeated the assessment and reported their perceptions of the therapeutic experience. Most also received a self-administered assessment in the mail at the 1- and 5-year followup points, with the rest contacted by telephone or in person. Research assistants telephoned patients when necessary to complete or clarify information.

In the initial assessment, men in the JSI-M group reported experiencing fewer negative consequences of alcohol and drug consumption, fewer symptoms of depression and anxiety, and less desire to abstain than No-JSI or JSI participants. Fewer mandated (45 percent) than voluntary patients (58 percent) met the standard clinical criteria for drug addiction. Voluntary patients more frequently recognized their addictions, connected them to other problems, and reported a readiness to change.

ARREST RATE FALLS, EMPLOYMENT RATE RISES AFTER TREATMENT At the 1-year and 5-year followup, mandated patients showed arrest rates similar to those of nonmandated offenders and nonoffenders. Patients in all three groups demonstrated improved employment rates at followups.



REARREST RATES FALL, REMAIN LOW

At the end of treatment, all three groups of patients demonstrated enhanced coping skills and expressed more confidence that they could resist alcohol or drugs in high-risk situations. Symptoms of psychological distress improved for participants in all groups. At the 1-year followup, larger proportions of JSI-M participants reported abstinence, successful moderation in their use of alcohol, and freedom from drug-related consequences (for example, missing work or fighting with a family member because of drugs) than JSI and No-JSI participants (see chart, page 1). Arrest rates for the two JSI groups fell dramatically after treatment. Mandated patients showed arrest rates similar to those of their No-JSI peers (about 20 percent) and lower than those of their JSI peers (32 percent) at the 1-year followup. Five years after treatment, most outcomes among the three groups did not differ (see chart).

The investigators believe that, in addition to the other positive effects of treatment, mandated patients may acquire motivation to change. "The high level of camaraderie in VA residential treatment, where these individuals interacted with self-motivated peers, may have contributed to a shift in attitude," says Dr. Kelly.

The implications of Dr. Kelly's findings go beyond the criminal justice population, says Dr. Beverly Pringle, formerly of NIDA's Division of Epidemiology, Services and Prevention Research. "The idea that patients must want to change seems to permeate current practice, but the drug abuse treatment field may need to reexamine its definition of motivation," she says. Clinical measures of motivation mostly indicate intrinsic drive to change, but extrinsic motivators as well as rewards can increase treatment entry and improve long-term outcomes. ■

SOURCE

Kelly, J.F.; Finney, J.W.; and Moos, R. Substance use disorder patients who are mandated to treatment: Characteristics, treatment process, and 1- and 5-year outcomes. *Journal of Substance Abuse Treatment* 28(3):213–223, 2005.

Checkup System Catches Relapse Early and Facilitates Return to Treatment

Researchers in Chicago apply an old medical maxim: "Chronic diseases require chronic cures."

BY LORI WHITTEN,
NIDA Notes Staff Writer

Supplementing regular recovery checkups with motivational interviewing and active linking to treatment can get relapsing patients back into treatment sooner and help them stay longer, report NIDA-funded researchers. In the 2 years following treatment, patients who received the additional interventions were three times as likely to reenter treatment as others who received assessments only.

Lead investigator Dr. Christy Scott and coinvestigator Dr. Michael Dennis developed the effective intervention, which they call the Recovery Management Checkup (RMC) system, to expedite the recovery of people who had attended treatment and were now living in the community and experiencing substance abuse problems. They say the findings suggest that their approach to treating substance abuse as a chronic condition may help patients shake off the shame of relapse. "By the time patients had participated in checkups for 2 years, many who were initially reluctant to reenter treatment would call a peer to link them with help after a slip," says Dr. Scott, of Lighthouse Institute in Chicago, a Division of Chestnut Health Systems, Inc.

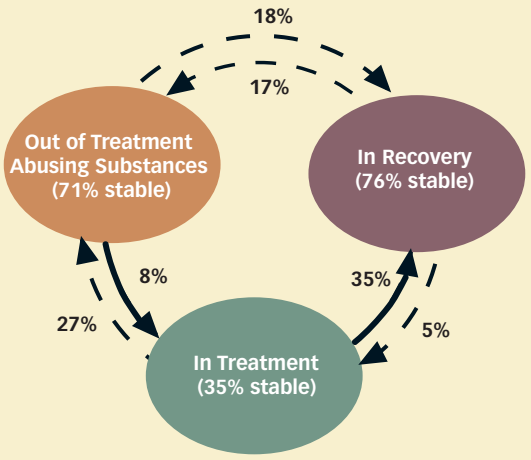
INTERVENTION MATCHES RELAPSE PATTERNS

In developing the RMC system, the researchers built on previous studies in which they had identified patterns of chronic substance abuse, relapse, and recovery. They found that, during the first 3 years after treatment, people frequently transitioned between recovery, substance abuse, and treatment—a cyclic pattern suggesting that periodic checkups, with intervention when necessary, might help shorten relapse episodes. They also researched approaches used to manage other chronic health conditions and found that monitoring for relapse and reducing the time from relapse to treatment reentry improved long-term outcomes.

To implement the RMC system, Drs. Scott and Dennis hired and trained a cadre of research assistants and linkage managers, many of whom were local recovering individuals. Chestnut staff and clinical colleagues at Haymarket Center, the largest addiction treatment provider in Illinois, interviewed 448 men and women who had met the standard criteria for a substance abuse diagnosis at some time in their lives, had abused alcohol or other drugs in the past 90 days, were not in protective custody, and intended to live in Chicago for the next year. Cocaine, alcohol, opiates, and marijuana were the most commonly abused drugs. Immediately following the interview, patients received a referral to Haymarket Center for treatment—60 percent as residents and 40 percent as outpatients—for 27 days, on average; 11 percent remained in treatment for 90 days or more. Upon leaving treatment, each patient scheduled eight quarterly followup appointments. Before the first checkup, researchers randomly assigned the patients to either the RMC intervention or an assessment-only control group.

At each checkup appointment, patients met with a research assistant. The assistant administered a 45-minute version of the Global Appraisal of Individual Needs assessment and ascertained information about the patient's living situation and substance involvement. If the patient had not abused any substance during the past 90 days, the assistant encouraged continued abstinence and scheduled the next appointment. Patients who reported slips were merely advised to reenter therapy if they were in the control group, but met with a linkage manager if they were in the intervention group and living in the community.

FOR MOST PATIENTS RECOVERY IS CYCLICAL, NOT LINEAR The researchers tracked the average percentages of patients moving between points in the recovery cycle—living in the community and abusing substances, in treatment, or in recovery—each quarter during the 2-year study. The goal of the Recovery Management Checkup system is to increase treatment reentry and recovery (movement along the solid arrows).



† "Stable" indicates that patients did not transition from one point to another in the cycle.

Reprinted from *Drug and Alcohol Dependence*, Vol. 78(3): 325-338, Scott, C.K.; Dennis, M.L.; and Foss, M.A.: "Utilizing recovery management checkups to shorten the cycle of relapse, treatment reentry, and recovery," © 2005, with permission from Elsevier.

The linkage manager conducted motivational interviews, usually lasting less than 30 minutes, in which he or she provided feedback on patients' substance abuse and related problems, discussed ways to work through barriers to treatment reentry, and considered motivations to return to therapy. If a patient was willing to reenter treatment (even with low motivation), the linkage manager scheduled an appointment, telephoned with a

[*Continued on page 13*]

Methamphetamine Evokes and Subverts Brain Protective Responses

Two new studies appear to highlight the role of glial cells—the nervous system's equivalents to the body's immune cells—in methamphetamine abuse.

BY PATRICK ZICKLER,
NIDA Notes Contributing Writer

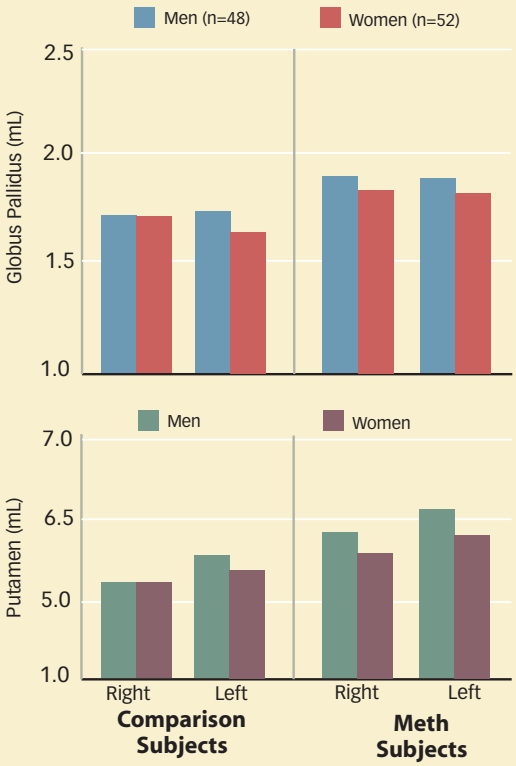
NIDA-supported researchers have produced brain images demonstrating that structures in an area called the striatum expand in volume during early methamphetamine abuse, then regress toward normal. The investigators believe their findings likely are attributable to neuroprotective cells in the brain mounting an initial attempt to counteract the drug's toxic effects, which continued exposure subsequently overwhelms. In a related result, scientists working with mice have produced evidence that methamphetamine may prompt cells that normally serve neuroprotective functions to instead attack healthy brain cells.

STRUCTURAL FLUCTUATION SUGGESTS GLIAL ACTIVATION

Dr. Linda Chang (now at the University of Hawaii) and colleagues at the University of California, Los Angeles, used magnetic resonance imaging to measure the volumes of striatal brain structures, including the putamen and globus pallidus, in a group of methamphetamine abusers. The studied individuals, 26 women and 24 men (average age 31 years), had abused methamphetamine (average 1.6 g/day on 6.3 days/week) for periods ranging from 4 to 15 years. All had been abstinent for periods ranging from 1 week to 4 years at the time of the study; 44 also took tests of verbal memory and intelligence, gross and fine motor function, mood, executive function, and other capacities likely to be affected by striatal damage.

The researchers expected to find that the methamphetamine abusers' striatal regions were smaller than those of a comparison group of age- and gender-matched individuals with no history of methamphetamine abuse. Such a finding would be consistent with previous research showing that methamphetamine reduces the density of striatal dopamine terminals. Instead, says Dr. Chang, "Contrary to our hypothesis, striatal volumes were larger in the methamphetamine abusers as a group." The size difference was greatest among individuals with less cumulative exposure to the drug, and smaller among those with more. Those with the most exposure also performed slightly worse on neuropsychological tests of verbal fluency and visual-motor coordination.

STRUCTURES IN THE BRAIN'S STRIATAL REGION ARE ENLARGED IN METHAMPHETAMINE ABUSERS
Average volumes of the globus pallidus and putamen—structures in the brain's striatal region—are larger in men and women with a history of methamphetamine abuse than in men and women with no exposure to the drug.



Dr. Chang believes the surprising increase in striatal volumes of methamphetamine abusers may reflect the activity of glia—cells that provide protective and reparative functions for the brain's main functional cells, the neurons. When molecules potentially harmful to neurons penetrate the brain, glia mount a response resembling the inflammation and scar tissue formation associated with immune responses in other parts of the body. Possibly, Dr. Chang suggests, methamphetamine provokes glia to react in this way, leading to an increase in regional volume analogous to the swelling seen in bodily immune responses. Subsequently, she speculates, the glial response may taper off as cumulative exposure to the drug—and neuron damage—mount. Continued abuse results in damage that is manifested in decreased cognitive performance.

"This work is consistent with an increasing body of research that shows a relationship between methamphetamine exposure and structural changes in the brain," says Dr. Steven Grant of NIDA's Division of Clinical

Neuroscience and Behavioral Research. "It links methamphetamine abuse, structural change, and functional deficits and suggests that the magnitude of these effects is related to the degree of abuse. We don't understand what is happening at deeper levels, but the observations made in this study suggest that the volume changes are related to methamphetamine's direct or indirect effect on glial cells. We still need to understand how structural changes result in functional deficits; how much, if any, of this damage can be reversed; and how methamphetamine acts at the cellular level."

IN MICE, METHAMPHETAMINE MISDIRECTS GLIA TO ATTACK BRAIN CELLS

A study by Drs. Donald Kuhn and David Thomas and colleagues at Wayne State University School of Medicine indicates that methamphetamine's toxic effects may include subverting some glial cells to attack rather than preserve neurons. Specifically, their results indicate that the drug incites a subset of glia called microglia to mount an immune response against dopamine neurons.

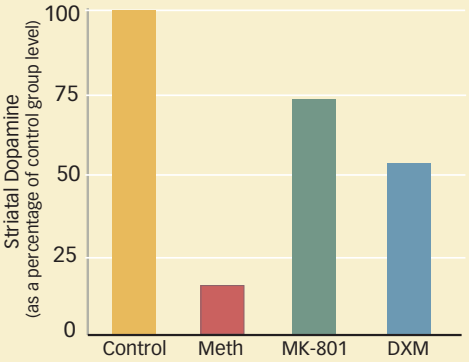
Normally, microglia protect neurons against toxic injury by several mechanisms. They detect and bind to invading molecules, including viruses or bacteria, making them easily accessible to destructive immune system cells such as lymphocytes. As well, they produce compounds, some toxic, to help contain or eliminate the danger. Methamphetamine, the new study suggests, causes dopamine neurons to release a signal that decoys the microglia into turning these normally protective responses against the neurons themselves. When that happens, Dr. Kuhn says, "The microglia aren't reacting to methamphetamine's neural damage. Instead, they are active participants in the drug's neurotoxicity."

To begin their experiments, the researchers reasoned that if microglia contribute to methamphetamine toxicity to dopamine terminals, compounds that protect against such toxicity might do so, at least in part, by inhibiting microglial activation. Their first hypothesis, accordingly, was that the compound MK-801, which is known to be protective, blunts microglial activation. The team showed this to be the case by exposing cell cultures of mouse microglia to two proteins known to precipitate damaging microglial responses: lipopolysaccharide (LPS) and HIV Tat, a derivative of the human immunodeficiency virus. Compared with LPS and HIV Tat exposure without pretreatment, exposure following pretreatment with MK-801 significantly reduced the amount of two protein products of microglial activation, called cyclooxygenase-2 (Cox-2) and tumor necrosis factor-α (TNF-α). Dextromethorphan (DXM), a compound biochemically similar to MK-801, had the same effect.

"These results suggested that both MK-801 and dextromethorphan exert direct action on the microglial cells in culture to block the activation process," Dr. Kuhn says. Having determined that the two compounds block microglial activation *in vitro*, the researchers next hypothesized that they would also do so in living animals.

Drs. Kuhn and Thomas injected mice with either MK-801 or DXM and then methamphetamine (5 mg/kg of body weight) 15 minutes later, repeating this sequence four times at 2-hour intervals. A control group of mice received the same regimen, but with saline substituted for methamphetamine. Forty-eight hours after the last injection, the researchers assayed the brains of the mice for Cox-2 and TNF-α, the indicators of microglia activation, and for striatal dopamine levels, a widely used index of damage to dopamine neurons. Dr. Kuhn says, "We found that both DXM and MK-801 significantly reduced the markers of striatal microglial activation associated with methamphetamine exposure and protected against dopamine nerve terminal damage in the striatum. The close association between the ability of MK-801 and DXM to significantly lower both microglial activation and neuronal damage suggests a causal link between the two. It looks as though the damage associated with methamphetamine abuse is the result of microglial action."

COMPOUNDS THAT BLOCK THE ACTION OF MICROGLIA COUNTER A TOXIC EFFECT OF METHAMPHETAMINE Striatal regions of mice exposed to methamphetamine contain decreased dopamine content, compared with those of unexposed controls. Treatment with MK-801 or dextromethorphan (DXM) prior to methamphetamine injection reduced the extent of depletion, suggesting that microglia play a role in methamphetamine's toxic effect on the brain's dopamine system.



The apparent association of microglia and damage to dopamine neurons has implications beyond what it may reveal about methamphetamine abuse, says Dr. Jerry Frankenheim of NIDA's Division of Basic Neuroscience and Behavioral Research. "Microglia are the primary immune defense cells in the brain. They safeguard neural functions, yet excessive activation can cause microglia to harm neurons. Other research implicates microglial involvement in a wide range of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and stroke. Understanding how methamphetamine is able to decoy microglia into a destructive rather than reparative role could also help explain the processes involved in these other disorders." ■

SOURCES

Chang, L., et al. Enlarged striatum in abstinent methamphetamine abusers: A possible compensatory response. *Biological Psychiatry* 57(9):967–974, 2005.

Thomas, D.M., and Kuhn, D.M. MK-801 and dextromethorphan block microglial activation and protect against methamphetamine-induced neurotoxicity. *Brain Research* 1050(1-2):190–198, 2005.

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*Issue numbers appear in parentheses, followed by page numbers.

Sensory Aspects May Drive Addiction in Obese Smokers

Obesity appears to reduce nicotine's rewarding effect in mice and humans.

BY PATRICK ZICKLER,
NIDA Notes Contributing Writer

For obese smokers, the taste and smell of a lit cigarette may play as powerful a part in addiction as does the nicotine buzz. For these smokers, nicotine replacement therapies that also replace some of the sensory aspects of smoking—lozenges, gum, or nasal spray—may be more effective than a patch, according to researchers at the University of Pennsylvania's Transdisciplinary Tobacco Use Research Center (TTURC).

Lead investigator Dr. Caryn Lerman and TTURC colleagues asked 37 smokers to describe the experiences of smoking two "brands" of cigarettes; although the smokers did not know it, one brand contained nicotine and the other did not. Obese smokers rated the two nearly equal, while nonobese smokers gave higher marks to the conventional cigarettes. When allowed to choose freely, nonobese smokers preferred conventional cigarettes, while obese smokers were equally likely to choose either type.

To validate these observations and investigate their physiological basis, Dr. Julie Blendy and colleagues tested nicotine's rewarding effect in mice. Given access to two chambers, nonobese mice gravitated to the one in which researchers had dosed them with nicotine, whereas mice made obese by a high-fat diet showed no preference. These results suggest that the nicotine provided the nonobese mice, but not the obese mice, with an experience they wanted to repeat. When the researchers examined the brains of the mice, they found that the obese animals, compared with those fed a normal diet, had reduced levels of opioid receptors, which have been implicated in nicotine addiction.

"For obese smokers, sensory cues such as sights and smells and taste may be at least as rewarding as the pharmacological reward of nicotine," says Dr. Lerman. "The mouse experiment suggests a possible biological mechanism for the observation in human smokers. Diet may influence nicotine reward through effects on the opioid system," Dr. Blendy adds.

OBESE SMOKERS DERIVE LESS PLEASURE FROM NICOTINE THAN OTHER SMOKERS
Obese smokers rated regular and nicotine-free cigarettes very similarly.

Item/Scale	Cigarette	Mean	
		Nonobese (n=20)	Obese (n=17)
Satisfaction	Nicotine-Free	2.1	2.9
	Nicotine	3.4	3.0
Psychological relief	Nicotine-Free	1.5	1.2
	Nicotine	1.7	1.4
Liking	Nicotine-Free	2.3	2.8
	Nicotine	3.7	2.9

OBESITY AND HUMAN RESPONSE TO NICOTINE

The research team recruited 17 obese and 20 nonobese men and women who were regular smokers. The obese and nonobese study participants' average body mass indexes were 39.1 (range, 31.0 to 59.4) and 23.0 (range, 18.3 to 26.3), respectively. In the first part of the study, the participants smoked one cigarette from each of two color-coded sets, one that contained nicotine and one that was nicotine-free, without being informed about the difference. Participants rated the two smokes on a scale ranging from 0 (none) to 7 (complete)—for "satisfaction," "liking," and "psychological relief." On average, obese smokers gave the conventional and nicotine-free cigarettes almost identical ratings for satisfaction (3.0 for nicotine versus 2.9 for nicotine-free), liking (2.9 versus 2.8), and psychological relief (1.4 versus 1.2). Nonobese smokers gave the conventional cigarettes higher ratings for satisfaction (3.4 versus 2.1) and liking (3.7 versus 2.3) and showed no significant preference in psychological relief (1.7 versus 1.5).

Next, the smokers were allowed to smoke cigarettes from either color-coded set in four sessions, spaced 30 minutes apart, but limited to four puffs per session. On average, obese smokers took as many puffs on the conventional (48 percent) as the nicotine-free (52 percent) cigarettes. Nonobese smokers took 70 percent of their puffs from the conventional cigarettes.

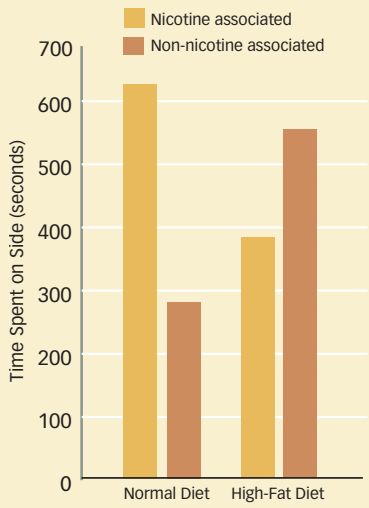
"Tobacco addiction involves an interplay of physiological influences, such as the effects of nicotine or other components of tobacco, with sensory influences associated with taste or aroma, the physical manipulation of cigarettes and lighters, or the sight of smoke," Dr. Lerman says. "It appears that for obese smokers, non-nicotine factors play a considerable part in maintaining addiction and therefore need to be considered in developing a treatment to help obese smokers quit. Obesity and smoking are both serious health risks, and some research suggests they act synergistically to create an even greater risk. If so, helping obese smokers to quit may have a greater impact on public health than an equivalent cessation among nonobese smokers."

OBESE MICE AND NICOTINE

In the animal component of their investigation, the researchers simulated human obesity in mice by feeding them a high-fat diet (45 percent fat, 35 percent carbohydrates, 20 percent protein) for 15 weeks. A control group of mice received a normal laboratory diet (12 percent fat, 60 percent carbohydrates, 28 percent protein). The researchers injected each animal with nicotine while confining it to one compartment of a two-compartment test chamber daily for 8 days. Subsequently, they placed each mouse in the test chamber and allowed it free access to either compartment for 15 minutes. Nonobese mice spent most of this time in the compartment where they received the drug, indicating that the nicotine injections had given them pleasure they would like to repeat. However, obese mice showed no preference for the side associated with the drug.

The investigators next examined the brains of the mice and found evidence that the animals maintained on a high-fat diet had less precursor associated with structures called mu-opioid receptors on cells in the ventral tegmental area (VTA) of the brain. The VTA is where nicotine acts to increase the availability of dopamine, a chemical that causes the pleasurable sensations associated with many drugs of abuse. Other animal research has implicated mu-opioid receptors in neurochemical processes that lead to nicotine addiction, and the finding that fewer of these receptors are activated in the brains of the high-fat-diet mice could in part explain their blunted response to nicotine's rewarding effect.

MICE RAISED ON A HIGH-FAT DIET HAVE DIMINISHED RESPONSE TO NICOTINE Mice fed a normal diet spent most of a 15-minute test period on the side of a cage in which they had been given nicotine, whereas mice fed a high-fat diet showed no such preference.



"In this mouse study, the animals could not control their diet. But humans choose what and when to eat," says Dr. Allison Chausmer of NIDA's Division of Basic Neuroscience and Behavioral Research. "The observations made in these mice suggest a fascinating chain of events leading from a behavior, selecting what to eat, to a measurable biochemical change in the brain and altered response to an addictive drug. They illustrate the complexity of factors that contribute to the powerful addictive grip of tobacco and—conversely—can potentially be manipulated to improve the effectiveness of treatments that help smokers quit." ■

SOURCE

Blendy, J.A., et al. Reduced nicotine reward in obesity: Cross-comparison in human and mouse. *Psychopharmacology* 180(2):306–315, 2005.

■ CHECKUP SYSTEM

[*Continued from page 7*]

reminder, and arranged transportation. The linkage manager provided assistance for 2 weeks, but afterward, responsibility for continuing therapy fell to the patient. Between RMC appointments, the patient received cards and calls from the research office; these served as a reminder of the next visit and carried a message of support from the research team.

CHECKUPS BOOST CHECK-INS

The researchers were able to interview patients at both the beginning and end of a quarter in 87.5 percent of cases. They categorized each patient's current status as in the community abusing substances, in treatment, in recovery (no substance abuse, problems, or treatment while living in the community), or incarcerated. Between the beginning and end of each quarter, about one-third of the patients, on average, transitioned from one status to another. Most (82 percent) transitioned at least once during the study, with 62 percent moving between points several times (see chart, page 7).

Among patients who relapsed, 67 percent of RMC patients reentered treatment within 90 days after the checkup, compared with 51 percent of assessment-only patients. RMC patients returned to treatment sooner (27 versus 45 days) and stayed in treatment longer (7.75 versus 4.68 days), on average, than the control group. Length of treatment predicted transition to recovery at the next quarterly assessment—for every 10.5 days in treatment, a patient was 1.2 times more likely to be abstinent at the next quarterly checkup.

"The checkups help a patient evaluate his or her behavior and recovery-related issues—much as a person with diabetes would report on blood sugar levels and diet and exercise patterns," says Dr. Thomas Hilton of NIDA's Division of Epidemiology, Services and Prevention Research. "By employing individuals in recovery as linkage managers, the program also offered an opportunity for the patient to return to treatment or at least receive support from someone who has been there."

Drs. Scott and Dennis plan to tailor the checkups for specific populations—for example, women involved in the criminal justice system. Treatment providers who want to implement the checkups can contact Dr. Scott (cscott@chestnut.org). ■

SOURCE

Scott, C.K.; Dennis, M.L.; and Foss, M.A. Utilizing recovery management checkups to shorten the cycle of relapse, treatment reentry, and recovery. *Drug and Alcohol Dependence* 78(3):325–338, 2005.

Drugs Affect Men's and Women's Brains Differently

Gender appears to influence biological responses to nicotine, cocaine, and alcohol.

BY CARL SHERMAN,
NIDA Notes Contributing Writer

Two recent NIDA-funded studies cast new light on men's and women's different responses to nicotine, cocaine, and alcohol. Dr. Steven G. Potkin and colleagues at the University of California (UC), Irvine, demonstrated that various brain regions are more strongly activated in women than in men while they perform certain tasks, and that nicotine equalizes the response. Dr. Elinore F. McCance-Katz and colleagues at the Medical College of Virginia found that women registered greater feelings of physical and mental well-being than men after receiving cocaine and had higher heart rates after drinking alcohol.

BRAIN EFFECTS OF NICOTINE

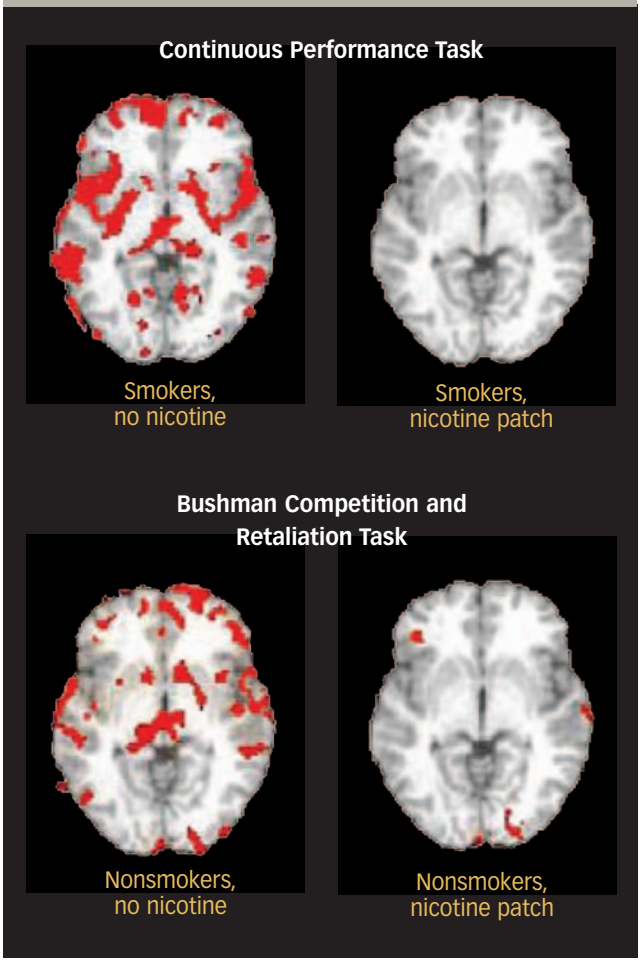
Men and women abuse the same drugs, but not always in the same ways. When women smoke cigarettes, they take shorter and fewer puffs and experience improvements in mood that men do not. Women generally are less successful in quitting. To the UC Irvine study team, these behavioral and experiential differences suggested that nicotine might affect men's and women's brains differently.

Using positron emission tomography (PET), the researchers tracked brain metabolism in 42 women and 77 men (55 smokers and 64 nonsmokers) while they performed two tasks. In the Continuous Performance Task (CPT), a test of vigilance, the study participant watched a series of numbers flashed on a screen and pressed a button when certain figures appeared. The objective of the Bushman Competition and Retaliation Task (BCRT) was to provoke an aggressive response: The participant and an unseen opponent (actually a computer) competed in a test of reaction time, with the loser receiving a blast of noise whose volume and duration were determined by the winner. When the participant lost, which was always the case in early rounds, he or she was shown the noise level that his or her opponent had set; when participants finally won, they could choose how loud and long to blast the opponent back. Participants performed each task once with a placebo patch and once with a transdermal nicotine patch.

When smokers performed the CPT wearing the placebo patch, women's brain metabolism was significantly higher than men's, particularly in the cortical and subcortical prefrontal systems—areas associated with choice, attention, executive function, mood, and memory. These differences largely disappeared when participants wore the nicotine patch: Brain metabolism increased for men and decreased for women. Among nonsmokers, there was little difference in brain activity in men and women while performing the CPT, either with the nicotine patch or with placebo.

With the BCRT, in contrast, it was among nonsmokers that the male-female difference was most marked: Women's brain activity was higher in virtually all regions when the task was performed with placebo, but both sexes exhibited equal activity with nicotine.

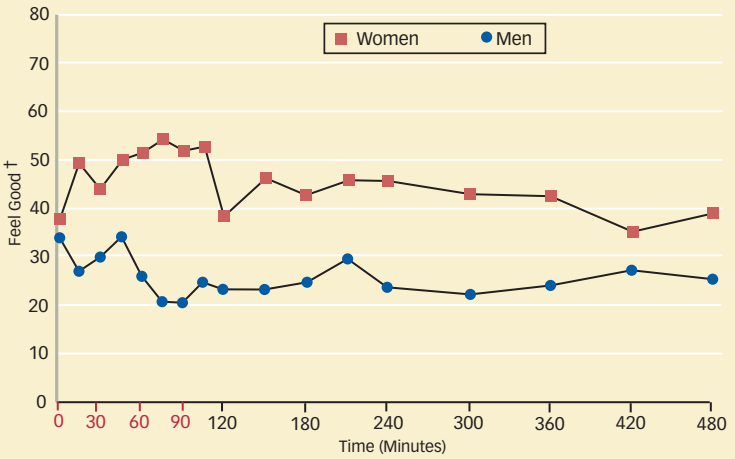
PET SCANS REVEAL DIFFERENCES IN METABOLIC ACTIVITY Red indicates brain areas where metabolic activity was higher in women than in men during the Continuous Performance Test and Bushman Competition and Retaliation Task. Exposure to nicotine greatly reduced the size of these areas, suggesting the drug's ability to neutralize gender differences in task-driven brain activity.



The gender disparity was smaller among smokers, and this, too, disappeared when they wore the nicotine patch.

"Some effects of nicotine on brain metabolism was not due to the effects of chronic smoking, but rather a fundamental biological difference between men and women in their response to nicotine," Dr. Potkin says. "Everyone knew that there were differences in male and female smoking behavior and smoking rates, but assumed they were just cultural. Based on our findings, a more likely explanation is an interplay of cultural and biological differences. That provides an interesting starting point for devising gender specific interventions."

"FEEL GOOD" RATINGS DIFFER BY GENDER Women consistently rated their overall well-being higher than men after ingesting four 1 mg/kg doses of cocaine at half-hour intervals. The differences persisted long after the last dose.



†Visual analog scale on which participants were asked to rate their overall score of mental and physical well-being ("feel good") in response to the drug (0=minimal, 100=maximal).

Time increments in red indicate dosing events (0, 30, 60, and 90 minutes).

EFFECTS OF ALCOHOL, COCAINE, AND BOTH COMBINED

Dr. McCance-Katz's study took as a starting point the observation that people frequently consume alcohol and cocaine simultaneously. "We wanted to understand why that might be and whether responses differed in men and women," says Dr. McCance-Katz.

In the double-blind study, nine men and eight women who were addicted to both cocaine and alcohol participated in three experiments performed on successive days. During the first, they received four 1 mg/kg intranasal doses of cocaine at 30-minute intervals, and two oral doses of alcohol 1 hour apart, in amounts calculated to maintain plasma alcohol concentrations of approximately 100 mg/dL; in the second, cocaine along with alcohol placebo; and in the third, alcohol along with cocaine placebo. The protocol was designed to approximate how cocaine and alcohol might be used together during a day-long binge, Dr. McCance-Katz says. The researchers monitored the participants' psychological and physiological status over an 8-hour period during and after the administration of the drugs.

By most measures, the men's and women's responses did not differ significantly. The researchers did note that women's hearts beat significantly faster than men's when given alcohol alone. Although men and women reported similar ratings of "rush," "any high," "cocaine high," "sad," "depressed," "nervous," or "paranoid" after taking cocaine, women consistently scored higher than men on "feel good"—a rating of combined mental and physical well-being—throughout an observation period starting with their first dose of cocaine and lasting until 6.5 hours after the last. On a scale from 0 to 100, the women's scores ranged from 36 to 54, whereas the men's ranged from a much lower 20 to 34, thus showing no overlap in scores. Gender differences in subjective response to cocaine and alcohol combined, or to alcohol alone, did not attain significance.

"We were a little surprised that women rated their well-being higher [after taking cocaine]," Dr. McCance-Katz says. In previous studies that involved single, somewhat larger doses, women had reported greater anxiety than men when they consumed cocaine. Although it is impossible to predict exactly how feelings of well-being might influence use of the drug, they could well increase the risk of toxicity, says Dr. McCance-Katz. "If you have a strong sense of good mental and physical well-being, you might not be attuned to the internal stimuli that signal the need to stop." Coupled with the fact that cocaine is the illicit drug most often cited by medical examiners in autopsies of female decedents, the finding underlines the importance of bringing more women into treatment and conducting further studies to explore which modalities are effective for women, she says.

Dr. Cora Lee Wetherington, Women and Gender Research Coordinator at NIDA, observes that Dr. McCance-Katz's findings echo animal research showing that female rats exhibit higher levels of motivation for cocaine self-administration than male rats and may be particularly sensitive to the drug's reinforcing effects. "The results of all these studies attest to the importance of not taking a unisex approach to the analysis of data," comments Dr. Wetherington. "Otherwise, you could come up with averaged findings that don't apply to men or women."

Dr. Jamie Biswas, Chief of the Medications Research Grants Branch at NIDA, says that larger studies should explore why substances of abuse appear to elicit a greater perception of well-being among women. Future research might include women in diverse locales and situations and directly address whether they are more easily addicted or harder to treat than men. ■

SOURCES

Fallon, J.H., et al. Gender: A major determinant of brain response to nicotine. *International Journal of Neuropsychopharmacology* 8(1):17–26, 2005.

McCance-Katz, E.F., et al. Gender effects following repeated administration of cocaine and alcohol in humans. *Substance Use & Misuse* 40(4):511–528, 2005.

Methamphetamine Increases, and HIV Decreases, Brain Volumes

HIV infection and methamphetamine addiction produce distinct, partly overlapping effects on brain structures.

BY JOHN S. DEMOTT,
NIDA Notes Contributing Writer

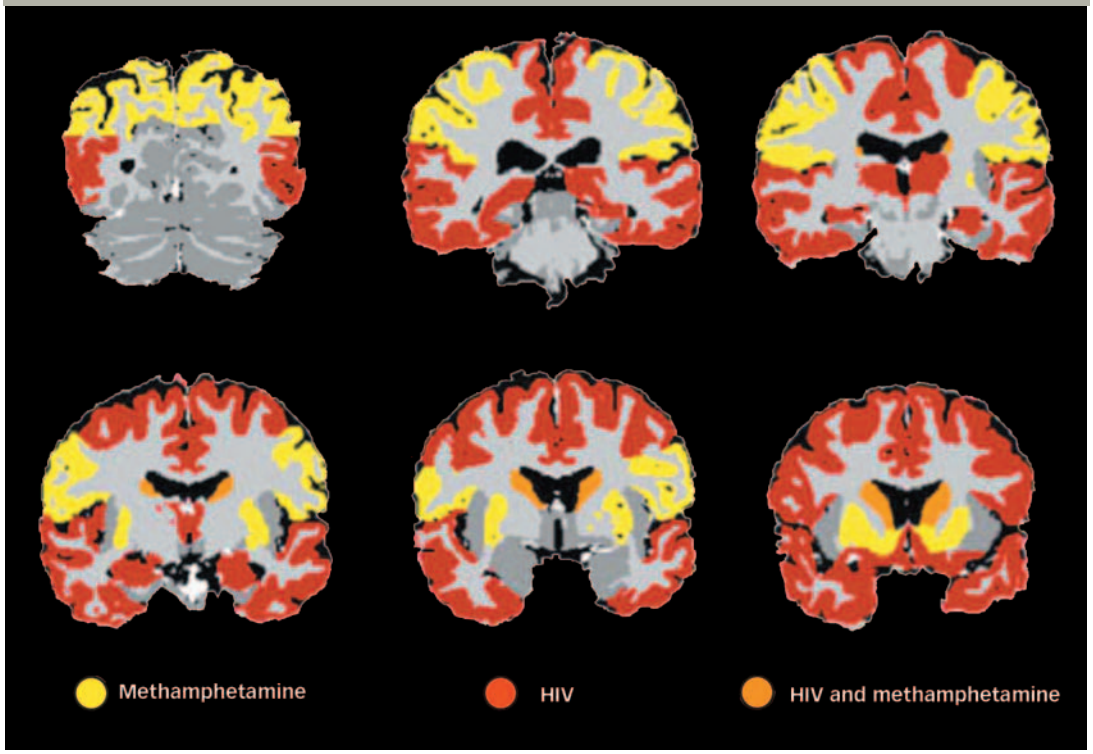
In a study that confirmed the association between HIV infection and loss of brain volume, NIDA-funded investigators also found an association between methamphetamine addiction and increased regional brain volume. Each type of volume change was associated with neurocognitive impairments, but it was unclear whether the two together caused any cognitive effects beyond the sum of what each produced individually.

Using structural magnetic resonance imaging (MRI), Drs. Terry L. Jernigan, Anthony C. Gamst, and colleagues at the University of California, San Diego (UCSD) mapped the major gray-matter brain structures of 103 people in four age- and education-matched groups: HIV-infected; methamphetamine-addicted; having both conditions; and having neither. The methamphetamine-addicted individuals were in recovery at UCSD's HIV Neurobehavioral Research Center.

After accounting for normal age-related reductions in brain volume, the participants with HIV had smaller volumes of cortical, limbic, and striatal structures, with the associations being most pronounced in the frontal and temporal lobes. Methamphetamine addiction was linked with increased volume in the parietal cortex and in all three segments of the basal ganglia—caudate nucleus, lenticular nucleus, and nucleus accumbens (NAc). In the caudate, volume reductions related to HIV and increases related to methamphetamine overlapped, producing a net volume approximating normal.

A further analysis of the volume data may reinforce existing evidence that drug abuse is especially damaging during adolescence and young adulthood, when the brain is still developing. The results showed that addicted individuals who were younger had greater NAc volume differentials compared

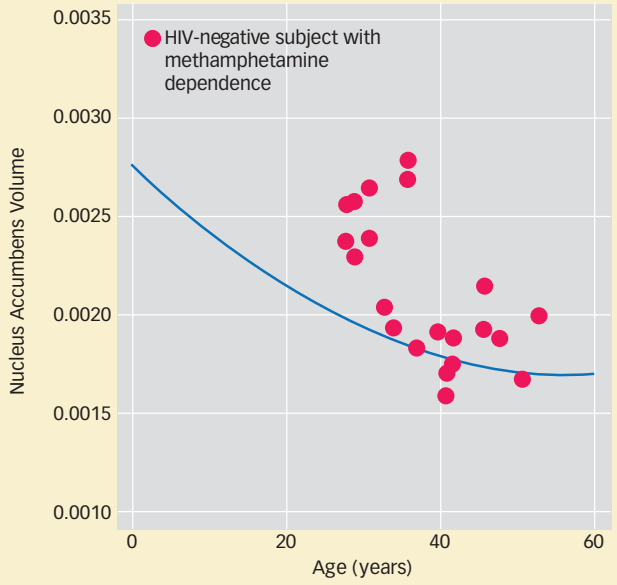
HIV SHRINKS BRAIN VOLUME, METHAMPHETAMINE ABUSE INCREASES IT Composite magnetic resonance imaging (MRI) scans of brain cross-sections show the effects of methamphetamine abuse and HIV infection on brain architecture. Volumes of regions shown in yellow were larger in methamphetamine-addicted individuals than in unexposed controls. Volumes of regions shown in red were smaller in HIV-positive than in noninfected individuals. The volume in the caudate nucleus, shown in orange, illustrates the superimposed effects of both conditions, which had an offsetting effect on volume. The offsetting volume effect did not cancel the functional brain damage associated with HIV infection and methamphetamine abuse.



with their non-drug-abusing age mates than did older addicted individuals. One possible explanation for this is that the drug interfered with the pruning of some NAc connecting fibers that normally occurs in the transition to adulthood, producing a small but measurable reduction in NAc volume. "While we can't be certain of the explanation, this finding highlights the concern that exposure during adolescence may alter the course of ongoing brain maturation," says Dr. Jernigan (see chart).

"The fact that brain alterations in methamphetamine dependence and HIV infection are distinct from each other is a clue that may help us to sort out the origins of different kinds of mental problems in these individuals."

NAc VOLUME DROPS WITH AGE, INCREASES WITH METHAMPHETAMINE ABUSE The volume of the nucleus accumbens (NAc) normally decreases with age, but this process appears to have been attenuated in younger methamphetamine-addicted subjects. Abusers in their 20s and 30s had average NAc volumes resembling those of drug-free 10- to 15-year-olds.



The healthy comparison curve is shown in blue.

Although the study results provided little information about specific drug mechanisms, the investigators note that animal studies have shown methamphetamine can incite inflammatory responses and abnormal growth of nerve fibers, each of which can increase tissue volume. "These findings emphasize that the brain's response to stimulant exposure, and indeed to HIV as well, is probably quite dynamic, characterized by overlapping responses in different glial, as well as neuronal, cell populations," says Dr. Jernigan. "The findings raise interesting questions for multiple-modality imaging studies, and underscore the degree of neural plasticity, and thus the potential for targeted intervention."

Dr. Jernigan says a finding of extensive change in the parietal cortex of methamphetamine abusers "helps to confirm the importance of parietal lobe involvement and may help correct a tendency in the field to neglect this region."

IMPLICATIONS FOR BRAIN FUNCTION

The researchers looked for correlations between the brain volume abnormalities and ratings of neuropsychological impairment. At the outset of the study, all other groups were significantly impaired relative to the HIV-negative and methamphetamine-negative group, which had a rating of 2.9 compared with 4.7 for those with both conditions, 4.2 for methamphetamine-addicted participants and 4.1 for HIV-positive individuals. Brain impairment was most pronounced in the HIV-positive participants with the most extensive loss of cortical volume and in the methamphetamine-addicted participants with the highest increase in cortical volume. The investigators found only one significant correlation between brain volumes and impairment in addicted individuals with HIV, a finding they believe probably reflects confounding by the opposed volume impacts of the two pathologies. The correlation was between hippocampal volume—a structure that both factors may damage—and severity of cognitive impairment in the dually diagnosed group.

"The fact that brain alterations in methamphetamine dependence and HIV infection are distinct from each other is a clue that may help us to sort out the origins of different kinds of mental problems in these individuals," Dr. Jernigan says." This is very exciting, because our results raise a number of specific questions that may not have been posed without these findings."

Dr. Ro Nemeth-Coslett, a NIDA psychologist, agrees. "As often happens in research, these results raise more questions than they answer. Dr. Jernigan's findings of structural inconsistencies in pathology are unaccounted for. Now we need mechanistic studies to provide a clearer understanding of what aspects of microscopic cellular organization actually drive the MRI measures." ■

SOURCE

Jernigan, T. L., et al. Effects of methamphetamine dependence and HIV infection on cerebral morphology. *American Journal of Psychiatry* 162(8):1461-1472, 2005.

NIDA Honors Dr. William L. Dewey

NIDA Director Dr. Nora D. Volkow presents the NIDA Service Award to The Friends of NIDA creator Dr. William L. Dewey.

Director Dr. Nora D. Volkow presented a NIDA Public Service Award to Dr. William L. Dewey at NIDA's National Advisory Council meeting on February 8. The Institute recognized Dr. Dewey for creating The Friends of NIDA—a private group that raises public awareness about the critical role of science in eliminating addiction and its consequences. Dr. Volkow praised Dr. Dewey's vision as founder of the organization and acknowledged his contributions to the field—including research on endogenous opioids and cannabinoids and opiate addiction, leadership of scientific organizations, and mentoring. The Friends of NIDA sponsors educational briefings for Congressional staff, committees, and caucuses on critical topics, including drugs and crime, methamphetamine addiction and its treatment, and prescription drug abuse. The organization builds support for bringing the power of science to bear on addiction as a brain disease (see *www.thefriendsofnida.org*).

HHS and NIH Recognize NIDA Staff

On June 29, NIDA's **Redonna Chandler, Ph.D.**, and **Harold Perl, Ph.D.**, received HHS Secretary's Awards for Distinguished Service. Drs. Chandler and Perl were honored for their deployment to New Orleans following Hurricane Katrina, and for providing increased capacity for mental health and substance abuse treatment services following Hurricanes Katrina, Rita, and Wilma.

On July 12, NIH Director Dr. Elias Zerhouni presented the annual Director's Awards to NIH staff. The following were recognized for their contribution to NIDA's mission in the past year:

Lisa Onken, Ph.D., for her outstanding contributions to the development and advancement of the behavioral treatment program within NIDA.

Donna M. Jones, in recognition of outstanding leadership and dedication that has advanced the mission of NIDA.

David Anderson, Timothy P. Condon, Ph.D., Gayathri Dowling, Ph.D., Jennifer Elcano, Lynda Erinoff, Ph.D., Mark Fleming, Jan Lipkin, Sheryl Massaro, Lucinda Miner, Ph.D., Joan Nolan, Jacques Normand, Ph.D., Michelle Person, Anna Staton, Susan Weiss, Ph.D., and Sara Wilson, in recognition of their roles in creation of the HIV Public Education Campaign, "Drug Abuse and HIV: Learn the Link."

Jonathan Pollock, Ph.D., for outstanding leadership in the planning and development of the trans-NIH Knockout Mouse Project.

Barry Hoffer, M.D., Ph.D., for exemplary performance while demonstrating significant leadership, skill and ability in serving as a mentor.

Laurence Stanford, Ph.D., for outstanding performance on the NIH MRI Study of Normal Brain Development, creating a database of normal brain development as a resource for developmental neuroscience communities.

ATLAS and ATHENA Prevention Programs Receive First *Sports Illustrated* Champion Award

L-R: Dr. Linn Goldberg, Oregon Health and Science University (OHSU); Dr. Elizabeth Robertson, NIDA; Dr. Diane Elliott, and Dr. Esther Moe, also OHSU, at the SI Champion Award ceremony.

Two NIDA-supported programs that prevent steroid and drug abuse and promote healthy behavior among high school athletes have been honored with *Sports Illustrated* (SI) magazine's first Champion Award. The ATLAS (Athletes Training and Learning to Avoid Steroids) and ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternatives) programs were developed by Dr. Linn Goldberg and Dr. Diane Elliot at the Oregon Health and Science University.

SI President Mark Ford announced the award on February 8, and disclosed that over the next year, SI will provide $1 million in support for the programs, including grants to establish SI Schools to serve as models. SI also will create a Web site that focuses on science-based nutrition, exercise, and drug prevention for coaches, athletes, and trainers. The SI Champion Award will be given annually to a nonprofit organization working for the betterment of sports.

ATLAS and ATHENA are the only prevention programs specifically designated as model curricula in the U.S. Anabolic Steroid Control Act of 2004. ATLAS was designed to help male athletes avoid steroid use and develop healthy approaches to training and physical development. ATHENA promotes exercise and nutrition as alternatives to reliance on diet supplements or unhealthy approaches to conditioning and weight control or dieting. Both programs use student athletes as leaders for team-centered instruction (see "ATHENA Program Reduces Substance Abuse by Girls on High School Sports Teams," *NIDA Notes*, Vol. 20, No. 1).

Drug Abuse Continues To Decline Among Adolescents

Drug abuse among adolescents aged 12 to 17 declined 9 percent between 2002 and 2004, according to a nationwide survey tracking substance abuse trends. Recently released results from the 2004 National Survey on Drug Use and Health (NSDUH) also found that the rate of substance abuse among all Americans in 2004 was similar to that of 2002 and 2003. Some 19 million Americans, or about 8 percent of the population aged 12 and older, used illicit drugs in the month leading up to the survey.

Nonmedical use of prescription pain relievers was the drug category with the largest number of new users in the 12 months prior to the survey—2.4 million—compared with 2.1 million for marijuana, 1.2 million for nonmedical use of tranquilizers, and 1.0 million for cocaine. Marijuana continued to be the most commonly used illicit drug in 2004, with a rate of 6.1 percent (14.6 million past-month users) for the U.S. population aged 12 and older.

"The study confirms some of the decreases in drug abuse we found in the Monitoring the Future survey, which is good news. It also confirms several problems we identified with prescription drug abuse that make us want to redouble our efforts to deal with this emerging epidemic," says Dr. Wilson Compton of NIDA's Division of Epidemiology, Services and Prevention Research. "It is remarkable that there are more new monmedical users of prescription pain medications than new marijuana users," he adds.

ABUSE RATES HIGHEST AMONG 18- TO 25-YEAR-OLDS

Young adults aged 18 to 25 had the highest overall rates of substance abuse among the age groups surveyed, as well as the highest rates for the abuse of specific substances, including binge and heavy drinking (41 percent and 15 percent, respectively), past-month cigarette smoking (39.5 percent), and nonmedical use of prescription medications. When asked if they had ever used a prescription medication not prescribed for them or just for the experience or feeling it caused, 29 percent of the young adults said yes; 6 percent said they had done so in the past month. Nearly one in four (24 percent) had misused pain medications in 2004, up from 22 percent in 2002.

By contrast, adolescents aged 12 to 17 showed a steady decline in past-month drug use—from 11.6 percent in 2002 to 11.2 percent in 2003 and 10.6 percent in 2004. In this age group, American Indian/Alaska Native youth had the highest rates of abuse, 26 percent, compared with their multiracial (12 percent), White (11 percent), Hispanic (10 percent), African-American (9 percent), and Asian (6 percent) counterparts. The decline was in part due to a substantial drop, from 9.1 percent to 8.1 percent, in past-month marijuana abuse by boys in this age group. Adolescents' abuse of methamphetamines, cocaine, and cigarettes also declined.

Young people who believed their parents would strongly disapprove of their trying marijuana were much less likely to try the substance than those who believed their parents would only somewhat disapprove or would be indifferent. Among the former, 5 percent reported past-month marijuana abuse, compared with 30 percent of the latter.

TOBACCO AND OTHER SUBSTANCES

Abuse of tobacco products declined in 2004, with the rate of past-month cigarette smoking falling from 26.0 percent in 2002 to 24.9 percent. Although NIDA officials are encouraged by the generally positive findings on smoking, one particular statistic has prompted concern: Pregnant young women aged 15 to 17 smoked at a rate similar to or higher than that of nonpregnant women in the same age group. Dr. Compton says NIDA has asked the Substance Abuse and Mental Health Services Administration, the study's sponsor, to work with NIDA to further explore the causes of this troubling statistic.

The findings for other substances were:

- **Alcohol:** Half the survey respondents said they had taken a drink within the past month, while 22.8 percent said they had participated in binge drinking (five or more drinks in one sitting at least once in the past month), and 6.9 percent said they had engaged in heavy drinking (five or more drinks in one sitting at least five times in the past month).
- **Hallucinogens:** The number of past-year abusers of LSD declined 41 percent between 2002 , with most of the decline occuring and 2004. Past-month abuse of ecstasy dropped 40 percent, with most of the abuse decline ocurring between 2002 and 2003. The rate of past-month abuse for other hallucinogens did not change significantly.
- **Methamphetamine:** The 2004 rates for methamphetamine abuse (4.9 percent lifetime, 0.6 percent past-year, 0.2 percent past- month) and cocaine abuse (14.2 percent lifetime, 2.4 percent past-year, and 0.8 percent past-month) were similar to those in 2003 and 2002.

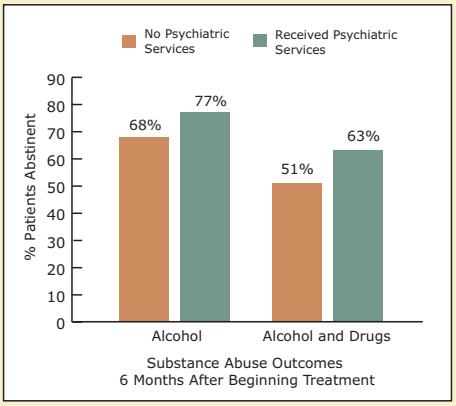
The NSDUH is available online at *www.oas.samhsa.gov*.

SOURCE

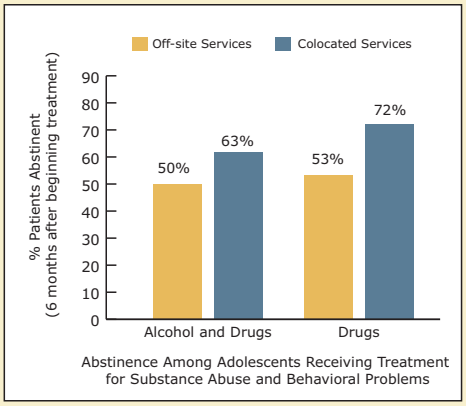
Substance Abuse and Mental Health Services Administration. 2005. *Results from the 2004 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H-28, DHHS Publication No. SMA 05-4062). Rockville, MD: SAMHSA.

WHAT THE NUMBERS SAY

On-Site Psychiatric Treatment Improves Abstinence In Teens With Co-occurring Disorders



Six months after they began substance abuse treatment, teens who also participated in therapy for their other psychiatric problems were more likely to demonstrate abstinence than peers who did not receive such services. The study group comprised 419 adolescents seeking treatment for substance abuse at a managed care system in California.



Among a subgroup of the adolescents receiving help for both substance abuse and behavioral problems, those receiving colocated services were more likely to be abstinent than those receiving services at separate locations.

SOURCE: Sterling S., Weisner C. Chemical dependency and psychiatric services for adolescents in private managed care: Implications for outcomes. *Alcoholism: Clinical and Experimental Research*. 29(5):801-809, 2005.

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