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## How Drug Abuse Affects the Brain and Alters Behavior Are Key Questions Driving Division's Work

Research Findings  
Vol. 21, No. 2 (February 2007)

BY DEBRA P. DAVIS, *NIDA Notes* Staff Writer

A compound that appears promising for treating cocaine relapse is wending its way along a chain of discovery and trial that links NIDA's various Divisions. Its discovery occurred under a grant from the Division of Basic Neuroscience and Behavioral Research (DBNBR), NIDA's locus for studies into the fundamental brain mechanisms underlying drug abuse and addiction.

Dr. David Shurtleff, director of the Division, sees his unit as the base of a pyramid upon which other NIDA Divisions and the scientific community at large build. "Much NIDA-supported research hinges on a basic understanding of the important biological components of drug abuse and addiction and how we can modify them to treat this disease," says Dr. Shurtleff. "Our research in DBNBR, which probes the genetic, molecular, neurobiological, and behavioral levels, is fed to all other Divisions at NIDA for further studies and for development of medications and new behavioral treatments."

**SEA OF NEURONS** This image appears on the Division's NIDA publications and posters.



With an eye toward developing a new medication for treating cocaine relapse, DBNBR "handed over" the JD<sub>T</sub>ic compound, a potent and selective kappa-opioid antagonist that has been shown to significantly reduce stress-induced cocaine relapse in rodents, to the Division of Pharmacotherapies and Medical Consequences of Drug Abuse for further tests in animals and—if warranted—in people. Ultimately, the compound may undergo large-scale clinical trials sponsored by NIDA's Clinical Trials Network.

The flow of research is two-way: As DBNBR feeds the findings of its grantees to other Divisions, it also relies on them for information that drives the development of its own research portfolio. For example, says Dr. Shurtleff, "The Division of Epidemiology, Services and Prevention Research tells DBNBR what the trends in drug abuse are and who is affected."

### KEY RESEARCH COMPONENTS

DBNBR's research portfolio is divided among four Branches: Genetics and Molecular Neurobiology, headed by Dr. Jonathan Pollock; Behavioral and

Cognitive Science, under Dr. Minda Lynch; Chemistry and Physiological Systems, under Dr. Rao Rapaka; and Functional Neuroscience, run by Dr. Nancy Pilotte.

Investigations fall into the following categories:

- Genetic, which seeks to pinpoint genetic variations that make some individuals more susceptible to addiction;
- Developmental, which examines, primarily in animal models, the effects of drugs on prenatal development as well as on the still developing brains of children and adolescents;
- Behavioral, which looks at the consequences of drug abuse on behavior and cognition, providing important information for the design of treatment and prevention interventions; and
- Neurobiological, which delves into the processes and mechanisms in the brain and nervous system underlying addiction.

The research projects touch on a broad range of drugs, health problems, populations, and scientific disciplines. For example, teams of scientists specializing in virology, immunology, neuroscience, and other disciplines are trying to determine how and why some individuals with HIV/AIDS develop a type of dementia called neuro-AIDS and how exposure to neurotoxic drugs such as methamphetamine exacerbates this condition. Another study, by NIDA-supported scientists using technology developed by the California-based pharmacogenetics company Perlegen, Inc., is probing how genes affect tobacco addiction. The goal is to lay the groundwork for developing antismoking medications tailored to individuals who are genetically predisposed to nicotine addiction. Other nicotine studies focus on the effects of this drug on adolescents. Research by Dr. James Belluzzi and others shows that adolescent rats are more sensitive than adult rats to nicotine and that a combination of nicotine and acetaldehyde, another ingredient of cigarettes, is particularly addictive to the adolescents (see "[Study Points to Acetaldehyde-Nicotine Combination in Adolescent Addiction](#)" (Archives)).

A number of studies are examining how drug abuse changes the brain's structure. They include research by Dr. Eric Nestler and colleagues looking at short- and long-term changes that cocaine engenders in the brain's limbic system and studies by Drs. Terry Robinson and Bryan Kolb indicating that repeated exposure to amphetamine and cocaine alters neuronal structures called dendrites, which, in turn, increases sensitivity to the drugs.

"Thanks to advances in neuroscience and genetics, we're finding answers to longstanding questions," Dr. Shurtleff notes. "Now we're able to view the human brain in action and understand how drug abuse affects the molecular mechanisms of cell signaling. As a result, we can develop new medications to stave off or reverse those effects. Information provided by the mapping of the mouse and human genomes is also helping us to answer longstanding questions about the etiology of drug addiction."

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Research in Brief  
Vol. 21, No. 2 (February 2007)

## Research in Brief

### Highlights of recently published NIDA-supported studies

#### Studies Focus on Acculturation and Hispanic Youth

**U.S.-Born Hispanic Women Have More Drug Problems Than Immigrants:** Among 19- to 21-year-old Hispanic women in South Florida, those born in the United States face a higher risk of drug addiction than immigrants, according to a recent study by Dr. R. Jay Turner and colleagues. The U.S.-born women reported more acculturation, measured as preference for English over Spanish, and greater exposure to stressful events, both of which were associated with increased risk for addiction. The gap in acculturation between the two groups accounted for 40 percent of the risk difference; a high score on either acculturation or stress exposure was associated with a nearly three-fold increase in the odds of addiction, compared with low scores on those measures (evaluated at one standard deviation above and below average). The investigators speculate that cultural influences help protect foreign-born Hispanic young women from stress. Native-born and immigrant young men reported similar levels of stress exposure and had similar rates of addiction. [Drug and Alcohol Dependence](#) 83(1):79-89, 2006. [[Abstract](#)]



**Latino Parent Training:** Men and women who completed a parent-training program adapted for Latino culture reported improvements in effective parenting practices and their children's (aged 13 years, on average) behavior compared with those who did not receive the intervention. Children whose parents received the program also reported that they were less likely to abuse tobacco, marijuana, and other drugs in the future. The parents also said their children's behavior improved.

Drs. Charles R. Martinez and J. Mark Eddy of the Oregon Social Learning Center randomly assigned 73 Spanish-speaking Latino parents (90 percent were of Mexican heritage) to participate in *Nuestras Familias: Andando Entre Culturas* (Our Families: Moving Between Cultures) or to receive no intervention. During each of 12 weekly 2.5-hour sessions, participants in the intervention group discussed developing effective family communication, bridging cultures, being positive, and encouraging success using appropriate discipline and limit setting, and practiced parenting techniques in role-play. [Journal of Consulting and Clinical Psychology](#) 73(5):841-851, 2005. [[Abstract](#)]

#### Medical Care During Addiction Treatment Reduces Hospital Use

On-site delivery of primary care reduces emergency department (ED) visits and inpatient hospital stays over the next 12 months among adult patients in methadone maintenance or in long-term residential treatment programs, according to a recent article by Dr. Peter D. Friedmann and colleagues. Their longitudinal analysis showed that offsite referrals reduced hospitalizations, but not ED visits, among those in long-term residential programs. Neither on-site care nor offsite referral curbed health service use by outpatients in nonmethadone treatment programs. In all three types of programs, health care use declined after substance abuse treatment. Overall, ED visits decreased from 47 percent to 23 percent, and hospitalizations from 42 percent to 13 percent; the greatest reductions were observed among patients with the longest stays in treatment. The National Treatment Improvement Evaluation Study included six methadone maintenance programs, 14 long-term residential programs, and 24 outpatient nonmethadone programs with over 2,000 patients. The investigators advocate future studies of the cost-effectiveness of integrating primary care into addiction treatment.



*Medical Care* 44(1):8-15, 2006. [[Abstract](#)]

### Brain Changes Accompany Cocaine Withdrawal

Rats repeatedly exposed to cocaine and then withdrawn from it exhibit neural changes in the lateral amygdala, a part of the brain involved in responding to pleasurable and aversive stimuli. Such changes may mediate the negative emotional effects that accompany drug withdrawal, say the researchers who documented the effect in a recent study. Dr. Vadim Bolshakov and colleagues at Harvard Medical School have shown that longterm potentiation (LTP), a process underlying learning and memory, occurs in the lateral amygdala when cocaine-exposed rats no longer have access to the drug. They found a clear link between LTP and enhanced levels of the neurotransmitter glutamate in the lateral amygdala and signs of withdrawal in the rats. The findings suggest that amygdala circuits might contribute to drug modulation of motivational states and influence addictive behaviors.



*European Journal of Neuroscience* 23(1):239-250, 2006. [[Abstract](#)]

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## Checkup System Catches Relapse Early and Facilitates Return to Treatment

Research Findings  
Vol. 20, No. 6 (July 2006)

**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

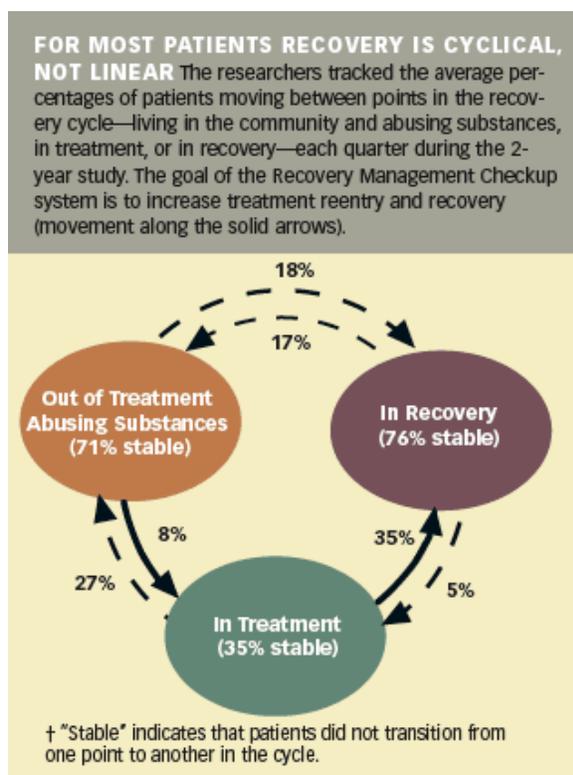
In developing the RMC system, the researchers built on previous studies in which they had identified patterns of chronic substance abuse, relapse, and recovery. They found that, during the first 3 years after treatment, people frequently transitioned between recovery, substance abuse, and treatment—a 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.

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 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.



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.

### 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](#)).

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](mailto: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.

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