RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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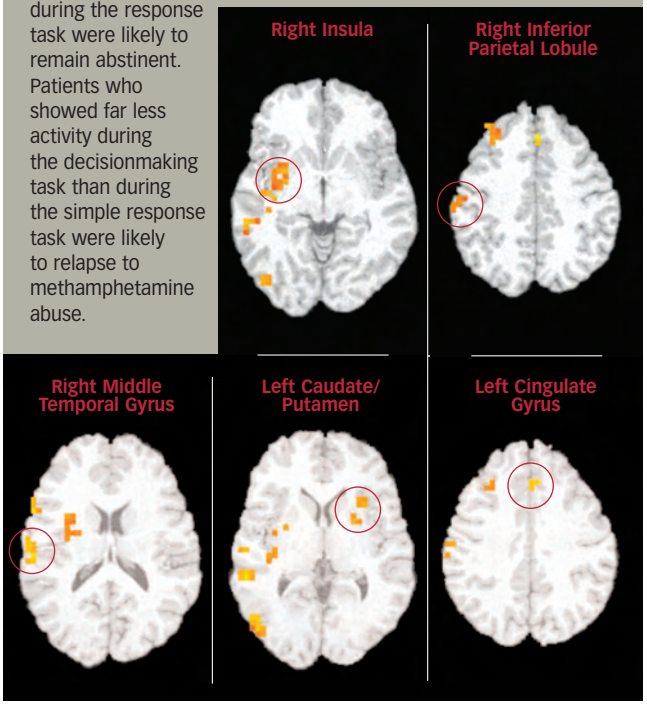
Brain Activity Patterns Signal Risk Of Relapse to Methamphetamine

Methamphetamine abusers who relapse after treatment appear to make decisions using different brain regions than do those who remain abstinent.

BY PATRICK ZICKLER,
NIDA Notes Contributing Writer

NIDA-supported investigators have found that functional magnetic resonance imaging (fMRI) of the brain, performed during a psychological test, can predict with high accuracy whether an individual will relapse following treatment for methamphetamine abuse. Their study revealed a characteristic pattern of brain activity in methamphetamine-abusing men who relapsed within 1 to 3 years after completing treatment and a different pattern in men who did not.

DRUG ABUSE AND DECISIONMAKING Researchers used functional magnetic resonance imaging (fMRI) to measure patterns of regional brain activity while abstinent methamphetamine abusers performed two tasks, one that required decisionmaking and one that required only a simple response. Participants who showed greater activity in selected brain regions (circled and highlighted in the brain images shown below) during the decisionmaking task than during the response task were likely to remain abstinent. Patients who showed far less activity during the decisionmaking task than during the simple response task were likely to relapse to methamphetamine abuse.



Dr. Martin Paulus and colleagues at the University of California, San Diego, took the point of departure for their work from previous research that showed methamphetamine abusers and nonabusers activating different brain areas during psychological tests of decisionmaking. These earlier studies showed that poor choices made by drug abusers correlate to distinctive patterns of activity in some areas of the brain. Dr. Paulus's team hypothesized that activity patterns in those regions might also be associated with relapse to drug abuse, which involves similarly destructive decisions.

To test their hypothesis, the researchers recruited 46 men who had voluntarily entered and completed a 28-day inpatient drug treatment program after abusing methamphetamine for periods ranging from 3 to 34 [*Continued on page 6*]

ALSO IN THIS ISSUE

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

Research Network Tests Drug Abuse Treatment Following Incarceration

A majority of current and former prisoners (60 to 80 percent) in the Nation's criminal justice system were convicted on drug-related charges: possession, trafficking, crimes committed while under the influence of drugs, or crimes committed to support an addiction. Drug abuse treatment is one of the most effective known means of helping such individuals avoid repeating the patterns that brought them into the criminal justice system. Research has shown that even prisoners who enter treatment primarily to avoid longer or more stringent sanctions have reduced post-release rates of drug abuse and arrest.

While we know drug abuse treatment works for offenders and ex-offenders, we do not yet know which interventions work best. Initiatives differ across the Nation in structure, approach, availability, and efficacy. To find out what types of initiatives and interventions are optimal for incarcerated or recently released individuals, NIDA is funding a national research network, the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) project, established in 2002. Working with Federal research partners in justice and public health, the nine centers and one coordinating site that make up CJ-DATS are building a knowledge base on the effective components of treatment for this population, strategies for successful transition from prison to community, and ways to reduce barriers to treatment within the community and the criminal justice system.

Initial CJ-DATS efforts are focusing on the pivotal period surrounding prison release. Researchers are testing interventions that help people learn healthy ways to deal with anger, improve communication, build social support, and stay engaged in addiction treatment. This last issue is vital: Many of the 600,000 people released from jails and prisons every year are referred to outpatient addiction treatment, but only about 30 percent attend regularly for the recommended minimum of 3 months. CJ-DATS investigators also are evaluating interventions designed to reduce risky sexual behaviors after reentry into the community. This, too, is a critical issue, because rates of sexually transmitted disease, including HIV/AIDS, are much higher among prisoners than in the general population. Studies also are examining how program structure, staff skills, resources, and culture affect service delivery and outcomes (see *www.cjdats.org* for more information about ongoing research).

People reentering the community after incarceration require help with housing, employment, finances, family relationships, and health issues. CJ-DATS will determine how different justice systems around the country coordinate supervised reentry with community health and social services, information that will enhance treatment and ultimately improve outcomes. The information on optimal approaches that CJ-DATS is designed to provide holds tremendous promise for easing the social and economic burdens that arise out of the nexus of drug abuse and crime.

NIDA Notes

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Nicotine and Cocaine Vaccines Move Forward

NICOTINE: A vaccine to prevent nicotine addiction demonstrated a good safety profile in a recent clinical trial with 68 healthy smokers. Dr. Dorothy Hatsukami of the University of Minnesota and colleagues found NicVAX to be safe and well tolerated, with side effects comparable to those of placebo. Overall, the reported side effects—most commonly general discomfort, headache, and muscle pain—were mild to moderate in severity. The vaccine triggers the production of antibodies that bind nicotine in the blood and keep it from reaching the brain. Nevertheless, healthy smokers who received the vaccine did not experience craving or withdrawal symptoms, nor did they increase the number of cigarettes smoked during a 38-week study and followup.

> Pharmacodynamics and Drug Action 78(5):456-467, 2005.

COCAINE: An investigational medication designed to induce the body's natural defenses to inactivate cocaine before it reaches the brain has cleared an important human trials hurdle. Dr. Bridget Martell, Dr. Thomas Kosten, and their colleagues at Yale University tested the compound, now designated TA-CD, in an open-label study involving 18 cocaine-addicted participants who took it for either 8 or 12 weeks. No participant reported adverse effects, and all still had cocaine-specific antibodies in their bloodstream 6 months after their first injection. At the 6-month followup, participants reported exposure to the drug produced only mild euphoric effects, even though blood tests showed waning concentrations of the antibodies.

> Biological Psychiatry 58(2):158-164, 2005.

No-Smoking Policy Did Not Deter Enrollment In Addiction Programs

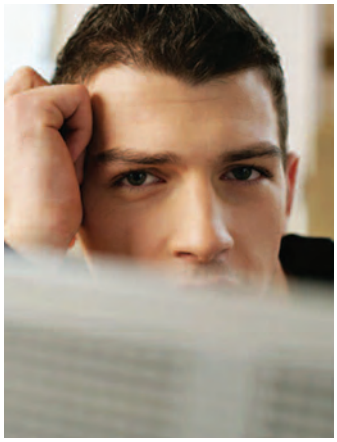
New Jersey's requirement that residential addiction programs establish completely smoke-free environments and help drug abusers quit smoking does not deter smokers from entering treatment for other addictions or increase the number of early discharges. Dr. Jill Williams, Dr. Douglas Ziedonis, and their colleagues at the University of Medicine and Dentistry of New Jersey found that half of the programs had tobacco-free facilities and grounds 1 year after the State implemented the new licensure standards. More than 90 percent of residential programs provided assessment, counseling, or education programs and materials for nicotine-dependence treatment, compared with 37 to 53 percent the year before. Most patients (77 percent) smoked and most smokers (65 percent) wanted to quit or cut back. To assist patients in smoking cessation, the State offered a free 8-week course of nicotine-replacement therapy and special staff training.

> Journal of Substance Abuse Treatment 28(4):331-340, 2005.

GVG Shows Promise In Early Human Trials

A potential medication for treatment of drug abuse and addiction—gamma-vinyl GABA (GVG)—has taken an important step in the medication development process. Having previously shown promise in tests with laboratory animals, it now has proven to be safe in a small clinical trial with cocaine and methamphetamine abusers. GVG also proved effective: 16 of 18 patients in treatment for addiction to cocaine, methamphetamine, or both tested negative for the drugs throughout the last 6 weeks of the open-label trial. What's next? A larger, randomized double-blind study.

> Synapse 55:122-125, 2005.



Methamphetamine Disrupts Focus

Methamphetamine abuse disrupts one aspect of attentional control more profoundly than others—the ability to ignore distractions. Dr. Ruth Salo and her colleagues at the University of California, Davis and Stanford University found that 34 methamphetamine abusers who had been abstinent for at least 4 weeks made more mistakes (17 percent) than did control subjects (13 percent) on tests requiring that they focus on a task and ignore distraction. No difference was found in error rates on tests requiring the participants to switch attention from one task to another. Deficits in the ability to pay attention undermine a patient's effective engagement in cognitive-behavioral therapy, Dr. Salo says, and it is therefore important to identify specific cognitive problems associated with methamphetamine abuse.

> Biological Psychiatry 57:310-313, 2005.

Community-Based Treatment Benefits Methamphetamine Abusers

A large California study finds favorable effects for inpatients and outpatients; women's gains are larger.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Methamphetamine abusers can achieve long-term abstinence with the help of standard community-based drug abuse treatment. Nine months after beginning therapy, 87 percent of patients treated for heavy or long-term methamphetamine abuse in California outpatient and residential programs were abstinent from all drugs, according to a NIDA-supported analysis. "In the public dialogue, and even among professionals in the field, one sometimes hears that meth abuse is 'not treatable.' But that view is not borne out by recent clinical trials or our study, which shows that community-based treatment reduces drug abuse and other problems," says lead investigator Dr. Yih-Ing Hser.

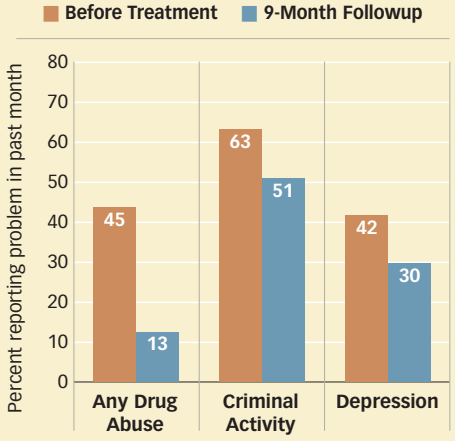
Dr. Hser and colleagues at the University of California, Los Angeles analyzed data from the California Treatment Outcome Project (CalTOP), an ongoing study that has followed the progress of adult substance abusers treated at 43 outpatient and residential programs throughout the State since April 2000. The researchers focused on 1,073 patients who reported that methamphetamine abuse was their primary drug problem (572) or that they had abused the stimulant regularly for at least 1 year before beginning treatment (501). Most were in their 30s or younger, White or Latino, unemployed, and on public assistance; most had an arrest history. They had abused methamphetamine for about 9 years, on average, and nearly one-quarter (22 percent) reported injecting drugs at least once. Although 64 percent had children aged 18 or younger, one-third of parents did not live with their children in the month before beginning treatment. One parent in five reported that a child protection court had ordered that his or her children live with someone else, and 6.3 percent had their parental rights terminated by the State.

"Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they may bear to the consequences of prenatal drug exposure."

The patients received the addiction treatment services routinely provided by each program. These usually included group therapy, with an average of 69 drug-related and 51 alcohol-related sessions during the first 3 months of treatment. On average, the patients also received 22 sessions on dealing with mental health symptoms and 13 addressing psychosocial problems, including family, parenting, and employment.

More than 60 percent of the patients completed 3 months of treatment. Among all the patients in the study—those who finished 3 months and those who did not—the average reported frequency of methamphetamine abuse fell from 2.7 to 0.5 days per month from the start of treatment to 9 months later. The portion who were abstinent from all drugs rose from 55 percent to 87 percent in the same interval, and 68 percent were abstinent and also not incarcerated. Patients improved in all areas—drug and alcohol abuse; mental health symptoms; and employment, family, and legal problems—except one: men's medical problems.

ABUSERS ACHIEVE GAINS WITH TREATMENT Nine months after methamphetamine abusers began addiction treatment, they had reduced past-month drug abuse and criminal activity, and fewer reported depression.



Dr. Thomas Hilton of NIDA's Division of Epidemiology, Services and Prevention Research says these findings should reassure professionals working in the addiction, social services, and criminal justice fields that current therapies work for these troubled patients. "Dr. Hser's findings suggest that treatments available in the community help meth abusers reduce drug abuse and start to get their lives back on track, echoing prior research," he says.

WOMEN'S EXPERIENCES

Dr. Hser's findings confirm gender differences seen in other studies: Women began treatment with more severe psychosocial problems than men (see chart, right) and benefited more. Although treatment retention levels were similar for the two sexes, the women made greater gains in the areas of family relationships and medical problems, while achieving similar improvements in all other areas at the 9-month followup. The women's better outcomes may have resulted in part from more intensive services (see chart below); as well, Dr. Hser says that many women in the study had a powerful motivator—family. "Many were trying to maintain or regain custody of their children by demonstrating improvement during treatment. Others had 'hit bottom,' saw how drug abuse was hurting their families, and decided to make a change," she says.

WOMEN RECEIVE MORE SERVICES IN SOME AREAS For some problems, women received more services than men during the first 3 months of treatment.

Services	Women (No. of interventions†)	Men (No. of interventions†)
Employment*	4.6	2.3
Family‡	6.5	4.6
Mental Health‡	23.6	19.9
Parenting*	4.2	1.7

†Includes counseling sessions, medical appointments, and prescriptions. *Outpatients. ‡Outpatient and residential.

MEN, WOMEN EXPERIENCE DIFFERENT PROBLEMS Women beginning treatment for methamphetamine abuse reported more psychosocial problems, while men reported more crime and criminal justice involvement.

Family and Social Circumstances	Women, % (n=567)	Men, % (n=506)	Total, % (N=1,073)
Children living with someone else by court order	29.3	9.9	20.1
Parental rights terminated	10.1	2.2	6.3
Family abused substances	21.7	10.5	16.4
Physically abused (past month)	5.5	1.8	3.7
Sexually abused (past month)	2.5	0.6	1.6
Employed	23.8	43.9	33.3
On public assistance	63.1	37.0	50.8
Criminal Justice System Involvement			
On parole	4.4	12.7	8.3
On probation	32.3	37.6	34.8
Ever arrested	76.7	88.3	82.2
Arrest in past year	36.7	45.1	40.6
Criminal activity (past month)	55.2	71.7	63.0
Psychiatric Symptoms (Past Month)			
Serious depression	38.8	29.8	34.6
Difficulties with understanding, concentrating, remembering	36.2	26.5	31.6
Suicidal thoughts	11.3	6.3	9.0
Prescribed psychiatric medicine	21.3	15.4	18.6

"Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they may bear to the consequences of prenatal drug exposure," says Dr. Hser.

Dr. Hser and her colleagues continue to analyze CalTOP data, aiming to determine the longer-term impact of therapy and identify ways programs can improve outcomes. "Enhancing psychiatric, parenting, and employment services would better match patients' needs, and my team plans to study the relationship between help for these problems and longer-term outcomes," says Dr. Hser. They also plan to investigate whether women-only treatment is more effective for pregnant methamphetamine abusers than mixed-gender programs.

"The field needs more research following meth abusers over time to get a picture of the long-term outcomes of treatment, relapse episodes, and whether these patients require additional support to sustain gains made during therapy," says Dr. Hilton. "Because the availability of community health and social services varies across States, we cannot generalize the findings from one State, such as California. We need data from across the country," he adds. ■

SOURCE

Hser, Y.-I.; Evans, E.; and Huang, Y.-C. Treatment outcomes among women and men methamphetamine abusers in California. *Journal of Substance Abuse Treatment* 28(1):77-85, 2005.

BRAIN PATTERNS

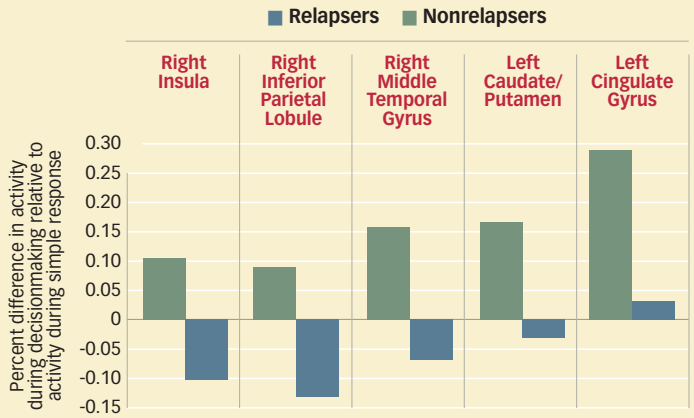
[*Continued from page 1*]

years. When each man had been abstinent for about 4 weeks, he participated in two psychological tests. During one, he was asked to watch a computer screen and press a button every time a symbol appeared. In the other, he was asked to try to predict whether a flashing symbol would next occur on the left side or right side of the computer screen. The difference between the two tasks was that, in the first, the test-taker needed only to react upon seeing the symbol, while in the second, he needed to decide which side to choose. The researchers recorded the men's brain activity with fMRI throughout the tests.

A year or more (360 to 967 days) after the imaging sessions, Dr. Paulus's team was able to locate and contact 40 of the 46 patients. Of these, 18 had relapsed to methamphetamine abuse (median time to relapse, 279 days; range, 36 to 820 days). Comparing their fMRI results with those of the 22 nonrelapsers, the researchers noted nine regions where the groups' brain activity had differed during decisionmaking. The relapse group showed less activation of the dorsolateral, prefrontal, parietal, and temporal cortices and the insula—regions associated with evaluation and choice among actions that may lead to either beneficial or harmful outcomes. The patterns of brain activation predicted relapse in 17 of the 18 men who had resumed methamphetamine abuse and predicted successful abstinence in 20 of the 22 patients who had not relapsed, Dr. Paulus says.

RELAPSERS, NONRELAPSERS MAKE DECISIONS DIFFERENTLY

During a decisionmaking exercise, nonrelapsers activated five brain regions that relapsers did not.



"The most striking aspect of this result is that the fMRI pattern has 90 percent accuracy in predicting outcome," Dr. Paulus says. "The differences in brain activity are pronounced, with little overlap." Differences in the right insula, right posterior cingulate, and right middle temporal gyrus differentiated relapsers from nonrelapsers. Other brain regions predicted the timing of relapse.

"The most striking aspect of this result is that the fMRI pattern has 90 percent accuracy in predicting outcome. The differences in brain activity are pronounced, with little overlap."

"Some of these predictive areas have not previously been strongly associated with drug abuse," observes Dr. Steven Grant of NIDA's Division of Clinical Neurosciences and Behavioral Research. "For example, while other investigators have reported alterations in the parietal lobe related to drug abuse, this is the first study to show the parietal cortex playing an important role. However, because so many brain regions were related to relapse, we still do not have a full understanding of what specific process might be dysfunctional in the relapse group."

The potential clinical implications of the new finding are promising, but uncertain. For example, no women were included among the participants, who were enrolled from treatment programs. "It's important to confirm the findings in women, for whom social, demographic, and other factors associated with relapse may differ," Dr. Paulus points out. Nonetheless, he says that, in principle, programs treating methamphetamine abuse might use the fMRI protocol to assess patients, then assign those likelier to relapse to higher levels of care. Dr. Paulus believes such an approach might prove cost-effective, even with typical fMRI charges of up to $700 per hour in academic imaging centers. "The human and social costs of relapse are high," Dr. Paulus says. "Using this imaging technique to precisely allocate care to the patients who need it most might well produce enough savings elsewhere to more than offset its expense. An alternative, more practical course of action might be to use these fMRI results as a benchmark for development of other assessments that are less costly, but have the same predictive strength." ■

SOURCE

Paulus, M.P.; Tapert, S.F.; and Schuckit, M.A. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Archives of General Psychiatry* 62(7):761-768, 2005.

Bupropion Helps People With Schizophrenia Quit Smoking

Data address physicians' concerns about prescribing the medication for smokers with schizophrenia.

BY LORI WHITTEN,
NIDA Notes Staff Writer

The smoking cessation aid bupropion is safe and effective for people with schizophrenia, researchers at Massachusetts General Hospital and Harvard Medical School have found. In a NIDA-funded study of smokers with schizophrenia, those who took sustained-release bupropion were more likely to stop smoking by their quit date and to achieve continuous abstinence for a month than those who received placebo, and they also remained abstinent longer. The researchers did not observe any adverse interactions with the patients' antipsychotic medications or exacerbation of psychiatric symptoms.

The U.S. Food and Drug Administration (FDA) approved sustained-release bupropion as a treatment for depression in 1996 and as a smoking-cessation aid in 1997, but physicians have been reluctant to prescribe the medication for patients with schizophrenia. "Although 75 to 85 percent of people with schizophrenia smoke, we have lacked data on treatments for nicotine addiction in this population, resulting in many not receiving advice to quit," says Dr. A. Eden Evins, lead investigator of the study.

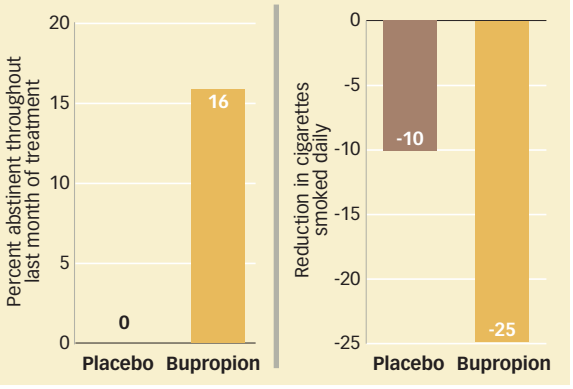
Dr. Evins and her colleagues treated 53 patients, aged 24 to 66, for nicotine dependence. When they began treatment, the patients smoked 30 cigarettes a day, on average, and typically had made two previous quit attempts. During the 12-week study, each participated in weekly sessions of group cognitive-behavioral therapy (CBT) and received either 300 milligrams a day of sustained-release bupropion or placebo. The CBT program was adapted for patients with schizophrenia from standard smoking-cessation therapy. Each patient visited the clinic once a week for evaluations of smoking (self- report confirmed by expired air carbon monoxide measurements), changes in psychiatric symptoms, medication compliance, and side effects.

Therapists encouraged all patients to set a quit date before the 4th week of treatment, and 36 percent of those taking bupropion—compared with 7 percent of those on placebo—achieved this goal, demonstrating abstinence at the 4-week assessment. Sixteen percent of patients in the bupropion group, but none taking placebo, achieved abstinence throughout the last month of treatment. Among patients who were not abstinent at the end of the study, those in the bupropion group reduced the average number of cigarettes smoked daily from 34 to 9, compared with a drop from 25 to 15 in the placebo group.

Bupropion was generally well tolerated and did not exacerbate the symptoms of schizophrenia. Depression and flat affect, as well as cognitive function, tended to improve among patients taking the medication. Common side effects experienced by people taking antipsychotic medications, such as muscle stiffness and shuffling gait, were not worsened by nicotine abstinence or bupropion. About 80 percent of patients in both the medication and placebo groups kept to their regimens throughout the study.

The findings confirm promising results from several smaller studies. Dr. Evins points out that the relapse rate was high after treatment discontinuation—75 percent of those who were abstinent at week 12 had relapsed to smoking at the 3-month followup. Only about 4 percent of patients in either group were abstinent in the week before the 3-month followup. Other studies of bupropion in the general population have shown that about half of patients tend to relapse after treatment discontinuation. "Patients with schizophrenia may need a longer course of bupropion with CBT or a combination of bupropion and nicotine replacement therapy to avoid relapse," says Dr. Evins.

BUPROPION ENHANCES OUTCOME OF COGNITIVE-BEHAVIORAL THERAPY Patients with schizophrenia who participated in weekly group cognitive-behavioral therapy for smoking cessation were more likely to remain abstinent throughout the last month of a 12-week study if they also took bupropion. Among patients still smoking at study's end, those receiving bupropion smoked fewer cigarettes daily than those on placebo.



SOURCE
Evins, A.E., et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology* 25 (3):218-225, 2005.

Cocaine Abuse and HIV Are Linked With Coronary Calcification

Cardiovascular changes that are potential risk factors for serious heart disease are detected in relatively young people with HIV infection or a history of cocaine abuse.

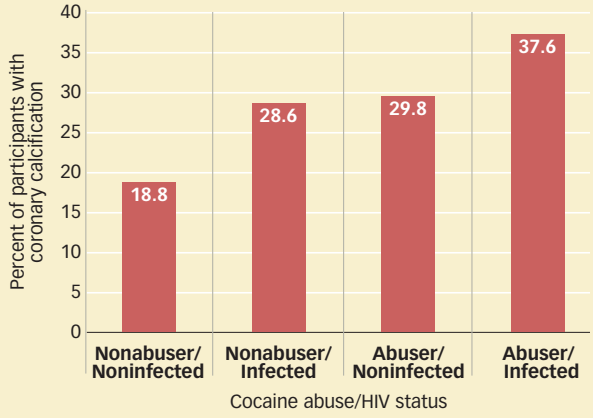
BY LORI WHITTEN,
NIDA Notes Staff Writer

Cocaine abuse and HIV infection each raise the likelihood that calcium deposits will form in coronary arteries, according to a NIDA-supported study. The findings, by Dr. Shenghan Lai and colleagues at The Johns Hopkins University, suggest that individuals with either problem may develop elevated risks for serious, potentially fatal heart disease. The gradual buildup of calcium deposits and fat along the inner walls of blood vessels produces atherosclerosis, the narrowing and obstruction of the vessels that is a major cause of strokes and heart attacks. Although none of the participants in the study had a clinical heart problem, all were relatively young to have coronary calcification.

Dr. Lai and his colleagues used cardiac computed tomography (CT) scanning to detect the presence of coronary calcification and the number, size, and volume of calcium deposits in 192 African-American men and women aged 25 to 45. Thirty-two of the participants did not have HIV infection and had never abused cocaine (HIV-/cocaine-), 28 had the infection and were nonabusers (HIV+/cocaine-), 47 did not have the infection and had abused cocaine (HIV-/cocaine+), and 85 had both conditions (HIV+/cocaine+). About two-thirds were men.

The results revealed coronary calcification in almost one-third (31 percent) of the participants. The prevalence was twice as high in the HIV+/cocaine+ group (38 percent) as in the HIV-/cocaine- group (19 percent). In the other two groups, the proportion of participants with the condition fell in between, with 29 percent of the HIV+/cocaine- and 30 percent of the HIV-/cocaine+ groups showing coronary calcification (see chart). In the U.S. population as a whole, the prevalence of coronary calcification among 25- to 45-year-olds is about 18 percent.

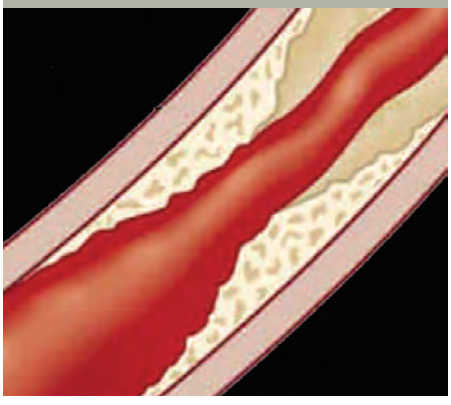
CORONARY CALCIFICATION LINKED WITH COCAINE ABUSE AND HIV INFECTION
Cocaine abuse and HIV infection were associated with a higher prevalence of coronary calcification in a study group of African-Americans aged 25 to 45.



Participants with HIV infection and/or a history of cocaine abuse had more

"Coronary calcification among people at such a young age is a striking observation and suggests that clinicians should monitor heart disease in these populations, advise patients to make lifestyle changes, and perhaps treat conditions that affect heart health, such as high blood pressure."

CALCIFICATION Calcuim deposit (white area) narrows the arterial opening, impeding blood flow.



calcium deposits and a greater volume of calcification than nonabusers without the infection. Compared with the HIV-/cocaine- group, the total volume of coronary calcium was 2.9 times as high in the HIV+/cocaine- group, 2.6 times as high in the HIV-/cocaine+ group, and 3.5 times as high in the HIV+/cocaine+ group. The associations held when the researchers took into account cardiovascular disease risk factors, including age, body mass index, lipid levels, blood pressure, and whether patients were taking HIV medication. The study was too small to determine whether HIV and cocaine contribute independently to calcification when both are present, or whether they interact physiologically to promote it even more.

Cardiovascular complications have been well documented in patients who abuse cocaine and also have HIV infection, but this study is the first to show arterial changes prior to the development of cardiovascular symptoms and to link them with cocaine abuse alone and HIV infection alone. Larger, longer studies are needed to confirm Dr. Lai's associations and to determine whether or how cocaine- and HIV-associated calcification progresses to clinical atherosclerosis and heart disease.

Dr. Jag Khalsa of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse says early signs of cardiovascular disease should be taken very seriously because they are strongly connected to two major causes of death—stroke and heart attacks. "Coronary calcification among people at such a young age is a striking observation and suggests that clinicians should monitor heart disease in these populations, advise patients to make lifestyle changes, and perhaps treat conditions that affect heart health, such as high blood pressure," says Dr. Khalsa. ■

SOURCE

Lai, S., et al. Human immunodeficiency virus 1 infection, cocaine, and coronary calcification. *Archives of Internal Medicine* 165(6):690-695, 2005.

Animal Research Shows GHB Acts On GABA Receptors

Baboon studies may help researchers learn how the club drug gamma-hydroxybutyrate exerts such a powerful grip when abusers try to quit.

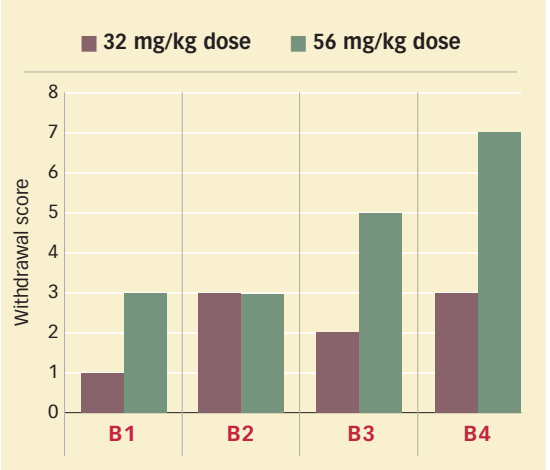
BY PATRICK ZICKLER,
NIDA Notes Contributing Writer

Baboons that are chronically exposed to gamma-hydroxybutyrate (GHB), a club drug known as "liquid ecstasy" and "Georgia home boy," develop withdrawal symptoms when drug administration stops, NIDA-supported investigators have shown. The animals' symptoms—tremors, loss of appetite, and agitation—are similar to those that occur when GHB-dependent people stop taking the drug. The finding, the first clear demonstration of GHB withdrawal in an animal, will enable researchers to use baboons as subjects in studies of the drug's effects in the brain and possible pharmacological treatments for withdrawal. Additional findings bolstered evidence from previous research suggesting that GHB dependence may be largely due to the drug's action at sites where the chemical messenger gamma-aminobutyric acid (GABA) attaches to brain cells.

"It is important to be able to study GHB's effect in another species because human studies involving high doses are too risky," says Dr. Minda Lynch of NIDA's Division of Basic Neurosciences and Behavior Research. "Chronic GHB abusers report severe withdrawal symptoms, which make it very difficult for them to quit abusing the drug. A slight increase in dose can tip GHB's sedative effects to a lethal level, and those who continue abusing the drug because withdrawal is so hard to bear are at risk for possibly fatal effects."

Dr. Elise Weerts and her colleagues at The Johns Hopkins University conducted a three-part study to evaluate GHB withdrawal in baboons. They observed the behavioral effects of GHB administered daily for 1 month, tried to precipitate withdrawal after

GABA-B BLOCKER INDUCES GHB WITHDRAWAL After 2 weeks of continuous administration (750 mg/kg/day) of GHB, four baboons (B1, B2, B3, B4) received injections of a compound (CGP36742) that blocks GABA-B receptors on brain cells; a 32 mg/kg dose of the compound produced mild withdrawal symptoms, and a 56 mg/kg dose produced moderate withdrawal symptoms in the four animals.



the baboons had been receiving GHB for 2 weeks by treating the animals with a compound that affects brain sites called GABA-B receptors, and discontinued GHB administration after 4 weeks to see if the baboons experienced withdrawal.

"Chronic GHB users report severe withdrawal symptoms, which make it very difficult for them to quit abusing the drug. A slight increase in dose can tip GHB's sedative effects to a lethal level, and those who continue abusing the drug because withdrawal is so hard to bear are at risk for possibly fatal effects."

During the first 2 weeks of daily GHB administration (750 mg/kg of body weight) the animals showed behavioral changes that confirmed to the researchers that GHB was having neurobiological effects at the dosage used; they spent more time in resting postures and had difficulty with tasks requiring fine motor skills, such as picking raisins or M&Ms from small cups. After 2 weeks of GHB administration, each baboon received injections (32 and 56 mg/kg, 8 days apart) of a compound that blocks GHB from attaching to GABA-B receptors—structures composed of proteins that influence brain cells' responses to the chemical GABA, one of the brain's primary carriers of intercellular communications. Immediately after injection of the GABA-B blocker, the baboons exhibited symptoms that included tremors, vomiting, and increased aggression, together with milder behavioral changes, such as assuming abnormal postures and sitting with their eyes closed. These symptoms increased with higher doses of the GABA-B blocker and dissipated after its effects wore off. When the researchers discontinued GHB administration after 1 month, the animals exhibited the same withdrawal symptoms as those triggered by the GABA-B blocker.

"The daily dose these animals received was equivalent to doses reportedly abused by humans and thought to produce dependence. The spontaneous withdrawal that occurred when GHB administration was discontinued and the withdrawal precipitated by the GABA-B blocker are evidence that the baboons were physically dependent on GHB," Dr. Weerts concludes. Moreover, the observed effects of the GABA-B blocker reinforce earlier findings that GHB acts at these receptors, Dr. Weerts says, as well as the suggestion that these sites are possible targets for therapies to counteract or inhibit GHB's effects. Dr. Weerts next plans to use her baboon model to try to quantify the combination of GHB dosage and duration of exposure that leads to dependence and to test other drugs that may precipitate or alleviate withdrawal. ■

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Animal Experiments
In Addiction Science

To learn how drugs promote abuse and produce addiction, researchers focus on animal behaviors that parallel human drug-related behaviors.

BY SUE YOUNG-WILSON, *NIDA Notes Contributing Writer*

Research using animals has contributed immensely to our understanding of drug abuse and its consequences, prevention, and treatment. Animal studies have yielded fundamental insights into why people abuse drugs and how drugs cause the compulsion and disordered thinking seen in addiction. They provide clues to strategies for preventing and treating abuse and addiction. They also provide the first tests of the safety and efficacy of potential new vaccines and medications.

Because animal research is so crucial, we have chosen it as the topic for this inaugural article in a new *NIDA Notes* Reference Series. Each article in the series will discuss a basic idea or theme in drug abuse science, citing *NIDA Notes* articles as illustrative references.

WHY EXPERIMENT WITH ANIMALS?

Researchers rely on experiments with animals to answer questions about how drugs and potential medications may affect the brain and body without exposing people to potential toxicity, risk of addiction, or invasive medical procedures. These experiments reduce or eliminate many factors that can make studies with people hard to interpret, such as differences in diet, health, drug history, genetic makeup, socioeconomic circumstances, understanding, and attitudes. While results from animal studies should be extrapolated to humans with caution, their value is incalculable. Researchers follow strict ethical guidelines to minimize animals' discomfort and ensure that any adversity animals suffer is unavoidable and warranted in terms of the perceived importance of the knowledge to be gained.

ANIMALS AND ADDICTION

Addiction is a human disease; only people normally have sufficient access to drugs to become addicted, and only people can report some of the hallmark experiences of the disorder, such as craving a substance or trying and failing to stop using it. Yet when laboratory animals (rats, mice, monkeys, baboons, and some other species) are exposed to addictive substances in controlled settings, they manifest equivalents of several of the behaviors we use to recognize and define abuse and addiction. They generally will:

- Take more and more of it,
- Devote much time and energy to getting it,
- Continue taking it despite adverse consequences,
- Undergo a withdrawal syndrome upon sudden cessation, and
- Relapse in response to environmental or stressful triggers or renewed exposure.

Researchers call these behaviors "animal models" of the corresponding aspects of human addictive behavior. The core procedures of animal research on addiction are a set of protocols that assess a substance's addictive properties by exposing animals to it and observing whether they exhibit the model behaviors. Each protocol focuses on one behavior.

THE CORE PROTOCOLS

The animal models of addiction enable researchers to translate questions about a substance's effects on people into parallel questions about whether animals exposed to the substance will exhibit the stand-in behaviors. For example, the question, "Will this substance provide people with an experience they want to repeat, leading to possible abuse?" becomes, "Once animals are exposed to this substance, will they push a lever to obtain more?"

The protocols for administering substances and documenting the model animal behaviors are standardized so that researchers can interpret and compare results. Quantification of the behaviors is indispensable: Investigators seeking to determine whether a substance is likely to be abused, for example, will use a computer to count the number of times test animals push a lever to self-administer it. Scientific instrument makers have provided specialized equipment for measuring the significant behaviors. Thus, for example, researchers assessing a substance's stimulant effects typically will measure a test animal's locomotor activity by putting it into a cage equipped with infrared sensors that automatically monitor its movements.

The most frequently posed questions about human responses to potentially addictive substances, the corresponding questions about animal behavior, and experimental protocols are as follows:

Does the substance have effects that will motivate people to abuse it?

Researchers have developed two independent protocols, each using a different animal model, to answer this question.

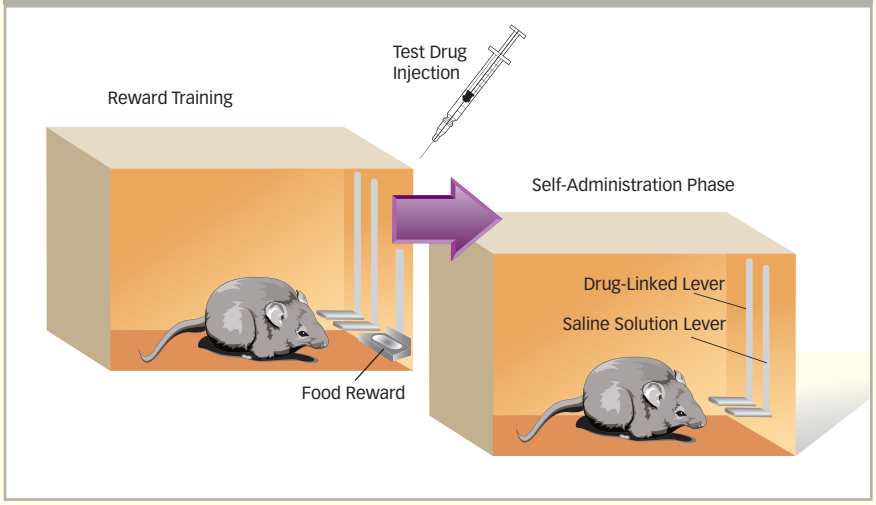
1. Self-administration experiments:
Once an animal has experienced a substance's effects, will it work to obtain more?

To answer this question, researchers first train an animal to obtain rewards—usually food—by some voluntary action, for example, by pushing a lever. They then give the animal an initial injection or infusion of the substance in question and place it in a cage where it can self-administer more doses by the same action. Staying with the example of a lever, two conditions must now be met for the researchers to conclude that the substance motivates self-administration:

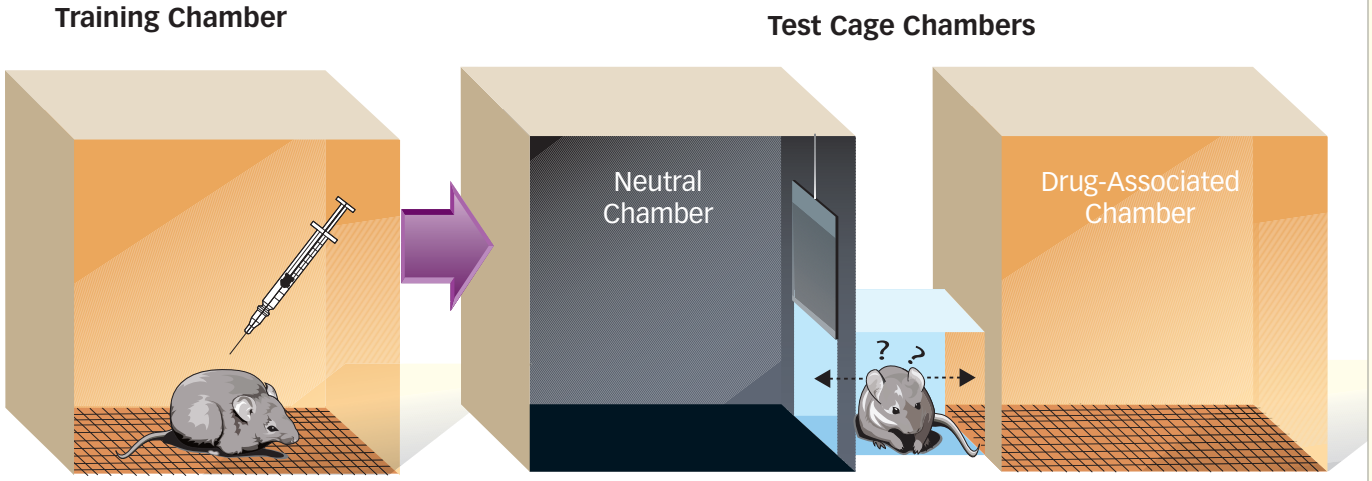
- The animal persistently pushes the lever; and
- The animal pushes the drug-linked lever more than it pushes an identical lever that delivers either nothing at all or infusions of a control substance, such as saline solution, that has no rewarding properties. This second condition ensures that the animal's goal in pushing the drug-linked lever is to get the drug and not, for example, just for exercise (in which case it would be expected to push both levers equally).

If test animals' behaviors meet both conditions, the drug is said to be reinforcing, meaning it provides an experience animals seek to repeat. NIDA-funded researchers recently used a self-administration experiment to verify their hypothesis that acetaldehyde, a component in tobacco smoke, contributes to adolescent tobacco addiction.[1]

SELF-ADMINISTRATION EXPERIMENTS Researchers train an animal to obtain rewards (usually food) by some voluntary action, such as by pushing a lever. Researchers then give the animal an initial injection or infusion of the substance under study, then place it in a cage where it can self-administer more doses by performing the same action.



CONDITIONED PLACE PREFERENCE EXPERIMENTS Researchers place an animal in a distinctively designed chamber and inject or infuse it with the substance being studied. Once trained to associate the chamber with the test agent, the animal is placed in an anteroom connecting a neutral chamber and the drug-associated chamber. The animal indicates its preferred chamber by spending more time there; its choice reveals the animal's preference for or aversion to the test substance.



2. Conditioned place preference experiments:
Once an animal has been exposed to a substance, will it prefer the place where it had this experience to other places where it has not?

For this protocol, researchers utilize a test cage consisting of two chambers with markedly different features: for example, one chamber may be black with a Plexiglas floor and the other white with a wire-mesh floor, or they may have distinctive aromas, lighting, or sounds. A passageway joins the two chambers, with doors that can be opened or closed to confine the animal in either chamber or allow free movement between them.

Preparatory to the experiment, the researchers inject a test animal with the substance under investigation and confine it to one chamber. They may expose the animal once or many times, always putting it in the same chamber; the goal is to train, or condition, the animal to associate the drug experience with that chamber and its distinctive features.

On the day of the experiment, the researchers place the animal, uninjected, in the hallway between the two chambers and monitor its movements. They will conclude that the substance is reinforcing if the animal spends most of its time in the chamber it has learned to associate with the substance. Sometimes animals will instead favor the other chamber—a sign they have an aversion to the substance. As in self-administration experiments, researchers incorporate control conditions in these experiments to eliminate alternative explanations for the animals' behaviors. Although conditioned place preference studies do not directly measure drug reinforcement, their results match those of self-administration studies fairly well.

How strongly does the substance motivate continued use?
How much effort will an animal expend to obtain a dose of the substance?

To answer this, researchers set up self-administration experiments just like those used to establish abuse tendency, but with one modification: They program the lever so that the animal must press it more times to obtain each successive infusion of the substance. Typically, the animal receives an infusion after the first press, the second, fourth, eighth, sixteenth, and so on. The strength of reinforcement is indicated by how far the animal goes in this escalation before the effort required for the next dose outstrips its motivation and it desists. Also measured is the pace of the lever-pressing: the shorter the intervals between presses, the more motivated the animal may be.

Will people be motivated to keep on taking the drug even when they know that negative consequences will result?
Will animals continue to press a lever that delivers the substance, but accompanied by an unpleasant sensation?

Researchers set up self-administration studies with yet another wrinkle: When the animal presses the lever, it receives, along with the substance, a discomfiting stimulus such as a tail pinch or an electrical shock to its foot. If the animal keeps pressing the lever nonetheless, it is considered likely that people, too, may overvalue the substance in relation to their health and well-being.

Will people who take the drug for long periods experience withdrawal?

Will animals that have been extensively exposed to the substance show signs of discomfort or dysfunction if they abruptly lose access to it?

A person is at risk for withdrawal symptoms when his or her body is dependent upon a substance—that is, has adapted physiologically to the substance and now needs it to function properly. To replicate this state in laboratory experiments, researchers will either directly administer a substance to an animal or place an animal in a cage where it can freely self-administer the substance. In the latter case, the researchers will watch for the animal to settle into a stable rhythm of lever-pressing or to steadily increase its intake of the substance, each of which suggests its body has reached a new physiological equilibrium that accommodates the substance's effects. At this point, the scientists cut off the animal's access to the substance and observe its response. Withdrawal is inferred if the animal develops certain abnormal behaviors. In one such experiment, described in this issue, baboons chronically exposed to the club drug GHB—also known as "liquid ecstasy"—developed tremors, loss of appetite, and agitation when drug administration stopped.[2]

Will a person who becomes abstinent be at risk for relapse?

Will a triggering stimulus cause an animal to start seeking a drug again after having stopped?

Experiments to test relapse have three basic steps:

- *Establishment of dependence:* As in studies to test withdrawal, an animal is steadily infused or placed in a cage where it self-administers the substance under investigation until its pattern of lever-pressing indicates dependence;
- *Extinction:* The researchers leave the animal in the cage but disconnect the lever from the substance delivery mechanism. The animal keeps on pressing the lever for a while, but with no substance forthcoming, eventually stops. In lab parlance, the animal's lever-pressing behavior is now "extinguished," and it is in a state comparable to that of a person who has achieved abstinence;
- *Exposure to a relapse trigger:* The researchers now expose the animal to a stimulus they believe can trigger relapse. If the animal resumes avid lever-pressing, the researchers conclude that the substance's effects include an abiding potential for relapse.

In relapse experiments, researchers test animals with stimuli corresponding to those that most commonly cause people who are abstaining from drugs to relapse: stress, environmental cues associated with the drug experience, and reexposure to the drug (for example, when someone decides it won't hurt to smoke just one cigarette and quickly is back to a pack a day). An environmental cue often used in animal models of relapse is a light that turns on when the lever is primed to deliver the substance during the self-administration stage, turns off in the extinction stage, and reappears in the last stage. Stress often is induced with mild electrical shocks.[3]

BEYOND THE CORE PROTOCOLS

Animal studies are useful beyond determining whether substances have addictive properties. They also guide the development of new treatments and provide key information about how drugs produce their addictive and other effects.

Evaluating treatments

To assess whether a vaccine or medication is likely to help prevent or treat abuse of a drug, researchers typically follow the same protocols

GLOSSARY OF TERMS

- **Animal Model:** In medical research, the use of animals to model—to provide simplified representations or replicas of, or close analogies to—human conditions and diseases so that researchers can investigate and perform experiments on aspects of these conditions and diseases using non-human subjects. It is widely accepted that animal models must fulfill three major criteria to be considered valid: 1) "face validity," or how closely the symptoms observed in the animals resemble those in human patients; 2) "predictive validity," or how similarly to their human counterparts the animals respond, e.g., to access to a given drug, or to a particular treatment regimen; and 3) "construct validity," to what extent the model is consistent with prevailing theory regarding the disease/condition.
- **Control:** A standard against which the effects of an experiment are evaluated. In animal studies, the "control group" typically comprises a second group of animals, very similar to the group being studied but not exposed to the procedure or agent under study. The use of controls helps researchers to isolate only those effects that are actually attributable to the experiment.
- **Extinction:** The process of eliminating or reducing a conditioned response by not reinforcing it. Or, the process in which the frequency of the learned response to the conditioned stimulus decreases and ultimately disappears, due to the lack of reinforcement. (See definition of reinforcement.) In drug addiction research, the extinction of drug-seeking behavior in animals is considered analogous to—a model for—a human addict becoming abstinent.
- **Protocol:** An explicit, detailed plan for a scientific experiment. In this article, "protocol" usually refers to one of a variety of standard and established procedures in the field.
- **Reinforcement:** The presentation of a stimulus, usually rewarding, immediately following a specific behavior, in order to increase the frequency of that behavior. Researchers have trained rats to repeatedly press levers (the behavior) by arranging for the rat to receive a positive reinforcer whenever it does so. In drug experiments, the reinforcer is often food to begin with, and then the drug under investigation. The fact that a rat will lever-press for cocaine is taken as evidence that it finds the cocaine reinforcing (pleasurable, motivating).

they use to assess the drug's reinforcement potential, but with two modifications. At an appropriate stage in the experiment, they give some of their animal subjects the potential vaccine or medication, and they use a control group of drug-exposed but untreated or placebo-treated animals.

In an experiment to test a vaccine, researchers ask: "Compared with the control group, will the animals we pretreat with the vaccine before giving them access to the drug self-administer less of it, or demonstrate less preference for the cage in which they were exposed to it?"[4] In a study to evaluate a potential medication to reduce withdrawal symptoms, they ask: "If animals are physically dependent on the drug, will a group that is treated with the proposed medication show fewer signs of withdrawal than an untreated group when the drug is stopped?" If a medication is being evaluated for efficacy against relapse, they ask: "If we bring animals through the progression of self-administration and extinction and then expose them to a relapse trigger, will the medicated animals revert to avid self-administration less readily than the control group?"[5]

Investigations into drugs' effects have contributed greatly to our general understanding of how the brain functions in such fundamental areas as learning and memory, motivation, and pain processing.

Studies of drug mechanisms

Information on how drugs act on the brain to produce abuse and addiction provides the basis for targeted medication development: Once research shows that a drug of abuse affects a particular brain process, pharmacologists can identify and test medications that have opposing effects. Research into the neurobiological mechanisms of abuse and addiction also sheds light on genetic and physiological traits that heighten or reduce vulnerability to drug abuse. Investigations into drugs' effects have contributed greatly, as well, to our general understanding of how the brain functions in such fundamental areas as learning and memory, motivation, and pain processing.[6]

Researchers learn about drug mechanisms and some effects, such as toxicity, by simply exposing animals to drugs and analyzing the impact on brain structures and systems.[7] Other studies try to decipher how drugs' biological effects give rise to the behaviors associated with abuse and addiction: Typically, these studies combine the core animal experimental protocols with specialized techniques of pharmacological, neurobiological, or genetic investigation.[8]

THE LIMITS AND FUTURE OF ANIMAL EXPERIMENTATION

Animal experiments shed light primarily on drug responses that are based in the many brain and bodily systems and processes that humans share with other species. Yet animal experiments can never yield a complete picture of human interactions with drugs. While evolution equipped people and animals with the same or very similar mechanisms for many basic aspects of motivation and inhibition, learning and memory, and pain response, the human brain integrates these with speech and writing, logic, and symbolic reasoning. Moreover, only in humans do social factors such as laws, culture, religion, and economics modify the likelihood and consequences of drug abuse. Accordingly, results from animal studies need to be interpreted with caution, and human studies alone can reveal influences on abuse and addiction that involve uniquely human traits and capacities.

Recent technological advances enable today's researchers to investigate some issues directly in humans that previously would have required animal experimentation. The most striking example, perhaps, is the use of noninvasive imaging techniques to monitor the brain's complex responses to drugs while they are occurring. The same techniques also permit new types of experiments in animals.[9] Other technological advances have extended the use of animal experiments into new fields of investigation; for example, researchers can now investigate the role of a particular gene in drug abuse through the use of specifically bred strains of mice.[10] Researchers' ingenuity continues to yield new ways to exploit the unique advantages of animal models to deepen our knowledge of drug abuse and addiction. ■

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Treatment During Work Release Fosters Offenders' Successful Community Reentry

Long-term studies are helping to determine the most effective drug treatment protocols for prisoners in transition.

BY LORI WHITTEN,
NIDA Notes Staff Writer

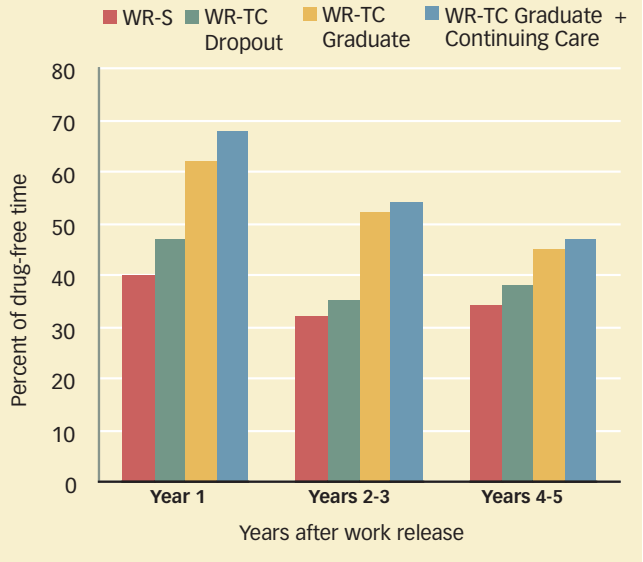
Addiction treatment for prisoners during the pivotal time when they are returning to the community has a strikingly persistent benefit and may create a 'turning point' that helps them stay off drugs and out of trouble, NIDA researchers have concluded after tracking the progress of more than a thousand released offenders. The investigators found that prisoners who participated in drug abuse treatment during a work-release program were three times as likely as untreated peers to remain drug-free up to 5 years. Treatment during work release delayed relapse and resulted in more drug-free time during the followup period. Attendance at continuing weekly group sessions following completion of work-release treatment further enhanced outcomes up to 3 years.

Dr. Clifford Butzin, a co-investigator of the study led by Dr. James Inciardi, at the University of Delaware compared the effectiveness of therapy given in different stages of incarceration, release, and reintegration into the wider community. Their project was part of the State's efforts to offer criminal justice-related treatment programs in three stages—during prison, work release, and parole. In 1990, Delaware established a work-release treatment program to ease the prison-to-community transition with funds from a NIDA treatment demonstration grant. The program utilizes the same therapeutic community model that is the format for Delaware's in-prison treatment. In the mid-1990s, the State added a continuing care component designed to help offenders who have completed work release adapt to living in the community with criminal justice supervision.

The research team analyzed the outcomes of 1,122 drug-involved offenders who participated in work release between 1991 and 1998 and in any followup. The participants' (80 percent male, 72 percent African-American) risk profiles included characteristics typically associated with relapse to drug abuse and crime: extensive criminal histories, low rates of marriage, and substantial unemployment before prison (see chart, page 17). The investigators assigned each participant to either standard work-release (WR-S) or the work-release therapeutic community (WR-TC). Because WR-TC slots were limited, priority for them was given to participants who had graduated from the in-prison therapeutic community or whose sentence required treatment as a condition for release.

The participants assigned to the WR-S program served the last 6 months of their sentences working for pay in the community and spent their nonworking hours in a

GREATER PARTICIPATION IN TREATMENT INCREASED DRUG-FREE TIME FOR MOST OF FOLLOWUP PERIOD
During the 5 years after prison release, Delaware offenders receiving treatment in a work-release therapeutic community (WR-TC) demonstrated more drug-free time than those in the standard work-release program (WR-S). For the first two followup periods, percentage of drug-free time increased with greater participation in treatment. Beginning 3 years after treatment, the four groups were not significantly different from each other; however, participants in WR-TC demonstrated more drug-free time than those in WR-S.



secured residence, but received no formal intervention focused on drugs. Participants in the WR-TC intervention served the last 6 months of their sentences in a secured TC—a "family setting"—in which peers in recovery help participants develop a sense of accountability for their behavior and change negative patterns that lead to drug abuse. They concentrated on treatment goals, performed assigned duties in the residence, and attended group and individual counseling sessions during the first 3 months of the program. They also participated in mock interviews and seminars on job seeking, started looking for work and housing, opened bank accounts, and developed household budgets. During the subsequent 3 months, they worked in the community and continued therapy during nonworking hours. WR-S participants received no additional services.

BENEFITS OF WORK-RELEASE TREATMENT

After completing work release and returning to the community, WR-TC participants continued treatment for at least 6 months. They attended weekly group sessions at the TC, visited a counselor once a month, and were encouraged to spend at least 1 day a month at the facility.

The investigators interviewed participants at work-release initiation and completion and at 18-, 42-, and 60-month followup points, confirming abstinence reports with urinalysis. The results showed that WR-TC participants who relapsed took twice as long to do so as WR-S participants (28.8 months versus 13.2 months, on average). After leaving prison, WR-TC participants had higher abstinence rates than WR-S participants (32 percent versus 10 percent). Employment rates were also higher with WR-TC (55 percent) than without (45 percent).

To further analyze the relationships between the levels of treatment and outcomes, the investigators subdivided the two groups into four: those in WR-S; those who participated in WR-TC but failed to complete it; those who completed WR-TC but did not participate in aftercare; and treatment graduates with aftercare. At each followup, each increase in level of care was associated with a higher percentage of time spent drug-free, for most of the followup period (see chart, page 16).

Participants in the WR-TC program typically had abused drugs once a day before incarceration, whereas those in WR-S had abused drugs several times a week. Because of their severe drug problems, more WR-TC participants (32 percent) than WR-S participants (5 percent) had received in-prison treatment. However, the researchers determined that treatment during work release was much more effective than in-prison treatment, contributing the bulk of the advantage attained by the WR-TC group. Treatment during work release halved the likelihood of relapsing, whereas other factors—including treatment before or during prison—did not have a significant impact. "Although addiction treatment episodes have a cumulative effect, several studies have shown that the benefits of treatment during prison seem to fade over time compared with therapy during the prison-to-community transition," says Dr. Butzin.

Among 690 participants who completed all followup interviews, treatment during work release also reduced arrest rates over the 5-year period. Rearrest was common in all groups, however, with 77 percent of WR-S participants, 58 percent of WR-TC treatment graduates who did not receive aftercare, and 52 percent of those who also received aftercare facing new charges at some point.

SUPPORTIVE ENVIRONMENT IS KEY

"It makes sense that a therapeutic community—a stable residence with a drug-free culture and supportive peers—helps people who are looking for a job and a place to live after prison. Continuing care for prisoners with drug problems during the transition back to the community is essential for sustained recovery and other public health benefits, including reduced spread of HIV/AIDS and hepatitis C," says Dr. Thomas Hilton of NIDA's Division of Epidemiology, Services and Prevention Research.

Although the prison-to-community transition is critical and may set the pattern for post-release behaviors, research is needed on the best ways to coordinate social and health interventions with criminal justice supervision. Recognizing the importance of science-based knowledge on the effective components of treatment for this population, NIDA established the Criminal Justice–Drug Abuse Treatment Studies (CJ–DATS) research network with Federal partners in justice and public health. CJ–DATS investigators around the United States, including the team in Delaware, are testing interventions and studying approaches for coordinating services for offenders reentering the community. ■

WORK-RELEASE PARTICIPANT CHARACTERISTICS Most participants in the Delaware work-release program demonstrated a long history of criminal activity, chronic drug abuse, and characteristics associated with high rates of relapse and recidivism.

Characteristic	Percentage
Ever married	29
Unemployed prior to incarceration	58
Treatment prior to incarceration	72
Incarcerated for drug-related crime*	33
Characteristic	**Average Number**
Arrests prior to incarceration	9
Prior incarcerations	4

* Does not include crimes committed to obtain money for drugs.

SOURCE

Butzin, C.A., et al. Treatment during transition from prison to community and subsequent illicit drug use. *Journal of Substance Abuse Treatment* 28(4):351-358, 2005.

Clinical Trials Network Adds Texas and Appalachia Sites

NIDA's Clinical Trials Network (CTN) now encompasses 17 sites across the United States. The CTN sites, called nodes, bring together community treatment providers and academic researchers in partnerships that speed clinical research and shorten the time needed from validation of new approaches to implementation in community treatment centers. The new additions to the CTN are:

- **The Texas Node**, centered at the University of Texas Southwestern Medical Center in Dallas, which includes 11 community treatment providers in Dallas–Ft. Worth, Austin, and El Paso; and
- **The Appalachian Tri-State Node**, which includes a research group at the Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center in partnership with five community treatment providers in West Virginia, eastern Ohio, and western Pennsylvania.

In the 6 years since its inauguration, the CTN has enrolled more than 5,000 patients in 16 protocols being evaluated at 103 community treatment programs. Five additional protocols currently are recruiting and enrolling an estimated 2,200 participants across 38 community treatment programs. For more detailed information, go to *www.drugabuse.gov/CTN/about.html*.

NIDA Launches HIV/AIDS Public Awareness Campaign

The link between drug abuse and HIV infection is the focus of a new public awareness campaign launched by NIDA on November 29, 2005. NIDA Director Nora D. Volkow, M.D., announced the campaign and screened "Text Message," a new public service announcement (PSA) aimed at teenagers, during a press conference at the National Press Club in Washington, D.C. "Drug abuse prevention is HIV prevention," says Dr. Volkow. "In recent years, the number of young people in the United States diagnosed with AIDS rose substantially. Because drug use encourages risky behaviors that can promote HIV transmission, NIDA views drug abuse prevention and treatment as essential HIV prevention."

The PSA shows young women text messaging on cell phones about a friend who contracted HIV after using drugs and having sex at a party. The dialogue says, "She got high, got stupid, and now she has HIV." The announcement is being aired on television stations across the country.

The PSA was produced in collaboration with students from the Duke Ellington School of the Arts, a Washington, D.C., public high school. Students were involved in developing the concept for the PSA and also performed the lead roles. The intent is to dispel the myth that only intravenous drug abuse can lead to HIV infection and to promote awareness of the consequences of the risky sexual behavior that can follow any type of drug abuse.

"Before working on the PSA, I was more concerned about pregnancy as a result of unprotected sex than HIV infection, which seemed only to affect older people," said Ellington student Rebecca Hollingsworth. Research has shown that this view is widespread: A large proportion of youths are not concerned about becoming infected with HIV, despite the fact that young people between the ages of 13 and 24 represent a growing percentage of new infections.

An image from NIDA's "Text Message" public service announcement

NIDA has formed a coalition with organizations including the American Academy of Child and Adolescent Psychiatry; the AIDS Alliance for Children, Youth and Families; and the United Negro College Fund Special Programs Corporation to get this important message about the link between drug abuse and HIV infection to teenagers and young adults. In addition to the PSA, which will be aired on television stations across the United States, posters advertising NIDA's message— "Drug Abuse and HIV: Learn the Link"—will be displayed on public transportation and buses in Washington, D.C., Chicago, and Dallas.

NIDA's public awareness campaign also includes a recently launched Web site, *www.hiv.drugabuse.gov*, where visitors can browse publications such as the new HIV/AIDS Research Report, download the PSA, and read about the latest scientific findings on the relationship between drug abuse and HIV infection.

MTF Survey Finds Overall Decline in Teen Substance Abuse

Substance abuse among teenagers in the United States declined 19 percent over the past 4 years, with 15.8 percent reporting past-month abuse in 2005, compared with 19.4 percent in 2001, according to the latest Monitoring the Future Survey. The nationwide survey of 8th-, 10th-, and 12th-graders found that the overall decline was tempered by increases or unchanged rates of abuse of some prescription drugs, inhalants, and other substances.

The 4-year decline has been driven largely by decreasing rates of marijuana abuse. For example, since 2001, past-month abuse of marijuana fell by 28 percent among 8th-graders and by 23 percent among 10th-graders. Although most year-to-year changes in the annual survey are not statistically significant, teen abuse of five substances—GHB, LSD, MDMA/Ecstasy, methamphetamine, and steroids—showed significant declines from 2004 to 2005.

The survey findings are encouraging because teenagers are most vulnerable to the effects of drugs and youths who abstain in their teen years are less likely to abuse drugs later in life, NIDA Director Nora D. Volkow, M.D., says. She notes, however, that teens' abuse of prescription medications and inhalants has continued unabated in the past few years. NIDA is particularly concerned about the nonprescribed use of opioid painkillers, such as OxyContin and Vicodin. In 2005, 9.5 percent of 12th-graders reported abusing Vicodin in the past year, and 5.5 percent reported OxyContin abuse, which has increased more than one-third since 2002. "Using these drugs without a prescription is dangerous. It's imperative that teens get this message," Dr. Volkow stresses.

Abuse of inhalants, which are found in common household substances such as nail polish remover, glue, and cleaning fluids and are very toxic, also has been rising in recent years. Abuse among eighth-grade students has increased significantly since 2002, Dr. Volkow says.

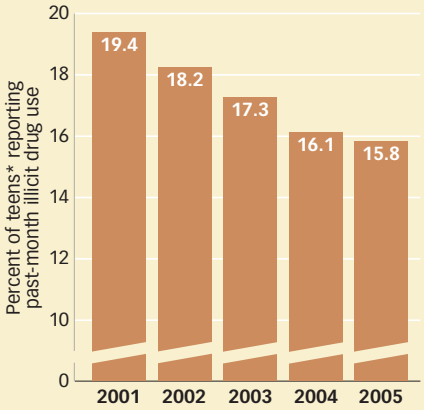
SMOKING DECLINE MAY BE TAPERING OFF

Dr. Lloyd Johnston of the University of Michigan, the principal investigator of the study, notes a worrisome signal that the decline in smoking may be tapering off: The smoking rate among eighth-graders held steady in the latest survey, following a long-term decline over the past several years. Eighth-graders are considered an important bellwether of drug-related trends among teenagers. Moreover, smoking declines in the upper grades also slowed in 2005. Survey data do not indicate long-term declines in the abuse of marijuana and other illicit drugs among 8th-graders, and declines among 10th- and 12th-grade students were very modest, Dr. Johnston notes.

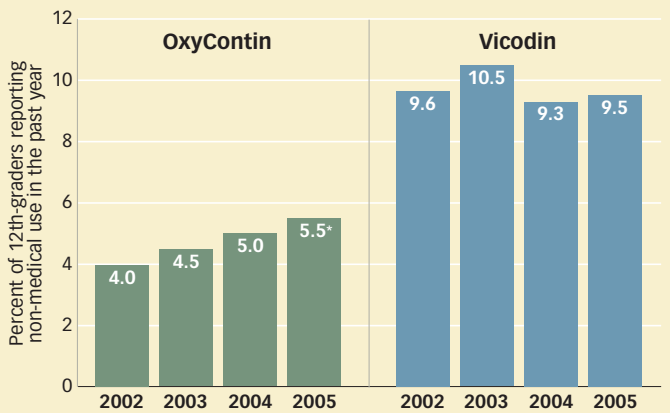
On the positive side, cigarette smoking is at its lowest rate in the 30-year history of the survey. Also, the proportion of eighth-graders reporting that they have ever tried to smoke cigarettes declined in the latest survey, which could reflect shifts in behaviors and intentions that occurred several years earlier.

The survey covered about 50,000 students in more than 400 public and private schools. The University of Michigan conducted the survey under a grant from NIDA, the National Institutes of Health, and the Department of Health and Human Services. Further details on the survey are available at *www.drugabuse.gov/DrugPages/MTF.html* and at *monitoringthefuture.org*.

ILLICIT DRUG USE DROPS AMONG TEENS, BUT NONPRESCRIPTION USE OF PAINKILLERS REMAINS A CONCERN While overall substance abuse among teenagers in the United States declined 19 percent over the past 4 years, abuse of prescription opioid painkillers such as OxyContin and Vicodin has continued unabated.



* 8th, 10th, and 12th grades combined.
SOURCE: University of Michigan, 2005 Monitoring the Future Survey.

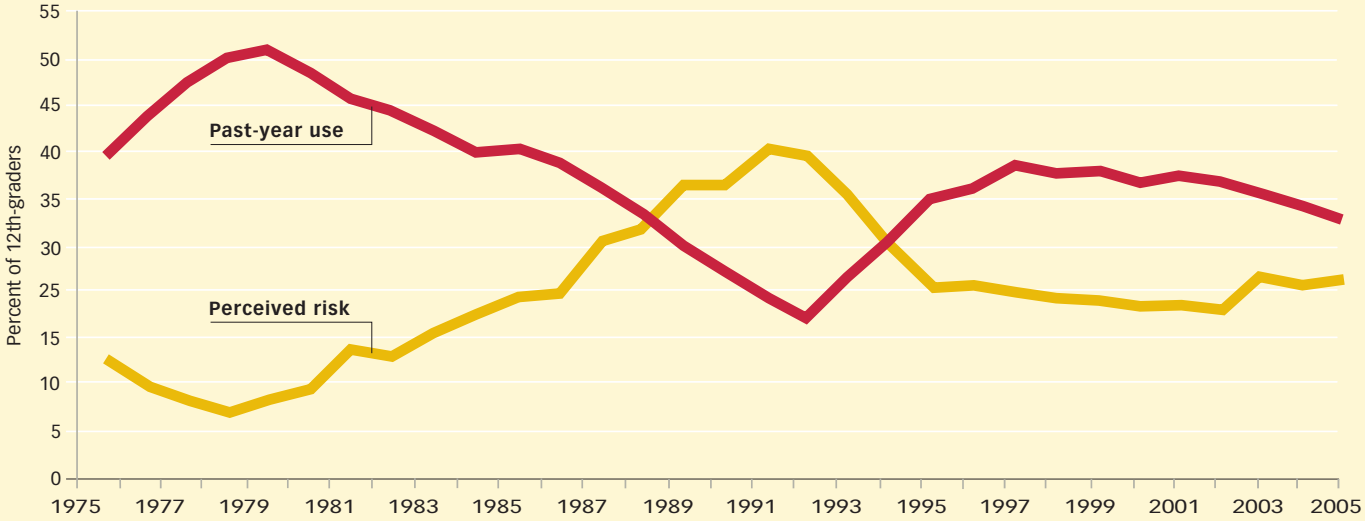


* Increase in the abuse of OxyContin by 12th-graders between 2002 and 2005 was significant.
SOURCE: University of Michigan, 2005 Monitoring the Future Survey.

WHAT THE NUMBERS SAY

Abuse Drops When High School Seniors View Marijuana as Dangerous

The graphic shows the relationship between two trends identified in the annual Monitoring the Future Survey of 12th-graders. The annual prevalence of marijuana abuse by high school seniors falls when the perceived harmfulness of marijuana use rises, and vice versa.



SOURCE: University of Michigan, 2005 Monitoring the Future Survey.

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