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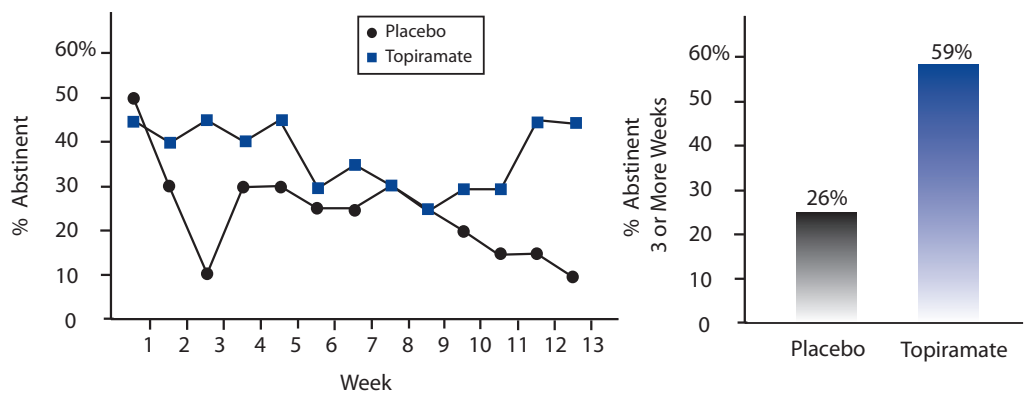
Topiramate Shows Promise in Cocaine Addiction

By Lori Whitten, *NIDA NOTES* Staff Writer

In a small pilot study, topiramate—a medication currently used to treat seizure disorders—has helped cocaine-addicted outpatients stay off the drug continuously for 3 weeks or more. That may not seem like a long time, but previous research has shown that outpatients who avoid relapse for 3 to 4 weeks during treatment with behavioral therapy and medication have a good chance of achieving long-term cessation. In other clinical trials topiramate has helped prevent relapse to alcohol and opiate addiction; these new results with cocaine add to hopes that it may prove a versatile treatment medication for several drugs of abuse.

Topiramate Helps Outpatients Abstain From Cocaine



In almost every week of the study, more patients were abstinent in the topiramate group than in the placebo group. Of the 40 participants in the study, more patients taking topiramate achieved 3 or more continuous weeks of abstinence from cocaine.

Dr. Kyle M. Kampman and colleagues at the University of Pennsylvania School of Medicine and the Veteran Affairs Medical Center in Philadelphia treated 40 crack-cocaine-smoking outpatients, mostly African American males, for 13 weeks at the University of Pennsylvania Treatment Research Center (TRC). All participants met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for cocaine dependence. They were typical of the chronic, relapsing abusers who seek treatment at the TRC: They abused cocaine an average of 10 years, preferring crack to the powder form, and demonstrated the average level of drug-related problems. However, participants' abuse was atypical in one way; they were on the "milder end of the addiction severity spectrum measured by cocaine withdrawal symptom severity and days of abuse and money spent on cocaine," says Dr. Kampman. On average, participants abused cocaine 6 to 8 days and spent $300 to $500 on the drug in the month before treatment compared with the 10 to 13 days and $400 to $600 reported by most patients at the facility. Because topiramate exacerbates cocaine withdrawal symptoms, the investigators selected patients who were able to attain at least 3 days of self-reported abstinence immediately before starting

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NIDA News and Information at Your Fingertips

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- Publications (including *NIDA NOTES*)
- Calendar of Events
- Links to NIDA Organizational Units
- Funding Information
- International Activities
- Links to Related Web Sites

NIDA Addresses Disparities in the Impact of Drug Abuse and Addiction

By NIDA Director Nora D. Volkow, M.D.

NIDA has developed a Health Disparities Initiative that will help uncover the reasons why minority populations incur serious health and social problems related to drug abuse at far higher rates than White abusers. African Americans and Hispanics represent roughly 11 percent and 12 percent, respectively, of the U.S. population and similar proportions of the drug-abusing population. Yet African Americans account for 50 percent and Hispanics 23 percent of injecting drug users diagnosed with HIV. Minority drug abusers also have disproportionately elevated rates of other illnesses—hepatitis B and C and tuberculosis, for example—that result from injection drug abuse. And African American cocaine abusers develop more severe drug-related cardiovascular disease than do White cocaine abusers.

The disproportionate representation of African Americans in the criminal justice system as a consequence of drug abuse is another important disparity. The U.S. prison population nearly doubled between 1990 and 2000, and research suggests that about 75 percent of the increase is drug related. African American males, who are nearly 8 times more likely to be incarcerated than White males, make up roughly 42 percent of the male prison population. African Americans constitute 45 percent of the female prison population, and female offenders are twice as likely as male offenders to be infected with HIV.

As part of its Health Disparities Initiative, NIDA recently announced an opportunity for supplemental research support for NIDA-funded scientists to investigate the reasons for minority involvement in drug abuse and criminal activity, and the impact of imprisonment and criminal justice supervision on drug use, continued criminal behavior, and HIV risk. Other projects supported through the Initiative will strengthen the institutional infrastructure for conducting research within minority populations, provide the scientific foundation for improved prevention and treatment for racial and ethnic groups at highest risk for drug abuse, and disseminate information about health disparities to the research community, minority populations, and the public.

Build Research Capacity. To conduct scientifically valid research into health disparities we need well-trained minority scientists in the research infrastructure. Our Initiative will continue support of the NIDA Intramural Research Program's Minority Recruitment and Training Program, and our Research Supplements for Underrepresented Minorities. NIDA will also continue support for programs such as the National Hispanic Research Network, which conducts workshops, conferences, and other programs that foster the development of Hispanic scientists.

Focus the Research Agenda. Over the next 5 years, the Initiative will support research that adds depth and detail to our picture of drug abuse and its consequences in racial and ethnic minority populations. This effort will help epidemiologists sample and provide statistically accurate descriptions of hard-to reach populations such as Pacific Islanders, Native Americans, and Hispanic subgroups such as Mexicans and Puerto Ricans. We also will support research in the science behind different responses to drugs and drug abuse in specific populations. Does the high preference for menthol cigarettes among African American compared with White male smokers contribute to their 40 percent higher death rate from lung cancer or poorer (35 percent v. 50 percent) success rate when they try to quit smoking? If biologically based differences lead to such disparities, they might also suggest a path to the discovery of new treatments, including tailored medication or prevention strategies. The Initiative will assure that minority populations are fully represented in treatment research. NIDA's Clinical Trials Network will include minority groups in the development of its protocols for evaluating pharmacological and behavioral treatments for addiction and abuse.

Disseminate Research Information. NIDA understands the importance of making research results available to the widest possible audience. We currently produce Spanish language versions of NIDA's science-based treatment and prevention information and, under the new Initiative, NIDA will intensify efforts to engage community leaders, educators, and service providers in helping to identify mechanisms for further dissemination. Communication with minority groups will range from simple translation of published information, to convening national conferences on drug abuse, to addiction research that focuses on minority populations.

NIDA's Health Disparities Initiative will bring us closer to the goal of effective prevention and treatment for everyone at risk of drug abuse, regardless of race, ethnicity, or socioeconomic status. NN

Save the Date: NIDA will host its second health disparities conference, "Bridging Science and Culture to Improve Drug Abuse Research in Minority Communities," October 24-26, 2005, at the Hyatt Regency in Atlanta, Georgia. Travel awards will be available. For more information, please contact LeKhessa Doctor at *ldoctor@nida.nih.gov*.

A Single Cocaine "Binge" Can Establish Long-Term Cue-Induced Drug-Seeking in Rats

By Lori Whitten, *NIDA NOTES* Staff Writer

When people abuse a drug, they learn to associate its pleasurable effects with the surroundings in which they experience them. This learning plays a major role in addiction. Former drug abusers find that even after years of successful abstinence, they may experience intense cravings upon encountering people, places, and things that were present during their drug-taking.

Researchers have been trying to understand how the brain forms such associations and how cues motivate drug-seeking. Until now, scientists have generally assumed that many pairings of drug use and environment are needed to establish drug-cue learning, but Dr. Friedbert Weiss and his colleagues at The Scripps Research Institute in La Jolla, California, recently showed otherwise. In a NIDA-funded animal study, they demonstrated that rats can acquire such long-term learning in the space of a single 2-hour session of access to cocaine. The rapid formation of drug-cue associations seems exceptional; the investigators also demonstrated that in contrast to cocaine, sweetened condensed milk—a food rats find highly palatable—does not produce persistent effects after a one-time exposure.

The investigators chose white noise as the cue they would pair with cocaine and then test. To begin, they placed rats in a special learning chamber where white noise signaled cocaine availability and pressing a lever produced an intravenous infusion of the drug. During a 2-hour session, the rats could press the lever freely; the only restriction on their cocaine intake was a 20-second time-out after each infusion to prevent overdose. On average, each rat pressed the lever 43 times.

The researchers hypothesized that during this initial session, the rats learned to seek out the cocaine experience and the rats' brains established a link between white noise and the drug experience similar to the environmental cues learned by people addicted to cocaine. Their next experimental step would put the rats into a state corresponding to abstinence in a former cocaine abuser. To accomplish this, they returned the animals to the test cage, now with the white noise turned off and the lever disconnected from the infusion device. The rats obtained nothing when they pressed the lever that previously had delivered cocaine, and they gradually gave up. When a rat had pressed the lever five or fewer times in three consecutive 1-hour sessions, the researchers concluded that its drug-seeking behavior was "extinguished." The animal's motivation was not strong enough for it to keep pressing a lever that had not delivered an infusion in many tries.

"...it takes very little experience with cocaine to establish environmental associations that become powerful cues for cocaine relapse..."

In the first two stages of their experiment, Dr. Weiss and colleagues had established white noise as the sole environmental feature in the rats' experience reliably associated with cocaine availability, and the rats had ceased drug-seeking (lever-pressing) behavior. The investigators were now ready to test whether the now "abstinent" rats would respond to white noise by reinstating drug-seeking. Immediately after the rats abandoned lever-pressing, and at 3-month intervals, the researchers returned rats to the test chamber and turned on the white noise. The rats indeed responded by pressing the lever. Moreover, the white noise cue motivated the rats to seek cocaine session after session, even though they never received any, for up to an entire year. In comparison, a different environmental cue associated with saline infusions motivated only a few lever presses throughout the experiment.

"Drug-cue learning has a well-known role in craving and relapse in addicted individuals," says Dr. Weiss. "Our observations demonstrate that it takes very little experience with cocaine to establish environmental associations that become powerful cues for cocaine relapse—and contribute to progression from initial sporadic drug use to addiction."

Food Doesn't Elicit the Same Cue Response

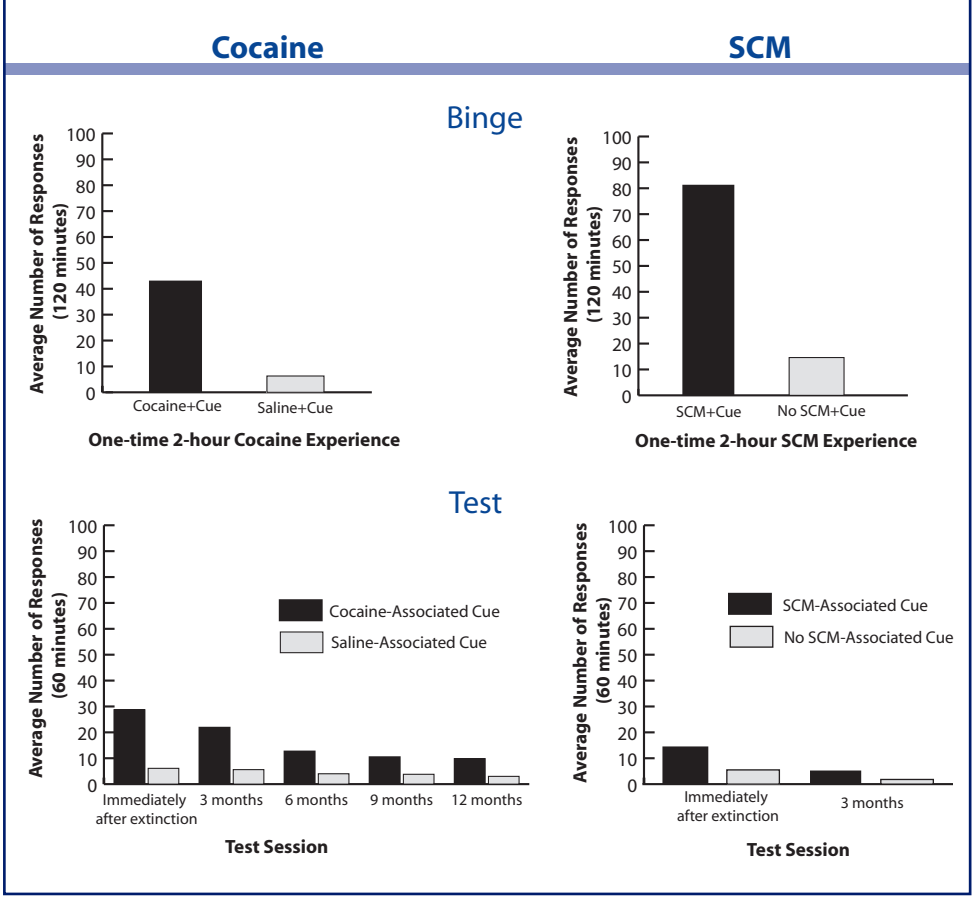
In a second experiment that demonstrated the unique reinforcing power of drugs, Dr. Weiss and colleagues showed that a highly palatable food did not produce persistent motivating effects. Following the same procedures they used in the cocaine experiment, the investigators trained a different group of rats to associate white noise with access to sweetened condensed milk (SCM). During access to SCM, rats pressed the lever 80 times on average. Subsequent sessions in the test cage extinguished the rats' SCM-seeking. The investigators then tested white noise's ability to induce the now "abstinent" rats to resume pressing the lever. It did not, either immediately or 3 months after extinction. The results indicate that a "natural" reinforcer does not have cocaine's ability to produce a long-lasting motivational association in a single session of exposure.

"Clearly, an exceptionally strong association is established when cocaine is paired with a cue," says Dr. Susan Volman of NIDA's Division of Basic Neurosciences and Behavior Research. "This finding is consistent with other evidence that drugs produce especially rapid and long-lasting learning."

Scientists don't yet know the exact neurobiological mechanisms that form learned associations from drug experiences. However, researchers have observed that drugs induce changes in brain cells, or neural adaptations, similar to those underlying normal learning. These adaptations result in a modification of the brain's neural circuitry—the interconnected networks of neurons responsible for behavioral, cognitive, and emotional and motivational processes.

Dr. Volman explains, "Drugs may produce such rapid and long-lasting learning because they have a double effect: They produce intense pleasure that reinforces behavior and they enhance neural adaptations at the same time. These brain changes might underlie sustained drug-directed behavior and the ability of cues to prompt drug-seeking." In future studies, Dr. Weiss and his colleagues intend to address the physiological mechanisms underlying the different behavioral responses to drugs and to natural reinforcers.

Study Underscores Power of Cocaine Cues to Re-Induce Drug-Seeking In Rats



Up to a year after a 2-hour session of free access to cocaine, rats responded more strongly to a cue paired with cocaine versus the control, a saline-associated cue. In a second experiment, a 2-hour session of free access to a desired food—sweetened condensed milk (SCM)—produced no such long-lasting cue responsiveness.

> ***"...an exceptionally strong association is established when cocaine is paired with a cue."***

Source:

•Ciccocioppo, R.; Martin-Fardon, R.; and Weiss, F. Stimuli associated with a single cocaine experience elicit long-lasting cocaine seeking. *Nature Neuroscience* 7(5):1-2, 2004. NN

Topiramate Shows Promise in Cocaine Addiction

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the trial and who, based on their level of addiction, were not likely to enter severe withdrawal. Dr. Kampman says that about 40 percent of patients treated at the TRC experience relatively mild withdrawal symptom severity.

After a 1-week baseline period, Dr. Kampman's team gave topiramate to 20 study participants, and placebo to the other 20. To avoid potential topiramate side effects, including sedation and slurred speech, they initiated treatment with 25 mg/d and increased it by 25 mg/d every week to 200 mg/d. They maintained this maximum dose during weeks 8 through 12, then tapered to zero during week 13. The patients also received cognitive behavioral coping skills therapy twice weekly throughout the study. The researchers verified cocaine abstinence two times a week with urine tests.

By the end of the 13th week, almost 60 percent of patients taking topiramate attained 3 or more weeks of continuous abstinence from cocaine compared with 26 percent of those taking placebo. All 40 patients showed improvement from week 1 to week 13, as reflected by lower Addiction Severity Index (ASI) scores. Patients taking the medication improved more, with average scores in the topiramate group falling by 69 percent, from 0.210 to 0.066, compared with 50 percent, from 0.162 to 0.081, in the placebo group. Dr. Kampman says the improvement in ASI scores reflects fewer days of cocaine abuse and patients' perceptions of reduced cocaine-related problems. "Patients saw the improvement in their condition, which is an important part of recovery," he says.

"Patients saw the improvement in their condition, which is an important part of recovery."

"Based on our findings and other work showing this medication's effectiveness as a treatment for alcohol and opiate addiction, topiramate appears to have great potential as a relapse prevention medication for people who have achieved initial abstinence from cocaine," says Dr. Kampman.

Possible Mechanisms

All addictive drugs deliver pleasurable effects by enhancing the neurotransmitter dopamine in the mesocorticolimbic pathway—areas of the brain involved in reward and motivation. Topiramate seems to change the brain's response to cocaine by indirectly influencing dopamine through two other neurotransmitter systems—gamma aminobutyric acid (GABA) and glutamate. Animal studies have suggested to scientists that either activating GABA-producing neurons or blocking glutamate receptors would lessen craving in cocaine-addicted human subjects. "Topiramate does both simultaneously, a unique dual action that appears to underlie its promise as a relapse prevention medication," says Dr. Kampman.

"These are preliminary results, but researchers are very excited about the potential topiramate has shown as a treatment for a range of problems, including addiction to several drugs and some impulse control disorders," says Dr. Frank Vocci, director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. In addition to its initial successes in preventing relapse in patients with alcohol, opiate, and now cocaine addiction, animal studies have suggested it may attenuate nicotine addiction. "Topiramate may prove an effective treatment for patients who are addicted to multiple drugs," Dr. Vocci adds.

"Topiramate may prove an effective treatment for patients who are addicted to multiple drugs."

Dr. Kampman plans additional studies to further evaluate topiramate as a treatment for cocaine addiction. In addition to confirming the present results, obtained with African American male crack smokers, the medication must be tried in other racial groups, women, and powder-cocaine abusers. Dr. Kampman and his colleagues also plan to study topiramate therapy for patients with coexisting cocaine and alcohol addiction—a group that comprises half of people treated for cocaine abuse.

Source:

•Kampman, K.M., et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug and Alcohol Dependence* 75(3):233-240, 2004. NN

Inhalant Abuse Disorders Tied to Cluster of Adolescent Behavior Problems

By Lori Whitten, *NIDA NOTES* Staff Writer

Two million teenagers in the United States have sniffed or inhaled a substance such as glue, gasoline, solvents, nitrous oxide, or spray paint to get high. Most young people who engage in this dangerous practice give it up over time, but a minority go on to develop serious problems with inhalants, greatly increasing the chances of permanently damaging their health. In a recent study of survey data, NIDA-funded investigators showed that the youths who progress to regular inhalant abuse and dependence tend also to exhibit a set of other problematic behavioral characteristics.

Dr. Li-Tzy Wu of RTI International in North Carolina, and her colleagues Dr. Daniel Pilowsky at Columbia University in New York City, and Dr. William Schlenger at RTI International, analyzed data on 36,859 teens aged 12 to 17 drawn from the combined 2000 and 2001 National Household Surveys on Drug Abuse (NHSDA). They found that adolescents with inhalant abuse diagnoses were likelier than others to have already abused these drugs by age 13 or 14 and to have abused two or more other drugs besides inhalants in the year prior to being surveyed. These youths also were more likely to have serious coexisting problems, such as a history of delinquent acts—for example, stealing, fighting, and carrying a handgun—and to have used mental health services for nondrug issues (see "Adolescent Inhalant Abuse More Likely in the Presence of Specific Behaviors"). Based on the characteristics they identified, the investigators concluded that adolescents with inhalant abuse disorder or dependence make up a subgroup of highly troubled youths with multiple vulnerabilities. The study did not identify any cause of this vulnerability, but it did paint a picture of youths with many problems.

"Although the kids who abuse inhalants seem to have other drug abuse, emotional difficulties, and delinquent behaviors, the cross-sectional design of this study means we can't say which came first—inhalant abuse or other problems. Longitudinal research is needed to identify the sequence and nature of behaviors involved in inhalant use disorders," says Dr. Pilowsky.

Overall, the NHSDA data showed that 9 percent of teenagers had abused an inhalant at least once. Inhalant abuse was most common among adolescents who were older than 14, residents of rural areas, or of Native American or multiethnic heritage. Girls were just as likely as boys to have abused inhalants—an unusual pattern with drugs of abuse. "Boys tend to get involved with drugs more than girls. Inhalants seem to be a notable exception," says Dr. Lynda Erinoff of NIDA's Division of Epidemiology, Services and Prevention Research. Boys' overall higher likelihood of involvement with drugs may relate to their more frequent exposure to situations in which these substances are available. Inhalants may be an exception because boys and girls have the same level of access to them—many inhalants are found in common household products, such as nail polish remover, cleaning fluids, toxic marking pens, and lighter fluid.

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Adolescent Inhalant Abuse More Likely in the Presence of Specific Behaviors

Characteristic	Probability of Abuse Disorder*, times more likely	Probability of Dependence Disorder*, times more likely
Age of first inhalant abuse 13-14 v. 15-17	Not more likely	5
Abuse of three inhalants v. one	4	3
Weekly inhalant abuse v. less-frequent use	2	4
Past-year delinquent behaviors three v. none	6	3
Past-year abuse/dependence of illegal drugs		
two other drugs v. no abuse	5	12
three other drugs v. no abuse	18	24
Past-year use of mental health services for nondrug problems v. no service use	2	4

**As defined by the DSM-IV. Abuse disorder is defined as having one or more drug-related problems in the past year, but not meeting the criteria for dependence; dependence disorder is defined as having three or more drug-related problems in the past year.*

Particular characteristics are associated with increased likelihood of inhalant abuse or dependence among young people who abused an inhalant once in the past year.

Nicotine Withdrawal Linked to Disrupted Glutamate Signaling

By Patrick Zickler, *NIDA NOTES* Staff Writer

More than a third of America's 46 million adult smokers try to stop each year, but fewer than 10 percent succeed. Some relapse because they cannot tolerate the discomfort and craving associated with nicotine withdrawal. In recent animal studies, NIDA-supported scientists identified sites on some brain cells that appear to be key promoters of the negative psychological symptoms of nicotine withdrawal. The sites, called glutamate receptors, are part of the communication network that uses the neurotransmitter glutamate as a chemical messenger.

Neurobiologists have previously shown that glutamate helps produce the good feelings smoking causes. When nicotine attaches to receptors on cells in the brain's ventral tegmental area (VTA), the cells release glutamate, which in turn triggers other VTA cells to release dopamine, a neurotransmitter that produces pleasure. Dr. Athina Markou of The Scripps Research Institute (TSRI) in La Jolla, California, and colleagues reasoned that just as glutamate surges caused by nicotine give rise to smoking pleasure, glutamate depletion related to nicotine abstinence might underlie the displeasure of withdrawal. The researchers speculated that when nicotine is withdrawn after chronic use, the feedback system that restores glutamate to normal levels following surges could overshoot its mark, resulting in a glutamate dearth—and symptoms of depression and irritability.

To test this idea, Dr. Markou and Dr. Paul Kenny at TSRI, along with Dr. Fabrizio Gasparini of Novartis Institutes for Biomedical Research in Basel, Switzerland, focused on a specific group of glutamate receptors called group II metabotropic glutamate (mGluII) receptors. These inhibitory receptors are key components of the glutamate feedback system: They detect high glutamate levels and signal glutamate-producing cells to reduce their activity to bring the levels back down. Inactivating the mGluII receptors interrupts this process, leaving glutamate levels high. The researchers hypothesized that if they inactivated rats' mGluII receptors while subjecting the animals to nicotine withdrawal, the plunge in glutamate levels may be avoided, and the animals' withdrawal symptoms attenuated.

The scientists implanted tiny pumps under the skin on the backs of adult male rats. The pumps dispensed a nicotine solution that maintained high nicotine levels equivalent to those produced in a human who smokes 30 cigarettes per day. After the rats had been exposed to nicotine for 7 days, the investigators removed the pumps, depriving the animals of nicotine and thus leading to nicotine withdrawal. Then, after 18 hours of withdrawal, half the rats were injected with a chemical that blocks the action of mGluII receptors, in effect switching off the inhibitory feedback signals to the glutamate-producing cells. Over the next 72 hours the scientists evaluated the rats at regular intervals using a technique, called intracranial self-stimulation (see "Asking a Rat, 'How

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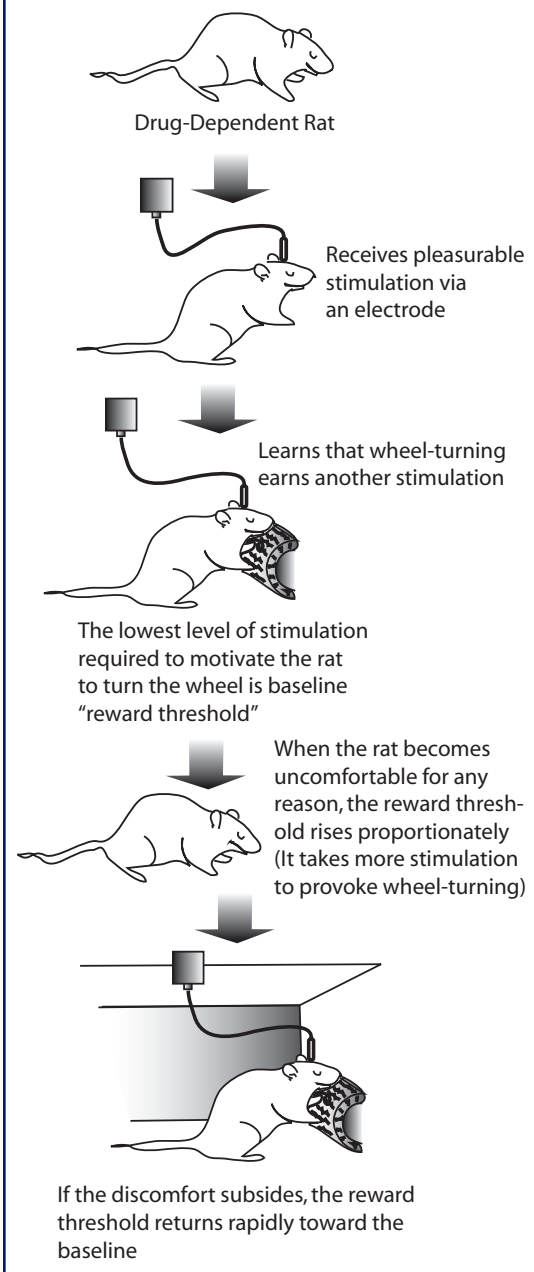
Asking a Rat, "How Do You Feel?"



Dr. Athina Markou and her colleagues used this experimental technique, known as intracranial self-stimulation, to assess animals' discomfort from nicotine withdrawal and evaluate the role of mGluII receptors in withdrawal.

Nicotine Withdrawal Linked to Disrupted Glutamate Signaling

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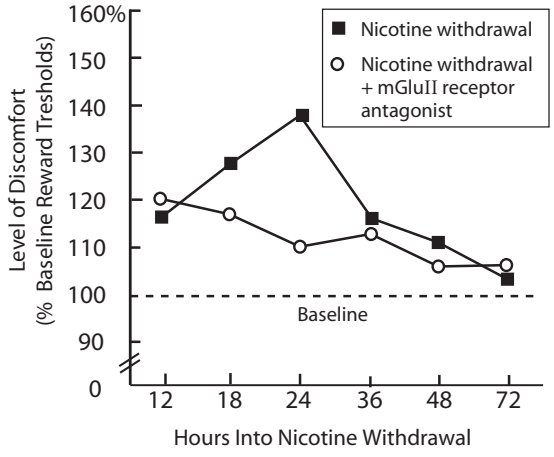
Do You Feel?'"), that measures withdrawal-like depression in laboratory animals. As the scientists had predicted, the rats with active mGluII receptors exhibited significant discomfort; the withdrawal discomfort rapidly dissipated in those in which mGluII receptors were turned off.

To help confirm the association between mGluII receptors and withdrawal-like symptoms, Dr. Markou's team treated nicotine-dependent rats with a compound that stimulates the same receptors. In these animals, activation of the inhibitory glutamate loop triggered discomfort comparable with that in nicotine withdrawal.

"Other research has shown how nicotine changes regulation of excitatory glutamate signaling," Dr. Markou says. "Our study helps explain how nicotine also commandeers inhibitory glutamate circuits. The altered function of the mGluII receptors appears to mediate, at least partly, the depression-like aspects of nicotine withdrawal." The effect, she explains, is a carrot-and-stick influence strong enough to thwart the most sincere attempts to quit smoking. "Nicotine provides a positive effect through the excitatory circuits, making smoking a rewarding and reinforcing experience. Now we see that nicotine has a similarly powerful aversive effect through the inhibitory circuits, making withdrawal an unpleasant experience."

The role of mGluII receptors in withdrawal suggests that these receptors might also offer a target for therapeutic intervention, Dr. Markou adds. "Easing the depression-like aspects of withdrawal would significantly decrease discomfort and make it easier for people to maintain abstinence and resist the temptation to relapse to smoking."

Blocking an Inhibitory Glutamate System Reduces Discomfort of Nicotine Withdrawal in Rats



Rats that had been exposed to nicotine for 7 days showed discomfort 12 hours after withdrawal from nicotine. Rats that were injected, at 18 hours into withdrawal, with a compound that blocked mGluII receptors showed no increase in withdrawal-associated discomfort. (Discomfort measurement technique is described in "Asking a Rat, 'How Do You Feel?'" on page 8). Untreated rats experienced increasing discomfort through 24 hours of withdrawal.

Source:

•Kenny P.J.; Fabrizio, G.; and Markou, A. Group II metabotropic and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)/kainate glutamate receptors regulate the deficit in brain reward function associated with nicotine withdrawal in rats. *Journal of Pharmacology and Experimental Therapeutics* 306(3):1068-1076, 2003. NN

Marijuana-Related Disorders, but Not Prevalence Of Use, Rise Over Past Decade

By Patrick Zickler, *NIDA NOTES* Staff Writer

More Americans suffer from marijuana-related disorders now than a decade ago, even though the prevalence of marijuana smoking has not increased. Survey results from 2002, compared with data from a decade earlier, showed that overall, rates of marijuana consumption in adults 18 and older held relatively steady at 4 percent of respondents. However, rates of marijuana-related disorders—discrete conditions defined according to criteria established by the American Psychiatric Association—increased from 1.2 percent to 1.5 percent of respondents, or from 30.2 percent overall to 35.6 percent among marijuana smokers. The increase was particularly sharp among young adult black men and women aged 18-29, among whom marijuana consumption rose only modestly while the prevalence of disorders tripled. Rates of marijuana-related disorders among Hispanic men in the same age span also increased sharply despite only a moderate increase in their rate of marijuana smoking.

"The rise in marijuana-related disorders means that there were approximately 800,000 more adults in the United States with marijuana abuse or dependence in 2002 than a decade earlier," says Dr. Wilson Compton of NIDA's Division of Epidemiology, Services and Prevention Research. "In the 1992 survey, these problems were more common among Whites than among minorities, but in 2002 the differences in rates among the different ethnic groups had narrowed, in large part because of a rate that more than tripled among young African American men and women and more than doubled among young Hispanic men."

Dr. Compton and colleagues at NIDA, and Dr. Bridget Grant and colleagues at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), evaluated data from two large, national epidemiologic surveys—the National Longitudinal Alcohol Epidemiologic Survey (NLAES), conducted in 1991-1992, and the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), conducted in 2001-2002. Both studies define abuse and dependence using criteria that match the diagnostic standards found in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV); see "Defining Marijuana-Related Disorders."

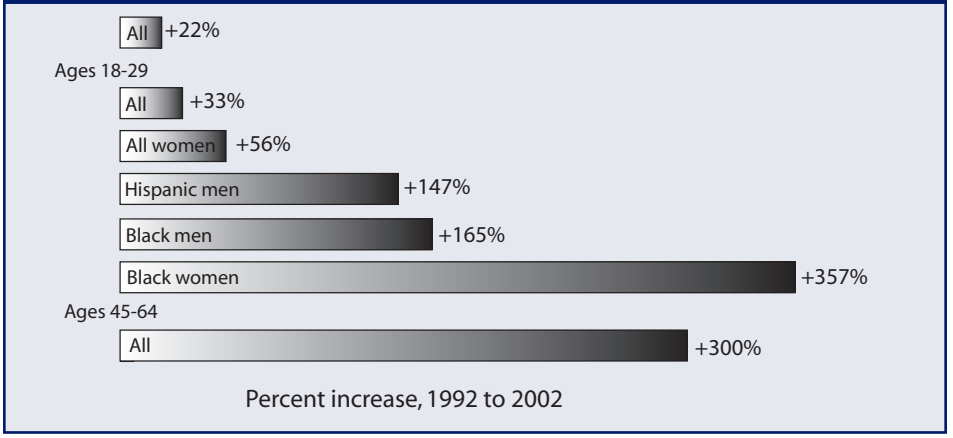
The study also reveals a shift in marijuana use and its associated problems among older adults, Dr. Compton says. "Marijuana smoking increased by 167 percent and the prevalence of marijuana-related disorders quadrupled among men and women aged 45 to 64," he observes. "Given this shift, the possibility that marijuana may contribute to health problems among the aging population deserves research attention."

The surveys do not explain why disorders increased in some groups and not in others. However, increased potency of marijuana in the last decade may be partly responsible for the overall upward trend of marijuana-related disorders, the researchers speculate. Regardless of the causes, the sharp increases among minority groups merit further investigation, Dr. Compton says. "We see what could be described as a possible epidemic of marijuana-related disorders among young adult minorities. It probably has been going on undetected for years, and points to the need for specifically targeted prevention and intervention efforts."

Source:

•Compton, W.M., et al. Prevalence of marijuana use disorders in the United States: 1991-1992 and 2001-2002. *JAMA* 291(17):2114-2121, 2004. NN

Older Americans, Young Blacks, and Hispanic Men Show Largest Increases in Rates of Marijuana-Related Disorders



Survey data collected 1991-1992 and 2001-2002 show little increase over the decade in rates of marijuana smoking, but overall prevalence of marijuana-related disorders increased by 22 percent. Increases in a few demographic groups accounted for most of this increase.

Defining Marijuana-Related Disorders

"Although the American Psychiatric Association's DSM-IV was not published until 1994, proposed diagnostic criteria for marijuana abuse and dependence had been circulated earlier," says Dr. Bridget Grant of NIAAA, who was the principal investigator of the National Longitudinal Alcohol Epidemiologic Survey fieldwork and, a decade later, in the National Epidemiologic Survey on Alcohol and Related Conditions. "These criteria were incorporated in their entirety into the structured interview used in both surveys." Survey respondents were considered to be suffering a marijuana-related disorder if they met DSM-IV diagnostic criteria for either abuse or dependence.

Marijuana abuse

A respondent had to report experiencing at least 1 of the following 4 criteria in the 12 months preceding the survey:

- Recurrent marijuana use resulting in failure to fulfill major role obligations;
- Recurrent marijuana use in physically hazardous situations;
- Recurrent marijuana-related legal problems; and
- Continued use despite recurrent or persistent social or interpersonal problems caused or exacerbated by marijuana use.

Marijuana dependence

This disorder's diagnosis required respondents to report past-year experience of at least 3 of the following 6 criteria:

- Need for increased amounts of marijuana to achieve desired effect;
- Use of marijuana in larger amounts or over longer periods than intended;
- Persistent desire or unsuccessful efforts to cut down marijuana use;
- A great deal of time spent obtaining, using, or recovering from the effects of marijuana;
- Giving up important social, occupational, or recreational activities in favor of using marijuana; and
- Continued use despite persistent or recurrent physical or psychological problems caused or exacerbated by use. NN

Inhalant Abuse Disorders Tied to Cluster of Adolescent Behavior Problems

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A relatively small number (0.2 percent) of the survey respondents met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for inhalant abuse disorder or dependence. Among youths who had abused inhalants in the past year, 6 percent had abuse disorder and 4 percent were dependent. Many (60 percent) past-year inhalant abusers said they abused more than one substance. It was not uncommon for these youths to report abusing inhalants weekly or more often (20 percent) and for more than a year (35 percent).

Understanding the prevalence of inhalant abuse and identifying characteristics of young people with serious inhalant problems are initial steps in the design of prevention and treatment interventions. Teenagers who abuse inhalants may do so under the mistaken assumption that common household products are not addictive or harmful. Less than half of eighth-graders perceived trying inhalants once or twice as a "great risk," according to the 2004 Monitoring the Future (MTF) survey, an annual NIDA-funded study of drug abuse among 8th-, 10th-, and 12th-graders. In fact, inhalants act on the same brain areas and neurotransmitter systems as cocaine, amphetamines, and other addictive drugs (see "Dopamine Enhancement Underlies a Toluene Behavioral Effect," *NIDA NOTES*, Vol. 19, No. 5, p. 4). Along with the risk of addiction, inhaling these chemicals occasionally can cause deaths from heart failure or suffocation. Regular abuse can cause damage to the brain, liver, kidneys, lungs, and heart.

Inhalant abuse among high school students peaked in 1995, when, for example, almost 22 percent of eighth graders sampled reported having abused an inhalant. That year, the Partnership for a Drug-Free America conducted an anti-inhalant media campaign highlighting the health consequences of inhalant abuse. Getting information about the dangers of inhalant abuse and signs of addiction to parents, teachers, and teenagers appears to have had positive results: Abuse of these substances decreased substantially among all three grades after 1995, according to the MTF survey. Trend analysis indicates that the percentage of teens who have abused inhalants fell from 15.6 to 14.2 percent between 2001 and 2004.

However, the most recent MTF survey suggests that inhalant abuse may be rebounding. In contrast to the decline in overall drug abuse among high school students, past-year inhalant abuse increased from 2003 to 2004 for all students surveyed. Lifetime inhalant abuse among eighth graders increased from 15.8 to 17.3 percent last year. "Although this is not a major change, we should watch these numbers carefully over the next couple of years," says Dr. Erinoff. MTF investigators point out that the number of 8th- and 10th-graders who believe inhalant abuse is dangerous has declined in the past 3 years, which may suggest a need to highlight the dangers in media messages and prevention programs.

Source:

•Wu, L.T.; Pilowsky, D.J.; and Schlenger, W.E. Inhalant abuse and dependence among adolescents in the United States. *Journal of the American Academy of Child and Adolescent Psychiatry* 43(10):1206-1214, 2004.
NN

Drug Abuse Treatment in Adolescents Should Address Co-Occurring Mental Health Problems

By Lori Whitten, *NIDA NOTES* Staff Writer

Adolescent substance abuse patients with co-occurring emotional and behavioral problems are more likely than peers without coexisting psychiatric conditions to relapse in the year following treatment, a NIDA-funded study has found. "We must improve identification of co-occurring psychiatric disorders among substance-abusing teens and move away from a 'one size fits all' approach to therapy, or treatment gains will remain limited for these vulnerable youth and their families," says Dr. Cynthia Rowe of the University of Miami School of Medicine in Florida, who led the study.

Following 182 adolescents for a year after substance abuse treatment, Dr. Rowe and her colleagues found that those with co-occurring externalizing disorders—a combination of aggressive and delinquent behaviors including persistent lying, stealing, fighting, and destroying property—recovered more slowly than those without psychiatric disorders. Youths with externalizing and internalizing disorders—acting out mixed with anxiety and depression—obtained the least favorable treatment outcomes. Dr. Rowe says this combination of symptoms often relates to multiple problems in life and indicates psychiatric severity—the best predictor of substance abuse treatment outcomes in adults. "Our results mirror those seen in adults: People with more severe psychiatric problems show a significantly diminished response to substance abuse treatments of known effectiveness," says Dr. Rowe.

All the youths had been referred to substance abuse treatment, almost 85 percent by the juvenile justice or child service systems; they ranged in age from 12 to 17 at the beginning of the study. Participants received manualized treatment—cognitive behavioral therapy (CBT) or Multidimensional Family Therapy (MDFT)—in weekly office-based sessions for an average of 10 weeks. At the outset of the study, the participants' reports of substance abuse frequency in the past month averaged 12.7 days; by the end of the treatment, this figure dropped by 2.5 days. Six months after treatment, past-month substance abuse had fallen another 2.5 days; at the 12-month followup, abuse incidence had dropped an additional 2.5 days. The rates and patterns of change, however, varied depending on coexisting psychiatric disorders.

Substance abusers with no co-occurring disorders (12 percent of the study population) showed the best long-term outcomes. Although initially unresponsive to treatment, they markedly and rapidly reduced substance abuse between the 6- and 12-month followups—changing at a rate approximately 1.5 times that of peers with co-occurring externalizing disorders (35 percent of the study population), who also were initially unresponsive to treatment and also recovered. Youth demonstrating mixed externalizing and internalizing symptoms (48 percent of the study population) showed the opposite pattern. Initially improving in response to therapy, they had relapsed to pretreatment levels of substance abuse a year later. The responses did not differ in patients participating in CBT and MDFT. The other 5 percent of substance-abusing adolescents were diagnosed with internalizing disorders only, a group too small to analyze, so the researchers did not include them in the analysis.

Dr. Melissa Racioppo of NIDA's Division of Clinical Neuroscience, Development and Behavioral Treatment says CBT and MDFT are very effective treatments for most adolescent substance abusers (see "Family-Based Treatment Programs Can Reduce Adolescent Drug Abuse," *NIDA NOTES* Vol. 17, No. 4, p. 7). Poorer treatment outcomes among people with co-occurring psychiatric disorders suggest that therapists may need to tailor substance abuse treatment for the patient's particular psychiatric condition, although the necessary level of specificity is not clear. "To adapt treatments for people with co-occurring psychiatric disorders, researchers must link particular therapeutic processes with outcomes," she adds—something that Dr. Rowe and her colleagues plan to do in future studies.

"Looking within the therapeutic process may help us discover what must happen to realize recovery from substance abuse. Effective components of therapy may vary for adolescents with different co-occurring mental health problems, and identifying such mechanisms of change may help us develop better interventions," says Dr. Rowe.

Girls Had More Severe Problems

Most (82 percent) of the study's participants were boys; however, girls were overrepresented in the group with the least favorable treatment outcomes. More girls (83 percent) than boys (44 percent) displayed externalizing and internalizing disorders. Dr. Rowe says the pattern is familiar to clinicians across the country—there are typically more girls among the substance abuse patients with pronounced problems and disorders.

"By the time a girl with substance abuse problems is referred to treatment, she is usually in considerable distress and experiencing severe psychiatric symptoms and relationship problems. Family, school, and legal problems will continue unabated without better identification, referral, and treatment of these vulnerable girls," says Dr. Rowe.

Dr. Racioppo emphasizes the need for more research on differences in how boys and girls develop and manifest behavior problems. Troubled youth often have experienced family conflict and instability in relationships, but boys and girls may react differently. Studies indicate that females tend to turn their stress inward, developing anxiety and depression, which are often unnoticed by adults. Dr. Racioppo says girls tend to act out in ways that don't necessarily grab the attention of adults—through sexual behavior, for example—whereas boys externalize in ways that are more obvious, such as fighting. "To improve identification and treatment outcomes of adolescents with co-occurring psychiatric disorders, we need to study gender differences in the root causes and expression of behavioral and emotional problems," she says.

Source:

•Rowe, C.L.; Liddle, H.L.; Greenbaum, P.E.; and Henderson, C.E. Impact of psychiatric comorbidity on treatment of adolescent drug abusers. *Journal of Substance Abuse Treatment* 26(2):129-140, 2003. NN

Depression Elevates Suicide Risk in Substance-Abusing Adolescents

A recent NIDA-funded study highlights the need for substance abuse counselors to be aware of depression and suicide risk in their adolescent patients. Drs. Thomas Kelly, Duncan Clark, and colleagues at the University of Pittsburgh School of Medicine identified 85 suicide attempters in a series of 503 substance-abusing teenagers studied from 1991 to 2000. Most of the teenagers abused alcohol (88 percent) and marijuana (80 percent). A large majority—87 percent—of those who had attempted suicide were diagnosed with major depression using the *Diagnostic and Statistical Manual, 4th Edition* (DSM-IV) criteria. Among substance-abusing teens who did not attempt suicide, major depression was diagnosed in only 40 percent. Girls were three times more likely to have attempted suicide than boys. Among the attempters, one-third of girls and one-tenth of boys reported multiple attempts—a finding consistent with general patterns of suicidal behaviors.

"Clinicians who work with adolescent substance abusers may not automatically think about suicidal behavior as something to watch for in their clients, but it's definitely a concern—especially for youth with co-occurring psychiatric disorders," says Dr. Lynda Erinoff of NIDA's Division of Epidemiology, Services and Prevention Research. There is an association between substance abuse, co-occurring psychiatric disorders, and suicidal behavior in adults and adolescents, but Dr. Erinoff explains that it's difficult to establish causal factors and sequencing of these problems.

Dr. Clark and his colleagues are pursuing another avenue of research that may provide clinicians with a biological marker to help assess patients' risk of suicidal behavior. In a recent prospective study, Dr. Clark found that depression and low blood levels of tryptophan—an amino acid found in protein-rich foods such as turkey and milk—were associated with increased suicide risk in adolescents who abused alcohol. Other studies have suggested that depleted tryptophan is related to depression and impulsivity, which seem to increase the risk for suicidal behavior. If additional studies corroborate the predictive value of this potential biological marker, clinicians could have a blood test to augment their behavioral assessment that a patient may be at risk for attempting suicide.

Sources:

•Kelly, T.M.; Cornelius, J.R.; and Clark, D.B. Psychiatric disorders and attempted suicide among adolescents with substance use disorders. *Drug and Alcohol Dependence* 73(1):87-97, 2004.

•Clark, D.B. Serum tryptophan ratio and suicidal behavior in adolescents: a prospective study. *Psychiatry Research* 119(3):199-204, 2003. NN

Society for Neuroscience Honors Dr. Antonello Bonci's Research

Dr. Antonello Bonci, a neurologist and electrophysiologist at the University of California, San Francisco, and the Ernest Gallo Clinic and Research Center, received the 2004 Jacob P. Waletzky Memorial Award for Innovative Research in Drug Abuse and Alcoholism. The award was presented at NIDA's "Frontiers in Addiction Research" symposium, October 22, 2004, in San Diego at the annual conference of the Society for Neuroscience.

The $25,000 award recognizes a young scientist for outstanding work that furthers understanding of the effects of substance abuse on the brain and nervous system. Dr. Bonci's work focuses on the long-term changes in brain cells that underlie addictive behaviors. In the Frontiers symposium keynote presentation, Dr. Bonci described his research on cocaine-induced alterations in the ventral tegmental area (VTA). He also highlighted his laboratory's more recent investigations of the VTA's role in stress-related behaviors and presented findings on brain cells in the nucleus accumbens, another region critical in drug abuse.

"Twenty years ago, many would not have believed that such a prestigious honor would recognize drug abuse research. The Waletzky Award indicates the incredible growth of addiction research, which is now a pillar of neuroscience," said Dr. Eric J. Nestler, chairman of the Selecting Committee and a Society Councilor, who presented the award. The 2004 Frontiers symposium program featured 20 presenters and more than 70 posters, attracting about 600 participants. NN

Dr. Antonello Bonci

Dr. Rochelle Schwartz-Bloom Is Recognized for Science Education Contributions

Also at the Society's annual conference, Dr. Rochelle Schwartz-Bloom of Duke University in Durham, North Carolina, received the $5000 annual Science Educator Award, which is presented to an outstanding neuroscientist who has educated the public about the brain and nervous system. Dr. Schwartz-Bloom developed curriculum modules that help high school students learn the biology and chemistry underlying addiction, drug testing, and nerve gas (see "Learning the Science of Drugs Helps Teens Master Biology, Chemistry," *NIDA NOTES* Vol. 19, No. 2, p. 4). She also developed a series of instructional materials that teach and reinforce several basic biology and chemistry concepts using examples from topics that fascinate young people—drugs and addiction.

High school teachers integrate the four modules into the standard science curriculum but can tailor the material to meet particular classroom needs. Students who learned the standard high school science content—including molecular structure, cellular structure, anatomy, physiology, and enzyme action—in the context of drug-related topics have scored higher on tests than those whose science classes did not include the modules.

"The curriculum is very innovative and worthy of recognition. It's founded on the idea that teenagers learn more if they think the course offers information that is relevant to their lives," says Dr. Cathrine Sasek, NIDA's science education coordinator. With funding from NIDA, Dr. Schwartz-Bloom is expanding the curriculum and developing Web-based and teacher training so more students and teachers can benefit. NN

Dr. Rochelle Schwartz-Bloom

Teen Drug Abuse Continues Its Three-Year Decline

Illicit drug abuse among the Nation's youth declined by almost 7 percent from 2003 to 2004, continuing an encouraging trend that began in 2001. At the same time, the latest report from the Monitoring the Future (MTF) survey shows a recent increase in the abuse of inhalants among eighth-graders and the painkiller OxyContin among all students surveyed.

Overall, the trends in the past 3 years have been positive, with a decline in past-month drug abuse among 8th-, 10th-, and 12th-graders combined from 19.4 to 16.1 percent. This reduction translates into roughly 600,000 fewer adolescent drug abusers than in 2001, advancing the goal President George W. Bush set in February 2002 to reduce drug use among youth by 25 percent in 5 years. The 2004 findings emerged from responses provided by nearly 50,000 students in 406 public and private schools across the country. In addition to declines in past-month use, students' past-year use fell from 31.8 to 27.5 percent; their lifetime use dropped from 41.0 to 36.4 percent between 2001 and 2004.

"Drug use is preventable. The overall reduction in drug abuse by America's young people shows the power of partnership among all working to address the problem—from scientists developing basic knowledge to people implementing services in the community to those making policy at all levels," said NIDA Director Dr. Nora D. Volkow. "Our concerted effort to provide students, teachers, and families with accurate information about addiction and drug abuse have had an impact, but we must sustain and advance this work to realize further reductions in drug abuse."

The MTF survey, launched in 1975, measures drug, alcohol, and cigarette abuse and attitudes about use among 8th-, 10th-, and 12th-graders nationwide. Funded by NIDA, the survey has been conducted annually since its inception by the University of Michigan's Institute for Social Research. Now in its 30th year, MTF questions and analyses have changed with informational needs—for example, expanding the list of drugs, analyzing data for all three grades combined, tracking students' attitudes toward drug abuse, and examining the impact of antidrug advertising.

Although generally positive, this year's MTF results for two drugs raise concerns and bear close monitoring. Lifetime abuse of inhalants among eighth-graders increased from 15.8 to 17.3 percent between 2003 and 2004. The survey showed that 8th- and 10th-graders' perceptions of the risks associated with abusing inhalants has declined in the past 3 years, suggesting a need to increase awareness of the potentially dangerous consequences of abusing these often inexpensive and easily obtainable intoxicants. The number of high school students using the painkiller OxyContin without medical supervision increased from 2002 to 2004. Past-year abuse of this drug—an opioid with a high potential for addiction—was disturbingly common at 1.7, 3.5, and 5.0 percent for grades 8, 10, and 12, respectively.

Key substance abuse patterns that emerged between 2001 and 2004 are:

- **Cigarettes.** Smoking among teenagers continues to decline from peak levels in the mid-1990s, although more slowly than in the past 8 years. Lifetime and current abuse of cigarettes declined among 8th-, 10th-, and 12th-graders. Lifetime cigarette abuse dropped 19.5 percent, from 49.1 to 39.5 percent, and current abuse fell 20.3 percent, from 20.3 to 16.1 percent.
- **Marijuana.** Current marijuana abuse declined 18.1 percent, from 16.6 to 13.6 percent; past-year abuse also declined 13.7 percent, from 27.5 to 23.7 percent; and lifetime abuse declined 11.2 percent, from 35.3 to 31.3 percent. In the past 2 years, students' perceived risk of abusing marijuana increased markedly; the proportion of teens reporting that it would be easy for them to get the drug has also declined.
- **Amphetamines.** Abuse of this class of drug without medical supervision has been widespread among youth in the past, but has been gradually declining. Lifetime abuse fell 19.6 percent—from 13.9 to 11.2 percent. Both past-year and current abuse fell as well, from 9.6 to 7.6 percent and from 4.7 to 3.6 percent, respectively.
- **LSD and MDMA (Ecstasy).** Students' abuse of the hallucinogens LSD and MDMA plummeted between 2001 and 2004. Lifetime abuse of LSD fell 55 percent, from 6.6 to 3.0 percent, and past-year and current abuse both dropped by approximately 60 percent.

  Lifetime use of MDMA dropped 40.7 percent, with past-year and current abuse falling by more than half, from 5.5 to 2.5 percent and 2.3 to 0.9 percent, respectively. In the late 1990s and until 2001, the sharp increase in the abuse of MDMA among teens was a concern. Increases in students' perceived risk of abusing the drug preceded the decreases in abuse seen since 2001. NN

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