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In Chronic Drug Abuse, Acute Dopamine Surge May Erode Resolve To Abstain

By Patrick Zickler, NIDA NOTES Staff Writer

In the past few decades, scientists have firmly established that the desire to take drugs has a biological basis in fluctuations in levels of the brain chemical dopamine. Now, a NIDA-supported experiment with laboratory animals strongly suggests that dopamine has a second, different but comparably critical role in prompting individuals to translate that desire into action.

People hanker for drugs largely to re-experience the intense pleasure they recall from past episodes of drug abuse. Much research has shown that this pleasure occurs because drugs of abuse—each by its own pharmacological mechanism—precipitate surges of dopamine in a part of the brain called the nucleus accumbens (NAc). In drug abuse as in other parts of life, however, there is a difference between desiring something and actually taking steps to achieve it. Chronic drug abusers often avoid acting on their drug-seeking urge for long periods. If their resolve to abstain fails, it often does so when they encounter something or someone they associate with past drug-taking. The new study suggests that like drugs themselves, such encounters produce surges in dopamine levels, and these surges push the individual toward active drug seeking and drug taking.

In the experiment, Dr. Regina Carelli and colleagues at the University of North Carolina at Chapel Hill (UNC-CH) exposed male lab rats to cocaine. After the rats demonstrated that they found the drug desirable—by voluntarily pressing a lever to receive doses—the researchers made a series of moment-to-moment measurements of dopamine levels in the animals' NAc. The researchers' key observation was a pair of dopamine spikes before the animals pressed the lever. The first occurred 8 seconds before the lever press; the second began 3 seconds later and peaked roughly 2 seconds after the lever press and drug delivery.

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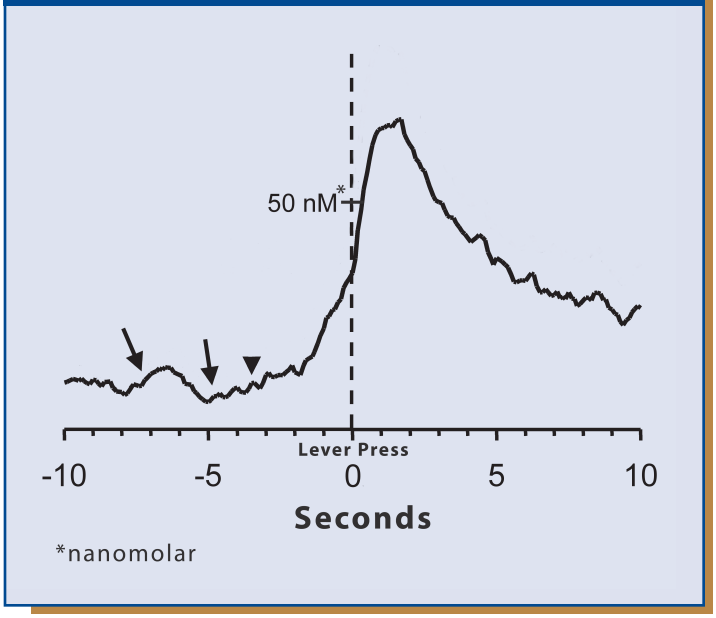
Anticipation of Cocaine Triggers Dopamine Increase in Rats



Rats trained to self-administer cocaine exhibited elevations in dopamine concentrations when they anticipated cocaine and again when they began to seek the drug. Arrows indicate when dopamine levels began to increase; the inverted triangle shows when rats approached the lever that triggered a cocaine infusion.

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NIDA at 30: Committed to Scientific Solutions for Drug Addiction Problems

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

This year, NIDA celebrates 30 years of scientific inquiry marked by tremendous strides in advancing the frontiers of drug abuse research and reducing the suffering, community disruption, and public health costs of drug addiction. In 1974, NIDA was a small institute striving to develop an effective Federal response to a critical public health crisis—burgeoning drug abuse in the United States. Today, the Institute is the world's foremost source of scientific knowledge on the prevention and treatment of the chronic, relapsing brain disorder of drug addiction.

In its first decade, NIDA established national data-collection systems to increase understanding of the nature and extent of drug abuse. In addition to developing a nationwide network of treatment, prevention, and clinical and research training programs, the Institute also initiated a basic science research program that produced groundbreaking discoveries on the brain and its molecular and neurochemical methods of communication. Today, scientists draw on these discoveries to create new medications to treat drug abuse and other mental disorders.

In 1981, a congressional mandate shifted NIDA's primary mission to expanding the borders of scientific knowledge about drug addiction and ensuring that this knowledge be used to prevent and treat the disease. Throughout the 1980s, NIDA-supported researchers mined information on the causes, correlates, and consequences of drug abuse and addiction and generated a range of prevention and treatment approaches for heroin, marijuana, and nicotine abuse and the new threat of crack cocaine. As a result, practitioners today have highly effective opiate and nicotine treatment medications, a range of behavioral treatments for cocaine abuse, and the underlying principles of successful prevention and treatment to use in reducing drug abuse.

In 1986, the Nation once again turned to NIDA, this time for help in addressing the emerging AIDS epidemic. Within a year, NIDA nearly tripled its research on AIDS and drug abuse to address the major role injection drug use plays in transmitting HIV, the virus that causes AIDS. The Institute's massive effort rapidly established AIDS outreach projects around the country, educated out-of-treatment drug users and their sex partners on ways to prevent HIV transmission, and proved that these approaches could reduce the risky drug use and sexual behaviors that were fueling the spread of HIV/AIDS. This body of AIDS research, bolstered by an additional decade of AIDS discoveries, informs the NIDA-promulgated principles of HIV prevention among drug users that now curb the spread of HIV/AIDS.

In 1992, Congress affirmed the importance of NIDA's research to the Nation's public health when it made NIDA part of the National Institutes of Health, the world's premier biomedical research agency. During the ensuing decade, NIDA mounted major new research and communications programs to counter alarming increases in young people's use of methamphetamine, heroin, and "club drugs," such as ecstasy (MDMA). The Institute's basic and clinical research programs applied revolutionary new techniques in molecular biology and brain imaging technologies to rapidly advance understanding of the underlying neurobiological and behavioral processes that increase vulnerability to drug abuse, foster the transition to addiction, and prevent many patients from achieving successful treatment results. At the same time, NIDA launched new initiatives to close the gap between research and practice. As a result, drug abuse scientists and practitioners now are collaborating to improve drug abuse prevention and treatment research and services in communities across America.

With its outriders of mental illness, HIV/AIDS, and hepatitis C; its public health and criminal justice costs; and its devastation of homes and neighborhoods, drug addiction continues to demand a comprehensive research program focused on these problems. NIDA has assembled such a program and remains committed to its purpose—the alleviation of suffering through scientific advance. NN

Cocaine Abusers' Cognitive Deficits Compromise Treatment Outcomes

By Arnold Mann, NIDA NOTES Contributing Writer

Cognitive impairment may be an important factor in explaining treatment failure among cocaine abusers, according to results from a new NIDA-funded study by Dr. Efrat Aharonovich and colleagues at New York's Columbia University. These findings are already leading researchers to modify current treatments for cognitively impaired cocaine abusers, with hopes of improving success rates.

Cognitive-behavioral therapy (CBT) is an effective treatment for cocaine addiction, but dropout rates range from 33 to 64 percent. This study is the first to examine the role of impaired cognition as a contributor to this statistic. The researchers found that patients with impaired attention, learning, memory, reaction time, and cognitive flexibility—all documented consequences of chronic cocaine abuse—were much more likely to drop out of the 12-week CBT program than those not cognitively impaired. In addition, the dropout rate was related to the degree of cognitive impairment, with the more impaired patients more likely to stop treatment.

"These data show very clearly that cocaine abusers with cognitive deficits are most likely to drop out of [CBT] treatment," says Dr. Aharonovich. This is particularly true during the first 4 weeks of treatment, when the dropout rate is highest. Further, she adds, cognitively impaired patients who manage to stick it out beyond the first 4-week course are "most likely not going to do as well" as patients without cognitive deficits.

The impetus for the study, Dr. Aharonovich notes, was realizing that "some patients were coming to sessions and just not 'getting it.' We were losing a lot of patients. I thought maybe we were delivering a treatment that they were receiving but not understanding."

In CBT's one-on-one therapy sessions, the therapist teaches the patient to recognize the connections between the thoughts, feelings, and actions that undermine his or her attempts to become abstinent. Patients are taught to avoid specific situations associated with their drug abuse, to use techniques like "thought stopping" to cope with cravings, and to focus on emotions that may trigger drug use.

"You have to be pretty intact cognitively to really stick with CBT," says Dr. Edward Nunes, a researcher in the study. "This is a therapy that involves a lot of analyzing, thinking ahead, planning, and controlling impulses. If the cognitive functioning is a little off, it's going to make it hard for those patients to thrive in treatment."

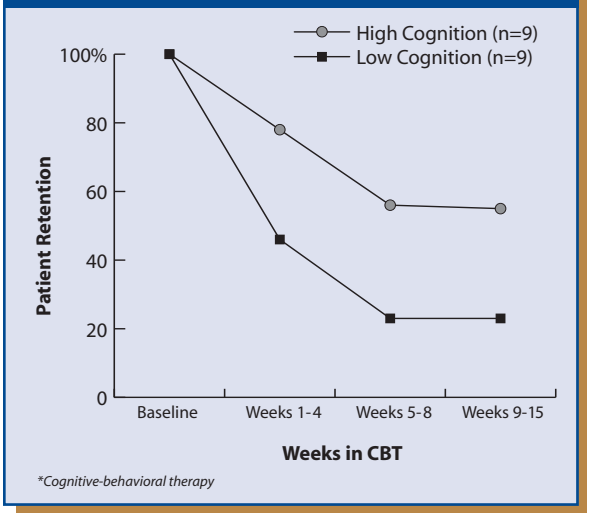
Cocaine abusers' cognitive deficits have been well documented. The drug constricts cerebral blood vessels, resulting in decreased blood flow to the brain. Magnetic resonance imaging (MRI) studies also reveal an increased presence of microvascular lesions and clots in cerebral blood vessels, which can also restrict blood flow. Chronic cocaine use can also deplete the neurotransmitter dopamine, which contributes to impaired cognition.

Eighteen cocaine-addicted patients participated in the study. All tested positive for cocaine use in the previous 72 hours and reported using cocaine at least four times in the month before admission and for at least 12 months before study enrollment. Patients were excluded from the study if they were HIV-positive or had conditions known to cause cognitive impairment independently of cocaine abuse, including mood disorders, psychosis, attention-deficit/hyperactivity disorder, seizure disorders, or a previously diagnosed learning disability.

Each patient was scheduled for 15 once-a-week, 1-hour CBT sessions. Eleven patients received gabapentin, a medication used to quell cravings; the remaining seven received a placebo. Urine specimens were collected three times a week and analyzed for cocaine and six other commonly abused drugs. Patients who attended at least 12 CBT sessions were considered completers, based on the standard 12-week CBT treatment.

When the researchers analyzed the data, there were no significant differences in age, sex, ethnicity,

Cognitive Status a Factor in Cocaine Abusers' Time in CBT*



Cognitively impaired cocaine abusers are more likely than abusers with higher cognition to drop out of outpatient CBT, particularly in the first 4 to 6 weeks.

employment, or education between treatment dropouts and completers. Prior duration of cocaine use was similar for both quitters and completers. Of the 11 patients on medication, 7 dropped out; 5 of the 7 patients on placebo dropped out. Thus, the overall completion rate for all patients in the study was 33 percent. Medication had no effect on the study results, the researchers concluded.

Big differences emerged, however, in the cognitive abilities of dropouts and completers. The researchers used MicroCog computerized testing to determine each patient's level of cognitive performance at admission. Treatment completers performed at higher cognitive levels than dropouts across all the measured cognitive domains—attention, abstract reasoning, memory, spatial processing, and reaction time. Completers also performed significantly faster and with greater accuracy on proficiency testing than did dropouts, and they required significantly less time to complete cognitive tasks than the dropouts.

Patients in the low-cognition group were more likely to drop out early, during the first 4 weeks of treatment, than those in the high cognition group—55 percent versus 22 percent. And the average proportion of drug-free urine specimens among patients in the high-cognition group was significantly higher than in the low-cognition group.

"The dropout rate was higher for patients with more impairment and lower for the patients with less impairment," says Dr. Nunes.

"We finally have empirical data to very clearly show that patients with cognitive impairments at treatment entry are more likely to drop out of CBT," says Dr. Aharonovich. "If you are able to process what the therapist is telling you, you are more likely to stay in treatment. But if you can't, you're more likely to drop out."

One potential response, Dr. Aharonovich suggests, is to prescreen patients and provide modified treatment for the cognitively impaired—a smaller curriculum, or "CBT Lite," as she puts it. The goal would be to simplify tasks and pare down the number of topics and skills covered, much as a teacher would do with learning-disabled children. "In the fragile first 4 to 6 weeks of treatment," she says, "I would, for example, propose increasing session frequency from 60 minutes once a week to 30 minutes twice a week. This would decrease session lengths and reduce the demands on memory and attention."

"If you are able to process what the therapist is telling you, you are more likely to stay in treatment. But if you can't, you're more likely to drop out."

To augment this strategy, greater use of visual techniques, like node-link mapping, is recommended. "This is a modification of CBT," says Dr. Nunes. "Instead of just talking about the sequence of events that leads up to use—the places, people, thoughts, cravings—the therapist diagrams it all out."

Cognitive remediation techniques, or "brain exercises," which recently showed positive results in a study by Dr. William Fals-Stewart, may help the cognitively impaired patient, observes Dr. Nunes, as may drug therapies designed to improve cognitive ability. At Yale University in New Haven, Connecticut, for example, Dr. Thomas Kosten has begun trials using amiloride to improve cerebral blood flow in patients addicted to cocaine. Drs. Aharonovich and Nunes and Dr. Adam Bisaga, also at Columbia, are now testing memantine, which has been used in Europe to prevent brain cell damage in Alzheimer's patients and patients suffering from other forms of dementia.

The problem with medications, Dr. Aharonovich says, is getting enough cognition restored quickly to combat the high dropout rate in the first 4 weeks of therapy. "Usually, these medications require more than 4 weeks to take effect," she says, "so we need to do something to modify the therapy at the very beginning to be able to capture patients and hold them in treatment."

"Dr. Aharonovich's research supports the notion that a substantial number of drug abusers have some degree of cognitive impairment that could impede their ability to get the most benefit from treatment," says Debbie Grossman, M.A., of NIDA's Division of Treatment Research and Development. "This study highlights the importance of considering the cognitive functioning of drug abuse patients so that cognitive remediation can be incorporated into treatment, and/or treatments can be adapted and matched to the cognitive ability of the patient. Further research is critically needed to develop, modify, and test 'cognitive-friendly' drug dependence treatments that could lead to improved treatment response and outcome."

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Chronic Drug Abuse

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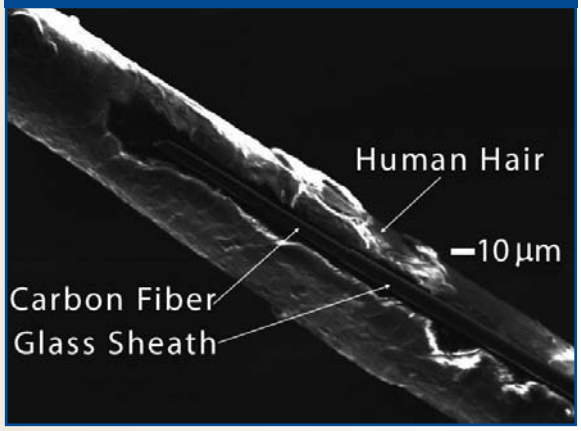
"Just the anticipation of receiving cocaine appears to cause significant increases in dopamine levels, suggesting that dopamine plays a much more complex role in addiction than simply triggering a drug's pharmacological reward," says Dr. Carelli. "Dopamine seems to alert the brain to the availability of cocaine and precipitate drug-seeking behavior. In the rats, this early spike in dopamine appears to cause them to seek the lever. In

Microscopic Probe Detects Changes in Brain Chemistry as They Occur

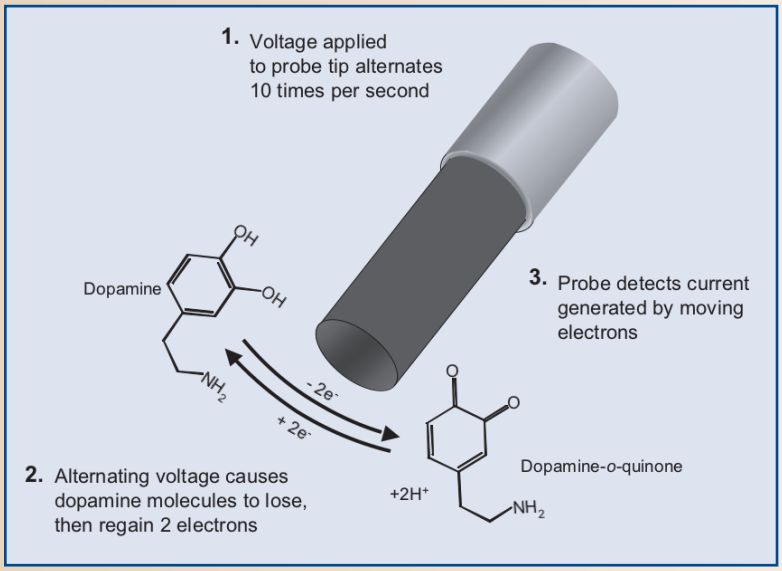
Fast scan cyclic voltammetry (FSCV) detects changes in electrical current that result from chemical changes in molecules deep within the brain. The technique was developed by Dr. Mark Wightman, professor of chemistry at the University of North Carolina at Chapel Hill (UNC-CH). The key to FSCV is a microscopic probe roughly 10 millionths of a meter (10 µm) in diameter—one-tenth the thickness of a human hair (see image, right). The probe consists of a carbon fiber partially sheathed in an insulating material and connected to instruments that control the electrical properties of the fiber and record changes in current at the probe tip.

Carbon Fiber Microelectrode



To explore the role of the neurotransmitter dopamine in rats during drug-seeking behavior, UNC-CH investigators inserted FSCV probes into the rats' nucleus accumbens. The probes are cycled through alternating positive and negative voltage (see image, below). Dopamine molecules in the region of the probe tip are oxidized (give off two electrons) when the probe has a positive voltage and reduced (retrieve two electrons) when the probe's charge shifts to negative. The transfer of electrons generates an electric current at the probe surface that is recorded by instruments attached to it. The voltage at the probe's tip can be reversed rapidly, and FSCV is able to measure current changes—whose magnitude directly reflects changes in dopamine concentration—at intervals as short as 10 times per second. The measurements made with FSCV in the UNC-CH dopamine studies are the fastest measurements of chemical change ever recorded in active living animals, the researchers say.

In 2001, NIDA awarded Dr. Wightman and UNC-CH colleague Dr. Regina Carelli a Cutting Edge Basic Research Award (CEBRA) grant to explore the potential of FSCV in drug abuse research. "CEBRA grants are designed to support research that is high-risk and potentially high-impact, and the first results of NIDA's support of this technology are impressive," explains Dr. Nancy Pilotte of NIDA's Division of Neuroscience and Behavioral Research.



The next stage of the UNC-CH scientists' dopamine research will simultaneously monitor dopamine-producing cells as they release the neurotransmitter and the electrical changes in dopamine-receiving cells as they respond to it." Measuring neurotransmitter and electrical activity as they occur may make possible the creation of a real-time map of neurons responding to changing dopamine concentrations," Dr. Pilotte says. "We could see brain cells self-assembling circuits in response to a stimulus. It would be like watching learning as it happens."

humans, the same thing may happen as part of the powerful urge to obtain drugs," she says.

Pressing the lever also triggered an audiovisual cue (light and a harmonic tone) that the rats learned to associate with the delivery of cocaine. The researchers also found that dopamine levels increased when the rats were exposed at random intervals only to the cue, in the absence of the lever and delivery of cocaine. "The dopamine activity we found in response to the cue may parallel what happens in humans who are addicted to drugs, who experience intense craving when they see drug paraphernalia or other environmental cues," Dr. Carelli observes.

To confirm the hypothesis that increases in dopamine alert rats that cocaine is available and direct their behavior toward finding the drug, the scientists used electrical stimulation to trigger dopamine release in the NAc. "In animals that had learned to self-administer cocaine, this stimulation was immediately followed by the behaviors that had preceded a lever press in the earlier sessions. The rats stopped whatever activity they were engaged in, began moving inquisitively around the chamber, and finally approached the lever," Dr. Carelli explains. "This is powerful evidence that the increase in NAc dopamine has a pivotal role in drug-seeking behavior."

To make their observations possible, the investigators used a technique called fast-scan cyclic voltammetry (see textbox, p. 6). This technique lets researchers measure dopamine levels 10 times a second—hundreds of times faster than other techniques, which are limited to measurement of minute-by-minute changes.

"No one had a way to detect dopamine changes on such a fast timescale before," Dr. Carelli explains. "We are able to monitor them almost as soon as they occur. It's like listening in on the communication between brain cells as it is happening."

"These findings reveal for the first time that rapid dopamine transmission occurs during key components of cocaine-seeking behavior, during presentation of cocaine-associated cues," observes Dr. Susan Volman of NIDA's Division of Neuroscience and Behavioral Research. "The extraordinary technology used in this research allows us to detect changes in the nucleus accumbens as they happen, to observe dopamine signaling that results from a learned association between a stimulus and the drug. This adds important levels of detail to the picture of how drugs alter behavior in ways that are so destructive yet difficult to change."

Source

• Phillips, P.E.M.; Stuber, G.D.; Heien, M.L.A.V.; Wightman, R.M.; and Carelli, R.M. Subsecond dopamine release promotes cocaine seeking. *Nature* 422(6932):614-618, 2003. NN

RESEARCH NEWS

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Researchers Adapt HIV Risk Prevention Program for African-American Women

By Jill Schlabig Williams, NIDA NOTES Contributing Writer

The HIV/AIDS epidemic has taken a disproportionate toll on racial and ethnic minority populations, especially women. In its surveillance report on the number of Americans living with HIV/AIDS in 2002, the Centers for Disease Control and Prevention estimates that among women with HIV/AIDS, non-Hispanic African-American women outnumbered non-Hispanic white women by three to one—a racial disparity not found among men.

African-American drug-using women were addressed in two recent studies by NIDA-funded researchers in Atlanta. Dr. Claire E. Sterk of Emory University, Dr. Kirk W. Elifson of Georgia State University, and colleagues developed and tested gender-tailored, culturally specific adaptations of a standard NIDA HIV prevention intervention. They found that female African-American injecting drug users (IDUs) and crack cocaine users who received either of two targeted 4-week prevention programs reduced their risk behaviors related to drug-taking and sex more than did women who received the standard intervention.

"These studies are examples of research that is responsive to community needs," says Dr. Dionne Jones of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse. "When it comes to designing a prevention program, it's not one-size-fits-all. You have to consider social context, be culturally sensitive and appropriate, and tailor your message to the group."

The researchers' goal was to develop culturally appropriate programs grounded in the reality of the daily lives of women most at risk and the difficulties they face in their individual, social, family, and sexual relations and activities. "We worked hard to develop interventions with input from this target population, deliver the interventions in a setting where they feel comfortable, and involve them in planning, implementing, and evaluating the interventions," says Dr. Sterk.

Over 1 year, using one-on-one interviews and small focus groups, the researchers sought to define the key issues in the women's lives and identify ways to address those issues, including such factors as gender dynamics, economic stressors, gender-specific norms and values, and power and control. Two interventions came out of this research phase. One, a motivation intervention, was designed to motivate the participants to change their behavior. The other, a negotiation intervention, recognized that women may fear verbal or physical abuse if they propose safer sex or safer needle use and thus sought to strengthen their negotiation and conflict-resolution skills.

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Tailored Interventions Build on NIDA Intervention To Help Drug-Using Women Reduce HIV Risk

	Behavior in Past 30 days	NIDA Standard Intervention Group		Motivation Intervention Group		Negotiation Intervention Group	
		Baseline	Six-Month Followup	Baseline	Six-Month Followup	Baseline	Six-Month Followup
Injecting Drug Users	Number of days injected powder cocaine	8.2	3.1	6.4	0.1	4.7	0.2
	Number of days injected heroin	16.4	8.9	12.7	1.5	9.8	3.2
	Percentage who traded sex for drugs	70.4	40.7	50.0	20.0	42.9	10.0
Crack Cocaine Users	Mean number of days crack used	17.7	12.9	18.2	15.6	18.7	13.8
	Percentage who had vaginal sex with one or more paying partners	43.9	24.6	34.3	19.2	30.8	20.5

African-American drug-using women in three intervention groups reduced behaviors that heightened their risk of HIV infection. However, women receiving the culturally specific, gender-tailored motivation and negotiation interventions generally reported greater reductions in risky behaviors after their participation than women in the NIDA standard intervention.

HIV Risk Prevention Program

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"Our goal in the motivation intervention was to reduce risk based on what's realistic in the context of the participant's life," explains Dr. Sterk. "We worked with the women to set short- and long-term goals, celebrate successes, analyze failures, and identify and overcome barriers." The negotiation intervention recognizes that many of the women's challenges dealt with the need to resolve conflict and that negotiation skills are key to reducing risk.

Once the interventions were ready, more than 300 African-American women ages 18 to 59 years—68 IDUs and 265 crack cocaine users—were enrolled in the studies. All were HIV-negative and heterosexually active. The women were randomly assigned to one of the three interventions. The NIDA standard intervention was delivered in two one-on-one sessions; the motivation and negotiation interventions each involved four one-on-one sessions. (See textbox, below, for descriptions of each intervention.) At the 6-month followup, both IDUs and crack cocaine users in all three groups reported lower levels of drug-using behavior and risky sexual behaviors than they had reported before receiving the interventions. Reductions were greater among women who received the tailored interventions.

Injecting Drug Users. The motivation and negotiation interventions were equally effective in reducing the incidence of needle and injection-works sharing. At 6 months, there was no sharing of drug injection paraphernalia in these groups; in the standard intervention group, 13 percent reported sharing needles and 18 percent reported sharing injection works. Although women in all intervention groups reduced their number of injections over time, only those in the tailored interventions reported statistically significant decreases. Participants in the motivation intervention were most likely to attend drug treatment, whereas women in the negotiation intervention reported more changes in their sexual behavior than did women in other interventions.

Crack Cocaine Users. All three interventions were associated with a drop in crack use in the 30 days preceeding followup. About 40 percent of the women in each group reported no use during that period. Among those still abusing crack at followup, women in the motivation intervention were more likely to have reduced their use of crack in risky settings, such as outside or in a crack house, hotel room, or car. Women in the standard and motivation intervention groups significantly decreased the number of paying partners for vaginal sex and the frequency of sex with paying partners.

Dr. Sterk suggests that the study's results show it may be optimal to create an intervention that combines

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Protocols for Standard, Motivation, and Negotiation Interventions

All interventions include discussion of the local HIV epidemic, sex and drug-related risk behaviors, safer sex and drug use, and HIV risk-reduction strategies. The two tailored interventions also include a discussion of the impact of race and gender on HIV risk and protective behaviors.

The NIDA standard intervention is an HIV/AIDS education program that was developed in the early 1990s. It builds on standard HIV testing and counseling developed by CDC and adds discussion of the principles of HIV prevention for drug users and their sex partners. The intervention involves testing, counseling, and educating participants through use of cue cards on such topics as the definition of HIV/AIDS, who is at risk, and ways to reduce risk. Also offered are demonstrations on condom use and equipment-bleaching techniques for IDUs. Referrals to counseling and other services are provided.

The motivation intervention follows the format of the standard intervention for the first session but ends with asking participants to consider what they are motivated to change in their lives. During the second session, this list is reviewed and short- and long-term goals are set. The third and fourth sessions involve discussion of experiences with behavior change, including the woman's sense of control and feelings of ambivalence about behavior change. Risk-reduction messages tailored to the participant's level of readiness to change are also delivered in the fourth session.

The negotiation/conflict-resolution intervention also follows the NIDA standard intervention for the first session, but it ends with a discussion of intended behavior changes. The second session reviews the list of possible behavior changes and the level of control the participant believes she has and introduces general communication skills and strategies to develop assertiveness. Short-term goals are set for strengthening communication, gaining control, and developing assertiveness. Negotiation and conflict-resolution strategies are introduced during the third session and tailored to the individual during the final session.

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skills taught in both the negotiation and motivation interventions. While participants in the negotiation intervention were generally more successful at reducing sexual risk behaviors, including decreasing the number of paying partners and increasing condom use with steady partners, participants in the motivation intervention had more success at changing drug-use behaviors.

Efforts were also made to assist program participants in their lives outside of the program, with success extending well beyond the study's parameters, notes Dr. Sterk. "A lot of the women who received the one-on-one support available through the tailored interventions said the program served as a re-entry into society. For example, they were encouraged to obtain a photo ID. Many reported that this simple act made them feel more connected to society again, part of the larger world." Program graduates returned to school, earned their GED, found jobs, joined the project to become counselors/interviewers, and stopped using drugs.

"Over and over, researchers are finding that we need to take a more holistic approach to intervention programs," says NIDA's Dr. Jones. "We can't just focus on drugs and sex. We must look at the big picture. It involves childcare, education, employment, housing, and job training. Community stakeholders need to develop programs that address multiple needs."

The project maintained a high retention rate—96 percent of the women enrolled in the studies completed the 6-month followup interview. Dr. Sterk attributes this success to the fact that the project was grounded in the community and to the value of involving community consultants—residents, both former drug users and others, who played key roles in recruiting, interviewing, and counseling participants.

In future research, Dr. Sterk intends to examine the cost-effectiveness of various intervention formats. "It appears that individual sessions may be more desirable and cost-effective," she predicts. Dr. Sterk would like to continue the research, assessing the long-term effects of specific interventions. She wants to develop an intervention that focuses on women's households, targeting both the woman and her main partner, and she is interested in capacity-building—translating her research into other settings and training people to develop similar programs in more communities.

Principles That Guide Format, Content of Interventions

The interventions used by Dr. Sterk and her colleagues in this study are firmly based in theoretical research. The researchers conducted a series of one-on-one interviews and focus groups with the target population. These interviews yielded the following key principles that guided both the format and the content of the interventions.

- **Offer counseling sessions on an individual basis.** "It was very clear that women wanted to start with one-on-one sessions," says Dr. Sterk. "HIV risk behaviors involve so many private, personal issues—previous abuse experiences, actions to support their drug habits, things they'd never before discussed. They found it easier to discuss these experiences with one person, not a group."
- **Adopt a holistic approach.** Along with this research project, a clothing fair was conducted and clothes made available to program participants. Food for breakfast was provided; daycare was close by; and ongoing services, such as help preparing for job interviews, were provided.
- **Make programs community-based.** The project was headquartered in a house in the community, which was key to participants' convenience and comfort. Researchers also found it important for the women to link participation in this project to local social and health services, including local drug treatment, daycare centers, health services, and other community-based organizations. Community consultants played a key role in the project.
- **Address women's multiple social roles in the intervention.** Participants insisted that they didn't want to be labeled simply as drug users. Instead, they wanted the social context of their daily lives to be addressed, including their roles as mothers and steady partners.

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Smoking Decreases Key Enzyme Throughout Body

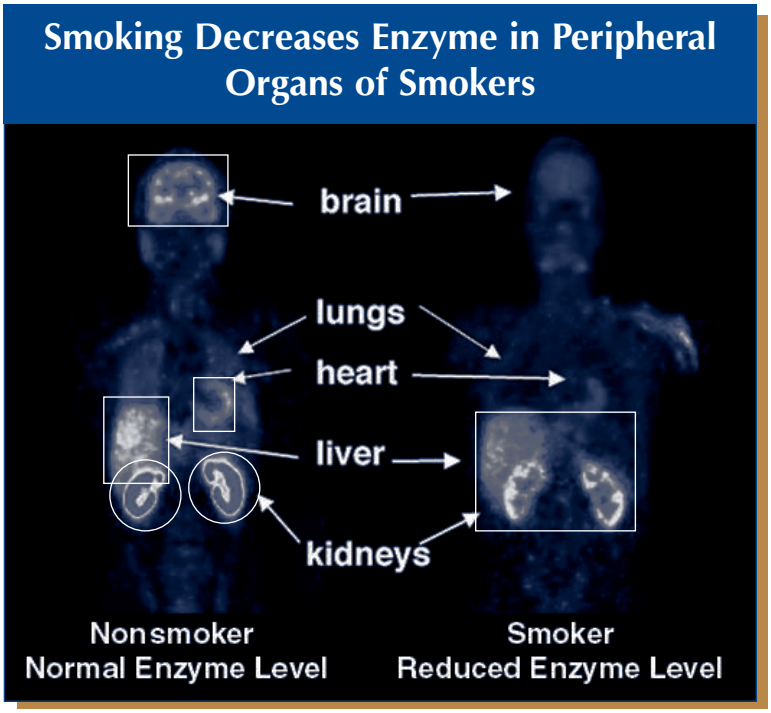
By Patrick Zickler, NIDA NOTES Staff Writer

Nicotine addiction and tobacco use wreak enormous worldwide health consequences, including more than 40,000 deaths in the United States each year from tobacco-related diseases. Most of this health toll involves disease related to the effects of inhaled smoke on the lungs and respiratory system and on the heart and circulatory system. However, recent NIDA-supported research has demonstrated that a compound found in cigarette smoke reduces levels of an important enzyme throughout the body—in the spleen, kidneys, and brain as well as the lungs. The enzyme, monoamine oxidase B (MAO-B), plays a critical role in breaking down neurotransmitters and helping to regulate blood pressure. Too much or too little of the enzyme can affect mental or physical health.

Dr. Joanna Fowler and colleagues at the Brookhaven National Laboratory in Upton, New York, and the State University of New York at Stony Brook used positron emission tomography (PET) imaging to show reduced levels of MAO-B in the kidneys, heart, lungs, and spleen of smokers. "When we think about smoking and smoking toxicity, we usually think of the lungs," Dr. Fowler observes. "But here we see a very marked effect of smoking on one of the major enzymes in the body, and we see that this effect extends far beyond the lungs."

In earlier research, the Brookhaven scientists—whose research also is supported in part by the Department of Energy and the National Institute of Biomedical Imaging and Bioengineering—had found decreased levels of MAO-B in the brains of smokers. "Because smoking exposes the entire body to the tobacco compounds that inhibit MAO-B, we believed it had the potential to limit MAO-B activity elsewhere in the body," Dr. Fowler says.

The study involved 10 men and 2 women (average age 41 years) who had been smoking for an average of 21 years. Each participant underwent PET scanning of his or her torso after receiving injections of radioactive MAO-B tracers. When the researchers compared these scans with scans previously performed on nonsmokers, they found that MAO-B distribution in the heart, lungs, kidneys, and spleen of smokers was 33 to 46 percent lower than levels seen in nonsmokers.



PET scans compare the distribution of the enzyme MAO-B in a nonsmoker and smoker. Circled areas indicate the highest MAO-B concentrations, areas captured in squares show intermediate levels, and areas with the lowest concentrations are unmarked. The smoker has lower MAO-B concentrations in peripheral organs than the nonsmoker.

The reduction in MAO-B levels is not due to nicotine, but to an unidentified component of tobacco smoke—one of roughly 4,000 chemicals to which smokers are exposed with each puff. "With the whole body exposed to the thousands of compounds in tobacco smoke, we need to be aware that these may contribute to the physiological effects of smoking," Dr. Fowler adds.

"Nicotine establishes the addiction, and continuous smoking maintains levels of all these compounds throughout the body," Dr. Fowler says. "The health consequences of reduced MAO-B levels in the organs are unclear. There may be adverse effects that are indirect and associated with the dietary substances or environmental compounds normally broken down by the enzyme. At the very least, however, it is clear that enzyme levels in smokers' peripheral organs are significantly affected by their tobacco use."

Source

• Fowler, J.S., et al. Low monoamine oxidase B in peripheral organs of smokers. *Proceedings of the National Academy of Sciences* 100(20):11600-11605, 2003. NN

Blending Research and Practice: CTN Update

By Barbara Shine, NIDA NOTES Contributing Writer

What is the best way to ensure that new drug abuse treatments—the fruits of long-term basic and applied research—are adopted quickly for the benefit of patients in community-based treatment settings? This is one of the major questions NIDA sought to answer when it launched the National Drug Abuse Treatment Clinical Trials Network (CTN) nearly 5 years ago.

The first CTN grants, awarded in September 1999, funded six research and treatment consortia, known as "nodes," each consisting of a Regional Research and Training Center (RRTC) and a group of 5 to 10 allied Community Treatment Programs (CTPs). The CTN grew rapidly through its second and third years, and today the network includes 17 regional nodes.

RRTCs are all university-based research institutions that have made important contributions to our knowledge of what works in drug abuse treatment. CTPs are prominent treatment programs in a variety of settings within each region. CTP patients represent a broad spectrum of social and economic groups as well as racial, ethnic, age, and gender characteristics. This makes it possible for the CTN to test the effectiveness of medications, behavioral treatments, and combination therapies with diverse populations in a variety of settings—from outpatient clinics to intensive residential treatment programs.

The CTN model is unique in that established researchers and clinicians collaboratively design trials to ensure that interventions to be tested are practical and sustainable. CTP staff members perform the interventions under investigation, another noteworthy feature of the CTN model.

"To date, more than 2,500 patients have taken part in 12 CTN clinical trials of drug abuse treatments, and another 11 trial protocols are now in development" says Dr. Betty Tai, NIDA's Director of the Center for the Clinical Trials Network. "And we're excited about results from the earliest trials, which will be released soon."

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The first CTN trials studied such treatment approaches as use of buprenorphine for opiate detoxification and motivational enhancement treatment to improve treatment engagement and outcomes. These nearly complete trials have established the effectiveness of the CTN model for conducting research and will provide valuable findings to treatment programs deciding which interventions to adopt.

Some of the newest trials, which are now recruiting patients, include studies of a treatment tailored for women with co-occurring substance abuse and post-traumatic stress disorder and an approach to training unemployed drug-dependent patients in job-seeking skills. Trial protocols recently submitted to NIDA for approval would address treatment approaches such as family management skills training, 12-step facilitation, and management of depression that co-occurs with drug dependence. CTN researchers and practitioners are continually generating concepts that could be developed into future trial protocols.

More detailed information on the CTN, its research studies, and the network of participants is available on NIDA's Web site at www.drugabuse.gov/CTN, which features user-friendly Web pages and brochures for clinicians and the public. Information is also available by calling NIDA's Center for the Clinical Trials Network, 301-443-6697. CTN updates will be featured in future issues of *NIDA NOTES*. NN

Instrument Wizard Works Magic With Web-Based Drug Abuse Research Tools

Shazam! A modern-day wizard stands ready to help anyone who needs information on instruments to measure substance abuse and related factors. The Instrument Wizard (IW), developed by ISA Associates, Inc., with NIDA funding, is a Web-based resource that helps users identify screening, diagnostic, and evaluation instruments for use in clinical settings and in every stage of drug abuse research—from planning to program evaluation.

The IW collects more than 200 instruments that have been empirically tested for reliability and validity, with particular attention to psychometrics, the measurement of psychological variables. IW users can search a wide array of elements, including target audience, specific substance of abuse, instrument's purpose, and other topics, such as risk factors. Those who want a specific tool can search by the instrument's title or author.

Potential IW users—drug abuse prevention and treatment professionals, behavioral health care providers, researchers, evaluators, educators, and criminal justice personnel—can take a "virtual tour" of the IW at www.instrumentwizard.com. The tour allows visitors to view a multimedia demonstration of the IW's functions and capabilities. Visitors can see how to search by title, author, or instrument characteristics and what the results of a search would look like. After a trial run, interested users can subscribe online for an individual or organizational membership by month or year; fees are based on membership type. Members incur no additional cost for instruments in the public domain. Some private instruments also are free; for all others, the IW provides cost information or contact information for costs.

"We want drug abuse professionals to think of and use the IW as a 'one-stop shopping' destination," says Dr. Royer Cook of ISA, the project's principal investigator. "The IW is unique in providing users access to high-quality research and clinical tools in a site where they can review properties of all instruments, print out the materials, and receive copyright information, if needed."

For More Information . . .

- To learn more about the Instrument Wizard, e-mail Dr. Tracy McPherson, of ISA, at instrumentwizard@isagroup.com or call 703-739-0880.
- For details on the Small Business Innovation Research (SBIR) grants program, which funded development of the IW, visit NIDA's Web site at www.drugabuse.gov/Funding or the Small Business Administration site at www.sba.gov. NN

Upcoming NIDA Science Meetings

Mark your calendars! The National NIDA Advisory Council will meet on May 19-20, with the second day open to the public. In addition, May and June offer an array of science meetings on key topics in drug abuse and addiction. For registration information, please visit NIDA's Web site at www.drugabuse.gov.whatsnew.

May 1-6	American Psychiatric Association (APA) 157th Annual Meeting; New York, NY; NIDA will sponsor a major track, "Integrating the Science of Addiction Into Psychiatric Practice"
May 9-11	"Cognitive & Affective Science Findings: Translation to New Behavioral Treatments for Drug Addiction"; Bethesda Hyatt, Bethesda, MD
June 11-15	"2004 NIDA International Forum: Progress Through Collaboration"; Caribe Hilton, San Juan, Puerto Rico
June 23-25	"Complexities of Co-Occurring Conditions—Harnessing Services Research to Improve Care for Mental, Substance Abuse, and Medical/Physical Disorders"; Marriott Wardman Park, Washington DC

NIDA, CADCA Team for Public Education

NIDA is partnering with the Community Anti-Drug Coalitions of America (CADCA) to raise public awareness about the effects of drug abuse on children and adolescents. One product of the collaboration, the *Practical Theorist* series of manuals, presents current, research-based knowledge on drug abuse in a concise format and suggests strategies for using the data to build drug-free communities.

The latest release in the series, *Practical Theorist 5: Marijuana Abuse: Using Science for an Effective Community Response*, was timed to correspond with opening of the schools in fall 2003. "A new school year means a highly vulnerable population, students in elementary and secondary schools, will be introduced to new teachers, new classes, and—unfortunately—the temptation to abuse drugs," says NIDA Director Dr. Nora D. Volkow. "Through the NIDA-CADCA collaboration, we're producing easily understandable scientific information to help parents, teachers, and others in the community guide young people toward positive life choices."

Practical Theorist 5 describes the scope of the Nation's marijuana problem; summarizes the latest research on marijuana's effects on the brain, body, and everyday functioning; and suggests how community anti-drug coalitions can move to address this growing problem. The booklet provides the factual ammunition to fire back at myths such as "Marijuana is harmless," and "It's not addictive."

Information about the *Practical Theorist* and other CADCA publications is available at 800-54-CADCA. Fact sheets on the health effects of marijuana and other drugs of abuse can be found on the NIDA Web site, www.drugabuse.gov. NN

Research Award Inaugurated at Neuroscience Conference

The Society for Neuroscience (SfN) and the Jacob P. Waletzky Memorial Foundation chose NIDA's "Frontiers in Addiction Research" symposium, held November 7, 2003 in New Orleans with the Society's annual conference, as the forum to announce the first recipient of the Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism.

Courtesy of SfN, 2004

Dr. Pier Piazza receives the Jacob P. Waletzky Memorial Award for Innovative Research in Drug Addiction and Alcoholism from Dr. Robert Malenka, NIDA Advisory Council member and Chair, SfN Program Committee.

The Award was presented to Dr. Pier Piazza, a behavioral neuroendocrinologist with INSERM, the French national institute for medical research at the University of Bordeaux. His work focuses on neurobiological factors that contribute to differences in individual vulnerability to the rewarding properties of drugs and the effects of stress on drug addiction.

The award was established in memory of writer Jacob Waletzky, who died at age 29 of cocaine-induced cardiac arrhythmia after relapsing to cocaine use. Waletzky's parents, psychiatrists active in drug abuse treatment, formed a memorial foundation that established the $25,000 award. "The goal of the Waletzky Award is to encourage innovative research into the neurobiology of drug addiction and alcoholism," said SfN President Dr. Huda Akil, presenter of the award. "Jacob Waletzky's parents endowed this award in the conviction that neurobiological advances in addiction research will lead to more effective treatment and a cure. NIDA's interest in inviting the Waletzky awardee to give a presentation at this satellite symposium underscores the importance of this award at the national and international levels."

NIDA's "mini-convention" will be an annual event at SfN meetings, said Dr. Timothy Condon, Deputy Director of NIDA. "We are pleased to be an integral part of the field of neuroscience and of the Society's annual meetings. This year, our full day of presentations included 30 speakers and 70 scientific poster presentations, reflecting the critical role of drug abuse and addiction research in this field," he said. "And we are honored that the Society allowed our convention to serve as the forum for the first annual Waletzky lecture." NN

Teens' Drug Use Declines Dramatically, According to MTF Survey Results

Falling to levels not seen in nearly a decade, past-month illicit drug use among the Nation's youth declined by 11 percent—from 19.4 to 17.3 percent—between 2001 and 2003, according to the newly released 2003 Monitoring the Future (MTF) survey. This reduction translates into roughly 400,000 fewer adolescent drug users than in 2001 and exceeds President Bush's call in February 2002 to reduce drug use among youth by 10 percent in 2 years. The 2003 findings emerged from responses provided by nearly 50,000 students in 392 public and private schools across the country. In addition to a decline in the numbers of teens reporting drug use in the month before being surveyed (past-month use), teens' drug use in the year before being surveyed (past-year use) fell by 11 percent, from 31.8 to 28.3 percent; teens claiming to have ever used drugs (lifetime use) also dropped—from 41 to 37.4 percent, a 9-percent reduction.

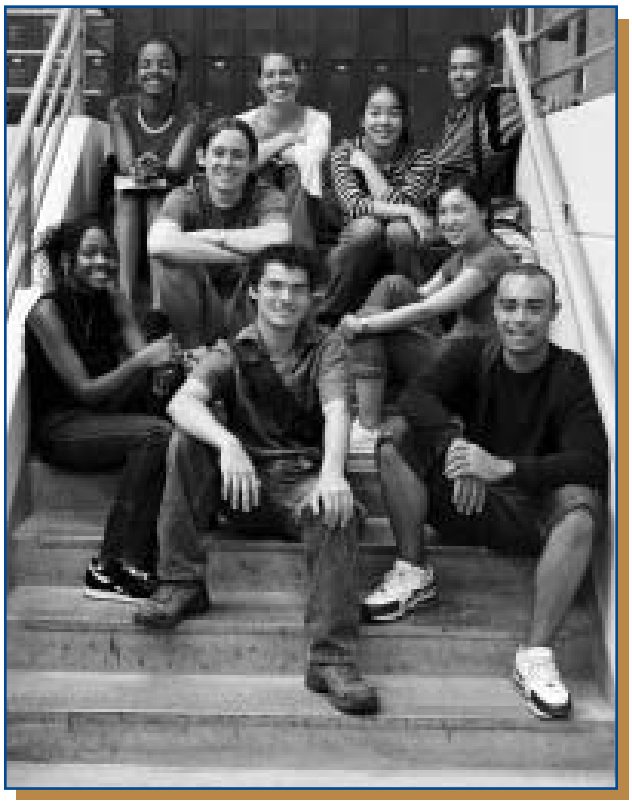
"The overall reduction in drug use by America's young people is heartening," said NIDA Director Dr. Nora Volkow. "We are confident that our concerted effort to provide students and teachers with informative, accurate information about addiction and drug abuse will contribute to further reductions in drug use."

The MTF survey, launched in 1975, measures drug, alcohol, and cigarette use and attitudes about use among 8th-, 10th-, and 12th-graders nationwide; the younger two grades were added in 1991. Participants report their past-month, past-year, and lifetime drug use behaviors. Funded by NIDA, the survey has been conducted annually since its inception by the University of Michigan's Institute for Social Research. Survey results help identify potential drug problem areas and ensure that resources are targeted to areas of greatest need.

MTF typically focuses on changes in use and attitudes among individual grades from the prior year. However, at the request of the White House Office of National Drug Control Policy, MTF researchers conducted special analyses, for all three grades combined, of the changes between 2001 to 2003 in students' use of illicit drugs, alcohol, and tobacco and in their anti-drug attitudes.

Key substance use patterns that emerged between 2001 and 2003 are as follows:

- **Cigarettes.** Lifetime and past-month use of cigarettes declined among 8th-, 10th-, and 12th-graders. Lifetime cigarette use dropped 17 percent, from 49.1 to 40.9 percent, and past-month use fell 18 percent, from 20.3 to 16.6 percent.
- **Alcohol.** The use of alcohol also declined. Past-year and past-month use each declined 7 percent, from 58.4 to 54.6 percent and 35.7 to 33.3 percent, respectively.
- **Marijuana**. Use of marijuana declined significantly. Past-month use declined 11 percent, from 16.6 to 14.8 percent; past-year use also declined 11 percent, from 27.5 to 24.5 percent; and lifetime use declined 8.2 percent from 35.3 to 32.4 percent. Among all three grades, students' perceived risk of using marijuana increased markedly.



- **Amphetamines.** These substances have been the second-most commonly used illicit drug among youth, but their use also dropped in the last 2 years. Lifetime use fell 15 percent—from 13.9 to 11.8 percent. Both past-year and past-month use fell as well, from 9.6 to 8.0 percent and from 4.7 to 3.9 percent, respectively.
- **LSD and Ecstasy (MDMA).** Students' use of hallucinogens LSD and ecstasy plummeted between 2001 and 2003. Lifetime use of LSD fell 43 percent, from 6.6 to 3.7 percent, and past-year and past-month use both dropped by nearly two-thirds. Lifetime use of ecstasy dropped 32 percent, with past-year and past-month use cut in half, from 6.1 to 3.1 percent and 2.4 to 1.1 percent, respectively. NN

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