

Nicotine's Multiple Effects on the Brain's Reward System Drive Addiction

By Patrick Zickler
NIDA NOTES Staff Writer

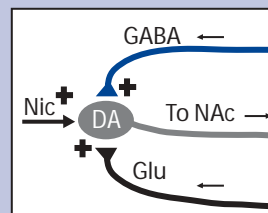
NIDA researchers have added another piece to the puzzle of what makes nicotine so addictive. Dr. Daniel McGehee and colleagues at the University of Chicago have shown that along with directly stimulating the brain's reward system, nicotine also stimulates it indirectly by altering the balance of inputs from two types of neuron that help regulate its activity level. This additional stimulation intensifies the pleasure from smoking and makes it last longer.

Scientists have long known that nicotine, like other addictive drugs, attaches to the core neurons of the brain's reward system, where beneficial behaviors (such as drinking water when thirsty) are rewarded and reinforced. Situated in a region of the brain called the ventral tegmental area (VTA), these reward-system neurons, called dopaminergic neurons, trigger release of the neurotransmitter dopamine (DA) in a nearby brain region called the nucleus accumbens (NAc). When nicotine attaches to these neurons they increase their activity, flooding the NAc with dopamine, which produces pleasure and a disposition to repeat the behaviors that

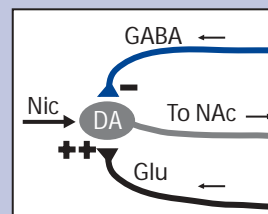
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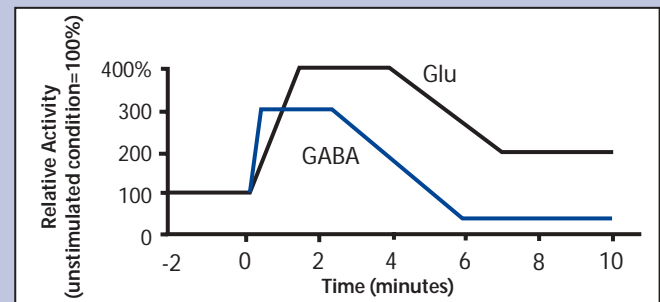
Nicotine's Double Effect on Dopamine Release



Nicotine (Nic) directly stimulates (+) neurons in the ventral tegmental area (VTA) to release dopamine (DA) in the nucleus accumbens (NAc). Nic also stimulates release of glutamate (Glu), triggering additional DA release. VTA cells stimulate release of GABA to moderate DA's effect.



Minutes later, Glu cells continue to stimulate DA release (++) , but release of GABA becomes inhibited (-), resulting in sustained high dopamine levels in the NAc.



The increase in the VTA's glutamate-to-GABA ratio lasts for more than 1 hour after a single exposure to nicotine, prolonging and intensifying the drug's pleasurable effects.

Exposure to nicotine has direct and indirect effects on dopamine release in the brain's reward center, the nucleus accumbens.

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NIDA's Continued Commitment To Nicotine Research

By NIDA Acting Director Glen R. Hanson, Ph.D., D.D.S.

Tobacco use is the Nation's most profound public health problem. Each year, tobacco use accounts for an estimated \$50 billion in health care costs, and the human cost is even more staggering. More than 400,000 Americans die annually from tobacco-related diseases. Of course, most smokers want to reduce their risks of heart and lung diseases, cancers, and strokes, but once addicted, smokers and other tobacco users find it very difficult to stop.

NIDA's contribution to the Nation's efforts to reduce tobacco use has been critically important. NIDA-supported research has led the way to development of smoking-cessation medications and has illuminated the causes of addiction. Recent studies have shown how the social and environmental influences that lead people to begin using tobacco conspire with powerful biological effects to quickly produce addiction to nicotine.

NIDA-funded investigations have made major advances in understanding, preventing, and treating tobacco use, but a complete understanding of the complex mechanisms of smoking initiation and nicotine addiction requires a comprehensive and coordinated research effort. NIDA has long recognized the need for an interdisciplinary approach to nicotine research and has forged partnerships with other research institutions in collaborative efforts to reduce nicotine addiction.

In 1998, NIDA cosponsored a groundbreaking conference that

brought together leading investigators from throughout the Nation. At this conference, the researchers identified research hypotheses and approaches that have great potential to yield information that will significantly improve our ability to reduce tobacco use and nicotine addiction.

Following up on ideas generated at the conference, NIDA joined with the National Cancer Institute and the Robert Wood Johnson Foundation to establish the Transdisciplinary Tobacco Use Research Centers (TTURCs). These research coalitions have improved our understanding of nicotine addiction at levels from the cellular to the societal, from the role of individual genes to the effects of gender. For example, TTURC researchers have found that genetic influences may help explain why some young people begin smoking while others do not (see "Genetic Variation in Serotonin System May Play Role in Smoking Initiation," *NIDA NOTES*, Vol. 17, No. 2). Other TTURC investigators have helped identify factors that may improve women smokers' chances of successfully quitting (see "Women and Smoking: Sensory Factors, Attitudes About Weight, Phase of Menstrual Cycle All Keys to Quitting," *NIDA NOTES*, Vol. 17, No. 4).

To amplify the success of these research partnerships, NIDA plans continued support for TTURC researchers and an expanded scope of collaborative efforts. We are joining with the National Institute of Mental

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NIDA-supported research has shown how the social and environmental influences that lead people to begin using tobacco conspire with powerful biological effects to quickly produce nicotine addiction.

NIDA's Continued Commitment to Nicotine Research

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Health in a research partnership (RFA MH-03-008) to identify and develop pharmacological compounds that can be used to investigate the roles of specific neurochemical receptors in mood disorders and nicotine addiction. These receptors are important: They are the sites on brain cells where nicotine initiates the cascade of neurochemical activities that contribute to development of dependence and addiction (see "Nicotine's Multiple Effects on the Brain's Reward System Drive Addiction," page 1). This collaboration with NIMH—the National Cooperative Drug Discovery Group Program—will encourage academic and pharmaceutical industry researchers to develop compounds that bind to specific subtypes of nicotine receptors. This will, in turn, make possible the development of specifically targeted medications for treating nicotine addiction.

Another NIDA initiative—Translating Tobacco Addiction Research to Treatment (RFA DA-03-010)—supports the development of

new treatment and prevention options. The initiative encourages researchers from diverse disciplines in

A complete understanding of the complex mechanisms of smoking initiation and nicotine addiction requires a comprehensive and coordinated research effort.

their efforts to move beyond animal studies and basic science to clinical applications. Specifically, it will support the use of phase I-style clinical studies or laboratory studies with human volunteers to investigate approaches built upon what we now know about the biological and behavioral mechanisms of nicotine addiction and tobacco use. Behavioral research, for example, demonstrates

the important role of environmental cues in drug craving; neurochemical research has identified some of the brain pathways involved in cue-induced craving. Under this new initiative, researchers could investigate the effectiveness of medications that target the neurochemical processes that underlie craving.

NIDA's achievements in nicotine and tobacco research are impressive. NIDA-supported research identified nicotine as the addictive component of tobacco smoke, and NIDA-funded research laid the foundation for the most effective medication now available to treat nicotine addiction—skin patches, gum, and inhalers used to deliver nicotine replacement therapy. But the research, and the results, must continue.

Each day, 3,000 adolescents start smoking; each year more than 30 million smokers try to quit, but most are unsuccessful. NIDA's commitment to new initiatives, as well as continued basic and clinical research, will speed the development of new programs that prevent young people from becoming smokers and will make available new treatments for the millions of Americans who smoke and want to quit. **NN**

NIDA Welcomes New Advisory Council Members



The National Advisory Council on Drug Abuse meets three times yearly to evaluate grant applications, review recent research findings, and provide guidance for NIDA programs and policy. Pictured here with NIDA Acting Director Dr. Glen R. Hanson (far right) and Deputy Director Richard Millstein (far left) are new Council members Dr. Claire Sterk (left rear) of Emory University; Dr. Constance Weisner of the University of California, San Francisco; Dr. Peter Kalivas (front left) of the Medical University of South Carolina; and Dr. Rodolfo Arredondo of the Texas Tech University Health Sciences Center. Other members newly appointed to 3-year terms on the Council are Dr. Dorothy Hatsukami, University of Minnesota; Mrs. Peggy Sapp, Informed Families of Dade County, Inc.; Dr. David Vlahov, New York Academy of Medicine; and Robert Woodson, National Center for Neighborhood Enterprise.

Cocaine's Effect on Blood Components May Be Linked to Heart Attack and Stroke

By Patrick Zickler
NIDA NOTES Staff Writer

Cocaine use increases the risk of sudden heart attack and may also trigger stroke, even in users who otherwise are not at high risk for these sometimes fatal cardiovascular events. The risk is related to narrowing of blood vessels and increases in blood pressure and heart rate. Recently, NIDA-supported researchers at the Alcohol and Drug Abuse Research Center at McLean Hospital in Belmont, Massachusetts, have identified changes in blood components that may also play a role in cocaine-related heart attack and stroke.

Dr. Arthur Siegel and his colleagues studied the effect of cocaine on blood factors that respond to inflammation by promoting clotting to initiate repair. They found that a component that promotes clotting—von Willebrand factor (vWF)—increases and remains elevated for hours after a single exposure to cocaine. They also found that, compared with less frequent users, heavy users of cocaine have elevated levels of vWF, fibrinogen (a clotting factor), and C-reactive protein (CRP), a blood protein that increases in concentration in response to inflammation and is a reliable indicator of risk for heart attack.

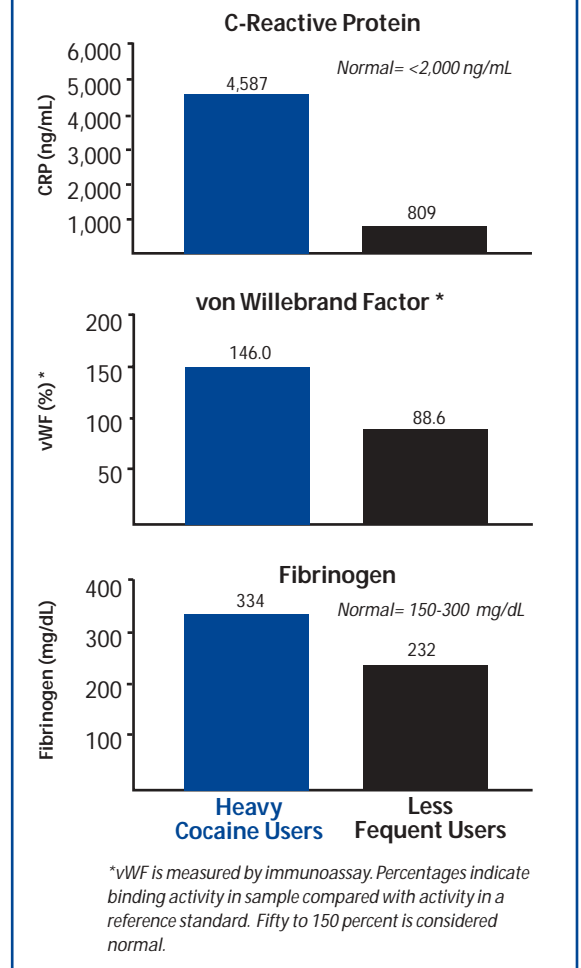
“These findings suggest that cocaine creates a temporary risk for heart attack or stroke by increasing clotting factors,” Dr. Siegel explains. “Elevated CRP levels could indicate that long-term use of the drug is triggering inflammation in the cardiovascular system.”

Participants in the study were 20 individuals (10 women and 10 men, average age 26 years) who used cocaine 2 to 6 times per month but were drug free at the time of the study. They received injections of low (0.2 mg/kg) or moderate (0.4 mg/kg) doses of cocaine or of saline solution, and their clotting-related blood components were measured every 30 minutes for 4 hours. In participants who received moderate doses of cocaine, but not those receiving low-dose cocaine or saline, levels of vWF increased by roughly 40 percent and remained elevated for 4 hours.

“With healthy subjects, it’s not unusual to see a temporary increase in vWF after normal activity such as exercise,” Dr. Siegel says. “But the increase is balanced by higher levels of factors that control clotting. The increases that followed cocaine administration were not accompanied by compensatory increases in protective factors.”

The researchers also compared the blood factor levels of the original study participants to those of 10 other individuals (6 women, 4 men, average age 41 years) who used the drug far more heavily—6 to 20 times per week, on average—when both groups were drug free. The heavy cocaine users had

Key Blood Component Levels Are Higher in Heavy Cocaine Users



Cocaine users who reported heavy use (6 to 20 times per week) show higher levels of C-reactive protein, von Willebrand factor, and fibrinogen—blood components that contribute to clotting—than do less frequent users (2 to 6 times per month).

higher levels of vWF, fibrinogen, and CRP.

“Elevated levels of CRP and clotting factors that we see in the heavy users suggest that repeated use of cocaine poses an exposure-related and cumulative risk for heart attack or stroke,” Dr. Siegel says. “The fact that

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Nicotine's Multiple Effects on The Brain's Reward System Drive Addiction

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led to it. That pleasure and disposition drive the process of addiction.

In the new research, Dr. McGehee's team followed up on a clue that nicotine attachment to the DA neurons in the VTA accounts for only part of the drug's pleasure-producing and ultimately addictive effect: Nicotine attachment stimulates the DA neurons for only a few minutes at most, yet dopamine levels in the NAc remain elevated for much longer.

To explain this discrepancy, the researchers studied nicotine's impact on two other types of neurons that affect dopamine levels. These neurons produce neurotransmitters, called glutamate and GABA, that act as fundamental pacemakers throughout the brain. Once released by its producing neuron, glutamate attaches to other neurons, including the DA neurons in the VTA, and stimulates them to speed up their activities. GABA has the opposite effect: It slows neurons down.

The researchers hypothesized that nicotine might act on these pacemaker neurons so as to increase the ratio of glutamate to GABA in the VTA. If the amount of glutamate acting on DA cells were to increase while the amount of GABA remained the same or decreased, the result would favor high levels of dopamine in the NAc. If the glutamate-GABA imbalance were long-lasting, it would explain why dopamine levels in the NAc remain elevated even after nicotine stops directly affecting the dopamine-producing neurons.

To test their hypothesis, Dr. McGehee and his colleagues exposed

rat VTA cells to nicotine for 10 minutes—roughly the time it takes a person to smoke a single cigarette. By measuring electrical properties of the brain tissue, they found that nicotine affected both pacemaker neurons. In glutamate-producing cells, the brief nicotine application induced a condition known as long-term potentiation, which promotes high-level activity for an extended time. When they

The combination of effects—increasing dopamine release and decreasing the inhibitory [GABA] response—results in an amplification of the rewarding properties of nicotine.

evaluated the effect on GABA-producing cells, the researchers found that after an initial increase in GABA transmission lasting only a few minutes, GABA transmission decreased and did not recover fully for more

than an hour after nicotine exposure ended. Overall, the result was what the researchers hypothesized: a sustained increase in the VTA's glutamate-to-GABA ratio.

“A brief application of nicotine can induce a lasting effect on excitatory [glutamate] signals to the brain's reward system,” summarizes Dr. McGehee. “This suggests that in humans a relatively short nicotine exposure, even for someone who has never smoked before, can cause long-lasting changes in excitatory neurotransmission. It may be an important early step in the process that results in addiction.”

“The combination of effects—increasing dopamine release and decreasing the inhibitory [GABA] response—results in an amplification of the rewarding properties of nicotine,” explains Dr. McGehee. “It would be difficult to design a better drug to promote addiction.”

“Understanding these mechanisms is an important step in explaining how a brief exposure to nicotine results in the long-term excitation of the brain's reward areas,” says Dr. William Corrigall, director of NIDA's Nicotine and Tobacco Addiction Program. “It gives us a clearer picture of how smoking can lead so quickly to dependence and addiction, and it also suggests a possible new avenue of investigation for pharmacological treatment.”

Sources

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- Mansvelder, H.D.; Keath, J.R.; and McGehee, D.S. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. *Neuron* 33(6): 905-919, 2002. [NN](#)

Few Middle Schools Use Proven Prevention Programs

By Patrick Zickler
NIDA NOTES Staff Writer

Since 1994, U.S. schools have been able to use Federal funds to provide education programs designed to prevent drug abuse. Under amendments to the Safe and Drug-Free Schools and Communities Act (SDFSCA) in 1998, however, the schools receiving Federal grants for drug abuse prevention were required to use an evidence-based curriculum. There are several such curricula, incorporating elements proven to be effective in reducing teen drug use: information about the effects of illicit drugs, alcohol, and nicotine as well as information about social influences, refusal skills, assertiveness, and decisionmaking.

In 1999, shortly after the SDFSCA amendments took effect, NIDA-supported researchers found only one in four middle schools that offer drug abuse prevention programs met standards set in the Principles of Effectiveness. Dr. Christopher Ringwalt of the Pacific Institute for Research and Evaluation in Chapel Hill, North Carolina, Dr. Susan Ennett of the University of North Carolina, and colleagues surveyed more than 1,900 U.S. middle schools to assess the use of evidence-based programs. They found, Dr. Ringwalt says, that relatively few schools appear to consider research results when selecting programs. “Only about a third of the Nation’s public schools and one-eighth of private schools are using substance prevention curricula for which there is evidence of effectiveness,” he says.

Criterion	Percentage of Programs/Instructors Meeting the Criterion
Effective Use of Content Some or most sessions include knowledge about drugs and alcohol, refusal skills, and generic skills such as decisionmaking, communication, assertiveness, and social skills.	62%
Effective Delivery Some or most sessions involve interactive methods such as role-playing.	17
Content and Delivery Combine effective content with effective delivery	14

Of 1,795 instructors surveyed, only 1 in 7 (14 percent) provided programs that combined effective content with effective delivery in some or most sessions as defined in the Safe and Drug-Free Schools and Communities Act’s “Principles of Effectiveness.”

The 1,656 public and 249 private schools surveyed all include some or all middle school grades (5 through 8). Respondents identified, from a list of 51 prevention programs, which program their school used. Programs on the list included 10 research-based programs identified as effective in reviews published by NIDA, the Center for Substance Abuse Prevention (CSAP), the Centers for Disease Control and Prevention (CDC), the Safe and Drug Free Schools Program of the U.S. Department of Education (SDFSP), or Drug Strategies, Inc. (DSI). The researchers also asked instructors to respond to questions about how the program was taught in the classroom.

Project Alert—identified as effective by CSAP, DSI, and SDFSP—was used by 19 percent of public and 6 percent of private schools. Life Skills Training—identified as effective by NIDA, CSAP, CDC, DSI, and SDFSP—was used by 12 percent of public and 3 percent of private schools. The most prevalent curriculum—used by 53 percent of public and 54 percent of private schools—is DARE (Drug Abuse Resistance Education), which has been extensively evaluated and found to be ineffective, Dr. Ringwalt observes.

Responses to questions about how the programs are taught suggest that only one school in five uses them to maximum advantage, according to

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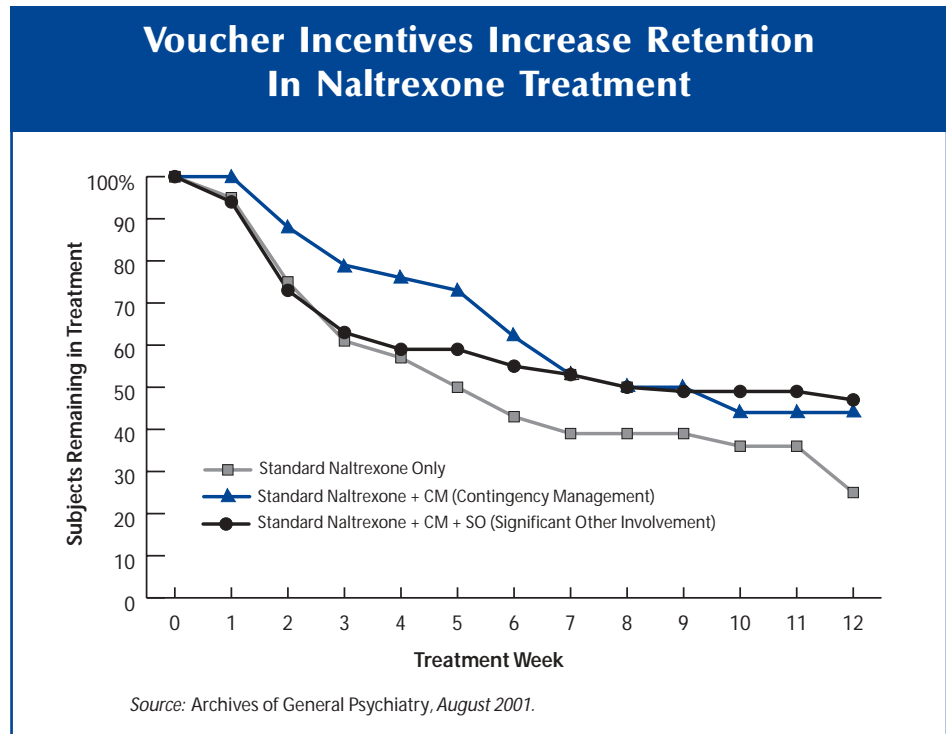
New Approaches Seek To Expand Naltrexone Use in Heroin Treatment

By Robert Mathias
NIDA NOTES Staff Writer

Naltrexone, an opiate treatment medication, is used to help patients make the transition from illicit opiate use to a drug-free life. Patients in naltrexone treatment are first detoxified from their dependence on opiates and then take thrice-weekly doses of naltrexone and participate in weekly group therapy sessions.

The medication provides a safety net for patients because it blocks the euphoric effects they normally would feel if they slip and use heroin or any other opiate. As a result, even relapse, which is common in addiction treatment, may have a therapeutic effect as repeated failure to get high may eventually break the neurobiological and behavioral links between taking drugs and the rewards that lead patients to resume regular drug use. With successful naltrexone treatment, slips to drug use become less frequent, the medication is discontinued, and patients continue behavioral treatment if needed.

Naltrexone treatment has been successful mainly with patients who are highly motivated to stop using opiates. Such patients include health care professionals who must stop using opiates to retain their licenses to practice medicine and individuals subject to criminal justice sanctions for relapse to illicit opiate use. The severe penalties that these patients would incur if they fail treatment enable them to overcome naltrexone's main drawback: It eliminates the powerful rewarding effects of opiates without any replacement to help



In a study with 127 heroin-addicted patients receiving naltrexone therapy, the 12-week dropout rate was about 50 percent among those in two groups that received voucher-based contingency management, and about 75 percent among those who did not.

patients cope with lingering effects of withdrawal.

Naltrexone's lack of a reinforcing effect has made it an unattractive treatment option for other patients who lack a strong external incentive to stop using drugs and do not want to go through detoxification and withdrawal from opiates. Most of these patients opt for treatment with medications such as LAAM and methadone, both of which help them to cope with the absence of the intense and rapid high that they are accustomed to getting from heroin by replacing it with a more moderate, stabilizing effect that can help them to maintain a nonaddicted lifestyle.

Despite its limited clinical use, naltrexone has many qualities that make it an attractive option for treating a broader range of opiate-dependent patients. It is not addictive, has few adverse effects, can be prescribed without concerns about diversion to the illicit drug market, and is not subject to the restrictive regulatory requirements that limit the use of methadone and LAAM to specialized clinics. Thus, like the recently approved opiate treatment medication buprenorphine, naltrexone can be administered in many settings, including private physicians' offices, making it more attractive to individuals who are reluctant to enter clinics.

Naltrexone's desirable therapeutic traits have continued to spark interest in finding new ways to expand its usefulness and application in practice. Two recent studies show that adjunctive behavioral and new pharmacological approaches may help to increase naltrexone's effectiveness for a wider range of opiate-addicted patients.

Voucher Reinforcement Increases Naltrexone's Effectiveness

A NIDA-supported treatment study that rewarded heroin-dependent patients with vouchers whenever they took their naltrexone or tested negative for drug use has found that this basic behavioral reinforcement approach achieved significantly better results than standard naltrexone treatment alone in keeping patients in treatment longer, having them complete treatment, and reducing their opiate use.

"A significant boost in treatment adherence was achieved not with highly motivated patient groups that have generally responded well to naltrexone treatment, but with predominantly unemployed 'street addicts,' most of whom had a history of extensive involvement with drug abuse treatment and the legal system," says Dr. Dorynne Czechowicz of NIDA's Division of Treatment Research and Development. She also maintains that the results are promising for expanding the types of patients who would benefit from naltrexone treatment.

The 12-week study, led by Dr. Kathleen Carroll of the Yale University School of Medicine, randomly assigned 127 recently detoxified opioid-dependent patients to 1 of 3 treatment conditions: standard treatment with naltrexone 3 times a week; standard naltrexone treatment plus a behavioral reinforcement approach called contingency management (CM);

Long-Lasting Formulation Also May Increase Naltrexone Compliance

NIDA-supported researchers have been testing a long-lasting "depot" formulation of naltrexone that is aimed at reducing the three-times-a-week frequency with which patients must now take the medication to prevent them from getting high if they use heroin. The formulation is packaged in microcapsules injected under the skin that slowly release medication for several weeks. The sustained release of naltrexone is meant to maintain enough medication in the patient to suppress heroin's euphoric effects for an extended time.

Clinical trials now under way are assessing the safety and efficacy of depot naltrexone. In a recent trial, Dr. Sandra D. Comer and a team of researchers from the New York State Psychiatric Institute and Columbia University tested depot naltrexone in an 8-week inpatient study with 12 heroin-dependent subjects to see how long the medication remains active in the human body and blocks heroin's effects. After detoxification, six patients received a low dose (192 mg) and six received a high dose (384 mg) of the medication. Patients in both groups subsequently were given a placebo or intravenous heroin once a day from Monday through Friday for 6 weeks. Each week, daily doses of heroin started at 6.5 mg and increased to 12.5, 18.75, and 25 mg; the placebo was administered randomly on one of the days.

Researchers assessed subjective, performance, and physiological effects after each dose of heroin or placebo and measured plasma levels of naltrexone over the course of the study. They found that both doses of depot naltrexone substantially suppressed the patients' ratings of heroin's pleasurable effects and how much they "liked" the drug and wanted to take it again. With the high dose of naltrexone, patients' positive ratings of heroin's pleasurable effects remained low for 5 weeks. In the 6th week, ratings increased significantly relative to week one after patients received the 18.75- and 25-mg injections of heroin. The low dose suppressed positive ratings of heroin for 3 weeks. Plasma levels of naltrexone remained above 1 ng/mL for 4 weeks with the high dose and 3 weeks with the low dose. Though these levels are low compared to those resulting from standard naltrexone treatment doses, other studies have reported that even with negligible plasma levels, naltrexone continues to counter heroin's effects. Other than initial discomfort at the site of naltrexone injection, there were no untoward side effects.

The results suggest that once-a-month administration of the depot formulation can provide safe, long-lasting blockade of the effects of intravenous "street-level" heroin doses in patients who have undergone detoxification. Future studies will address questions that remain about optimal dose levels for naltrexone treatment of heroin dependence, such as what effects different doses have on withdrawal, craving, and the ability to reduce heroin use.

Source: Comer, S.D., et al. Depot naltrexone: Long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology* 159:351-360, 2002.

or standard naltrexone treatment and CM plus involvement of a significant other (SO) in up to 6 family counsel-

ing sessions. SO treatment was added to CM for patients in the third group to test the idea that encouragement

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New Approaches Seek To Expand Naltrexone Use in Heroin Treatment

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and positive reinforcement from a significant other might help patients cope with any protracted drug withdrawal symptoms and remain in treatment longer. Patients in all three groups participated in weekly cognitive-behavioral group counseling sessions.

Patients in the CM groups could earn vouchers, which they could exchange for goods and services, in separate tracks for naltrexone compliance or drug-free tests. In each track, the voucher value started at \$0.80, escalated in \$0.40 increments for continuous compliance or abstinence, and were reset to the starting point for each failure to take the medication or pass a drug test. Over the course of the study, patients in the CM groups earned an average of \$189 in vouchers out of the maximum \$561 that could be earned for perfect medication compliance and all negative drug tests.

The researchers found that on average, patients in the two CM groups stayed in treatment 7.4 weeks, significantly longer than the 5.6 weeks for those in standard treatment. A much higher percentage of CM patients also completed the full 12-week treatment period—47 percent of CM plus SO patients, 42.9 percent in the CM group, and 25.6 percent of patients in the standard treatment group. These retention rates with CM added to standard treatment also compare favorably with rates achieved in previous studies of standard naltrexone treatment, which have reported that 60 to 70 percent of patients dropped out of treatment over a 12-week period, Dr. Carroll notes.

Patients in the CM groups also had significantly better treatment outcomes than those in the standard naltrexone group—more days of abstinence, longer periods of continuous abstinence, more opiate-free tests, and a higher percentage of drug-free specimens. Additional analyses suggested CM patients made greater reductions than standard treatment patients in the frequency with which

they used opiates as the study progressed. Thus, 100 percent of patients reported weekly opioid use at the beginning of the study, but fewer than 10 percent of those who completed treatment reported weekly use over the last 4 weeks of the study. Although adding SO to CM did not improve most treatment outcomes, further analysis suggested it did produce a significant reduction in family problems over time.

“Our study shows you can really bump up medication compliance and outcomes with very simple behavioral interventions,” Dr. Carroll says. “It doesn’t take much effort or cost for treatment programs to do this, particularly if you look at the potential savings from keeping patients in treatment longer where they can learn how not to be drug users.”

Source

- Carroll, K.M., et al. Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: Efficacy of contingency management and significant other involvement. *Archives of General Psychiatry* 58(8):755-761, 2001. **NN**

Cocaine’s Effect on Blood Components May Be Linked to Heart Attack and Stroke

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neither group showed any compensatory increase in ant clotting mechanisms suggests that cocaine use upsets the body’s ability to maintain a balance between risk and protective factors and tips the scale toward increased risk for heart attack or stroke.”

The findings are preliminary, Dr. Siegel cautions, and based on a relatively small sample of cocaine users. “Other factors certainly play a role in CRP levels, and cocaine alone is

probably not responsible for the elevated levels we found. For example, age is a factor but does not account for all of the difference. Smoking also may be a factor. In our study, cocaine users who smoked had higher CRP levels than those who did not. On the whole, these findings suggest that cocaine compounds the effects of other risk factors.”

If larger studies confirm the relationship between elevated CRP levels and cumulative cocaine exposure, the blood component may serve as a marker for damage, Dr. Siegel says. Moreover, he adds, “measuring CRP is simple and inexpensive, and could be used as a test for the effects of cocaine

in much the same way as blood composition is used to test for diabetes. It could serve as an objective measure of risk for heart attack and stroke and provide a way for patients and treatment providers to assess progress during drug treatment.”

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Animal Studies Show Sex Differences in Impact of Efforts To Reduce Drug Seeking

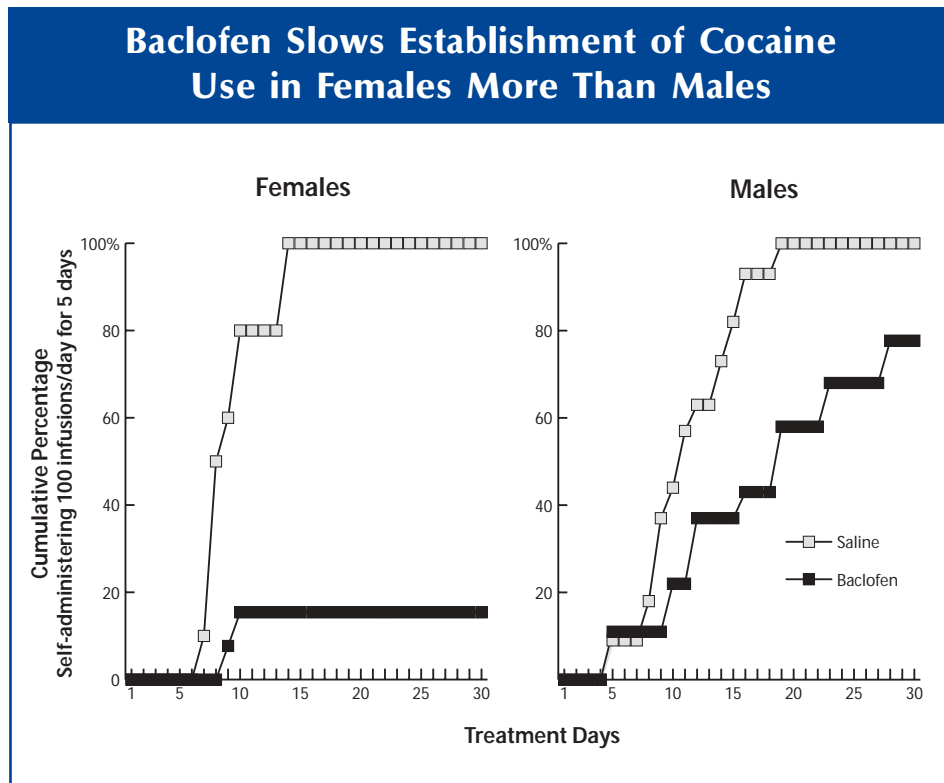
By Jill Schlabig Williams
NIDA NOTES Contributing Writer

In recent studies, Dr. Marilyn Carroll and her colleagues at the University of Minnesota looked at the impact of two interventions on self-administration of heroin and cocaine by rats and found that, in each case, the intervention produced a greater effect on the female rats studied than on the male rats. These findings and the results of other studies looking at sex differences suggest that the most effective drug abuse treatments for men and women may be quite different.

In one study, Dr. Carroll found that administering baclofen, a muscle relaxer, suppressed the establishment of cocaine use significantly more in female rats than in males. The other study looked at the effect of offering wheel-running as an alternative to drug-seeking behavior; again, the result was that only female rats significantly decreased their levels of drug self-administration—in this case, cocaine.

“These studies highlight the importance of paying attention to sex differences in the development of pharmacotherapies and in other drug abuse research,” says Dr. Cora Lee Wetherington, NIDA’s women and gender research coordinator. “For example, some smoking cessation medications seem to work better for men; others work better for women. As new medications are developed for other forms of drug abuse, the story may be similar. Treatment effects may not be the same in males and females.”

“We are increasingly finding that sex and hormonal status are impor-



Pretreatment with baclofen has been shown to slow the establishment of cocaine use in rats. Among rats pretreated with baclofen, only 15.4 percent of females self-administered an average of 100 cocaine infusions for 5 consecutive days during a 30-day trial, compared to 77.7 percent of males. Under saline pretreatment, all of the animals tested reached this injection frequency and consistency within 30 days.

tant determinants of drug abuse at all phases of addiction—acquisition, maintenance, escalation/dysregulation, and reinstatement,” says Dr. Carroll, whose previous animal research has consistently found that females tend to use more drugs, more quickly. Recent epidemiological data indicate that in humans, females also tend to progress to dependence at a faster rate than males.

In the first study, Dr. Carroll and her colleagues examined the effects of baclofen on 44 rats that had never

been exposed to cocaine. Previous animal studies have demonstrated the promise of baclofen, which modulates several neurotransmitter systems, as a potential treatment medication. Each rat participated in 30 daily sessions. During the first six hours of each session, the rats were given repeated, random infusions of baclofen at a relatively low dose of 0.2 mg/kg. For each infusion, a lever extended into the cage where it stayed for 15 seconds, after which the cocaine was administered and the lever retracted.

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Animal Studies Show Sex Differences in Impact of Efforts To Reduce Drug Seeking

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If the animal touched the lever during the 15-second latency period, cocaine was administered immediately. In this manner, the rats learned within a few days to associate the lever with drug infusions and to push the lever to self-administer cocaine. A second 6-hour component each day allowed the rats to freely self-administer cocaine; the lever remained extended into the cage and a dose of cocaine was delivered each time the lever was pressed.

To test the effects of baclofen on the rate of acquisition of a habit of regular drug-taking, investigators divided the rats into four groups. One male and one female group were injected with baclofen prior to each session; another male and another female group were pretreated with saline. Researchers measured the number of infusions each rat received during the self-administration session until it reached the acquisition criterion or level at which it was considered to have developed a habit of cocaine use, defined as an average of 100 infusions per day for 5 days.

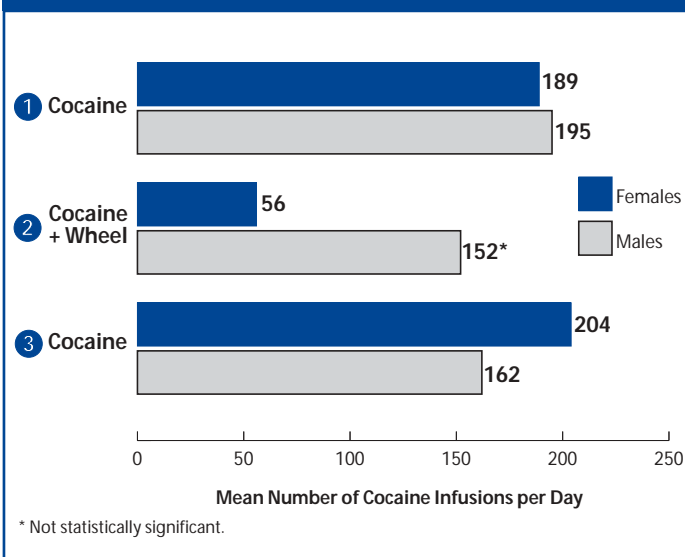
All of the female rats pretreated with saline reached the acquisition criterion by day 14. All males pretreated with saline met the criterion by day 19. In the group of female rats pretreated with baclofen, only 15.4 percent met the acquisition criterion within the 30-day limit. In contrast, 77.7 percent of males pretreated with baclofen met the criterion within the 30-day limit. When baclofen treatment was discontinued, all of the females who initially did not meet the acquisition criterion did so within 11 days.

“Pretreatment with baclofen slowed the rate at which the rats reached the specified level of cocaine self-administration and reduced the percentage of rats reaching that level to a greater extent in females than in males,” says Dr. Carroll. “The propensity of the female rats to use cocaine at the specified levels was no different than that of the males, because they all acquired a habit of cocaine use without baclofen. It was just that the baclofen had a different effect on the females.”

The next study looked at sex differences identified as a result of a behavioral intervention to reducing drug use. “Enriching the environment is a promising approach to reducing the initiation, maintenance, and reinstatement of drug abuse,” says Dr. Carroll. (See also, “Social Environment Appears Linked to Biological Changes in Dopamine System, May Influence Vulnerability to Cocaine Addiction,” *NIDA NOTES* Vol. 17, No. 5.) In this study, rats were offered access to a running wheel as an alternative to self-administering cocaine. Wheel-running is an activity rats enjoy, and research has shown that when given a choice between food and running wheels, rats often chose running over eating.

Seventeen rats were initially given access to a running wheel alone until

Access to Wheel-Running Decreased Cocaine Self-Administration in Females



Having access to a running wheel as an alternative to drug-seeking behavior caused a 70-percent reduction in cocaine self-administration among females. The difference for males was not statistically significant. In succession, the rats studied were given access to (1) cocaine only; (2) cocaine and the wheel; and (3) cocaine only.

their average daily number of wheel rotations stabilized. Next, rats were trained to self-administer cocaine (0.2 mg/kg) until they reached an average of 100 infusions a day for 5 consecutive days. The rats were then given concurrent access to cocaine and the running wheel. Researchers calculated the mean number of wheel rotations and mean number of cocaine infusions during the last five sessions of each phase.

Under cocaine-only conditions, both males and females averaged 30 infusions per hour. Females saw a reduction of 70.6 percent in infusions to fewer than 10 per hour when there was concurrent access to the running wheel. In males, while infusions decreased slightly (21.9 percent) to an average of 25 infusions per hour, the reduction was not statistically significant.

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Dr. Nora D. Volkow Named NIDA Director

Dr. Nora D. Volkow, a prominent drug abuse researcher who pioneered the use of new imaging technologies to investigate neurochemical functions in the human brain that underpin drug addiction, has been appointed to the post of NIDA Director by Dr. Elias Adam Zerhouni, director of the National Institutes of Health. Dr. Volkow will assume her duties on April 15, 2003. As NIDA's fifth director since the Institute was created in 1974, Dr. Volkow succeeds Dr. Glen R. Hanson, who has served as NIDA's Acting Director since December 2001. Dr. Hanson will resume his professorship in the Department of Pharmacology and Toxicology at the University of Utah and his research on the neurochemical and neurotoxic consequences of psychostimulants. He also will serve as the director of the Utah Addiction Center.

Dr. Volkow comes to NIDA from Brookhaven National Laboratory (BNL) in Upton, New York, where she served for 15 years in a variety of leadership, research, and teaching positions. Among the BNL positions she held concurrently at the time of her NIDA appointment were associate director for life sciences, director of nuclear medicine, and director of the Regional Neuroimaging Center funded by NIDA and the U.S. Department of Energy. The Center has been a world leader in the development of radio-labeled compounds that make it possible to track biochemical activity and see how aging, mental illness, and abused drugs affect the human brain. Dr. Volkow also was associate dean of the School of Medicine and a professor in the Department of Psychiatry



Dr. Nora D. Volkow will become the fifth director of NIDA on April 15, 2003.

at the State University of New York (SUNY)-Stony Brook.

"With Dr. Volkow's appointment to head NIDA, drug abuse researchers, practitioners, and patients have gained a strong leader capable of focusing scientific investigation on the root causes of drug addiction and the factors that influence its progression," said Dr. Zerhouni. "The research, leadership, and communication skills Dr. Volkow exhibited during her tenure at Brookhaven demonstrate her ability to advance NIDA's mission of increasing knowledge about drug addiction that will foster improved prevention and treatment of this destructive disease," he said.

At Brookhaven, Dr. Volkow's research revolved around the concept that drug addiction changes the brain in fundamental and long-lasting ways that promote continued addictive behavior. With support from NIDA,

other NIH Institutes, and the Department of Energy, Dr. Volkow used rapidly evolving brain imaging technologies, such as positron emission tomography (PET), to investigate the neurochemical mechanisms underlying the addictive and toxic properties of drugs of abuse in the human brain. Dr. Volkow's studies document fundamental changes in the addicted brain, such as decreased functioning of the neuronal system that relies on the neurotransmitter dopamine to modulate moods, pleasurable feelings, and other important functions. These functional impairments in the dopamine system are associated with changes in frontal brain regions that may contribute to the loss of behavioral control that characterizes addiction. Dr. Volkow's findings support a biomedical model of drug addiction that has gained widespread acceptance in recent years: the concept that addiction is a chronic brain disease that should be treated medically.

Dr. Volkow's research also has helped to shed light on underlying neurobiological mechanisms that appear to play a role in individual differences in vulnerability to drug abuse, alcoholism, and other compulsive disorders characterized by loss of behavioral control. Her studies have focused on neurochemical mechanisms responsible for variations in how different individuals respond to drugs of abuse. For example, Dr. Volkow's PET studies indicate that whether individuals have low or high levels of a specific receptor for dopamine in the brain's reward circuits may determine their reaction to dopamine-boosting drugs of abuse

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and can affect whether or not they are likely to continue to abuse drugs.

Dr. Volkow's work includes more than 275 peer-reviewed publications, three edited books, and more than 50 book chapters and other manuscripts. Her career has been distinguished by numerous awards since she garnered several outstanding scholarship

awards as a medical student at the National University of Mexico in Mexico City, where she received her M.D., and at New York University, where she received postdoctoral training in psychiatry.

After a 3-year assistant professorship at the University of Texas Medical School, Dr. Volkow joined BNL as an associate scientist and SUNY-Stony Brook as assistant professor in the Psychiatry Department. Over the ensuing decade and a half, she filled a series of successively

more senior administrative, research, and teaching positions, culminating in the leadership posts she currently holds at both institutions. In the last 5 years, Dr. Volkow's work has been honored with awards from the Society of Nuclear Medicine and the American College of Neuropsychopharmacology, among others. In 2000, she was elected to membership in the Institute of Medicine in the National Academy of Sciences. **NN**

Few Middle Schools Use Proven Prevention Programs

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Dr. Ennett. "To be successful, prevention programs need more than effective content," Dr. Ennett explains. "They also must be delivered effectively, by instructors who involve students in role-playing and other interactive, participatory activities. Unfortunately, we found that only about 21 percent of instructors used effective, interactive delivery."

In all, the researchers summarize, only one school in seven offers prevention programs that incorporate elements proven to be effective and

delivers the content in the most effective way.

These findings paint a discouraging picture, observes Dr. Elizabeth Robertson of NIDA's Prevention Research Branch, but it may be improving. "Dr. Ennett and Dr. Ringwalt gathered their data only a year or so after the Department of Education issued the Principles of Effectiveness that could help schools select the most effective prevention programs. It's likely that more schools are now using materials that meet the guidelines for demonstrated effectiveness," Dr. Robertson says. "And instructors working with effective programs are likely to deliver the program content effectively. When both

content and delivery are combined day-to-day in the classroom, we should begin to see, in studies such as the annual Monitoring the Future survey, major reductions in substance abuse among school-age youth."

Sources

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- Ringwalt, C., et al. The prevalence of effective substance abuse prevention curricula in U.S. middle schools. *Prevention Science* 2(4):257-265, 2002.

NN

Animal Studies Show Sex Differences in Impact of Efforts To Reduce Drug Seeking

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"Taken together, these studies suggest that females rats are more responsive than males to treatments for drug abuse," says Dr. Carroll. Although few data exist on sex differences regarding treatment of drug abuse in humans, research is

beginning to point to hormones as one cause of sex differences in drug abuse. "A growing body of research indicates that ovarian hormones, such as estrogen, may account for many of the sex differences in drug abuse, increasing the subjective effects of drugs and their reinforcing potential." More studies are needed, both in animals and humans, to better understand these sex differences and to use this knowledge to improve treatment options.

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Teen Smoking Dropped Dramatically in 2002

Cigarette smoking by 8th-, 10th-, and 12th-grade students decreased sharply in 2002, reaching the lowest levels ever reported by the annual Monitoring the Future (MTF) survey. The survey, which is supported by NIDA and conducted by the University of Michigan, began gathering smoking data for high school seniors in 1975 and added 8th- and 10th-graders to the survey in 1991. Smoking rates peaked in 1996 for students in grades 8 and 10 and in 1997 for seniors.

The declines in cigarette smoking reported in 2002 occurred across the board—among white, African-American, and Hispanic boys and girls in all regions of the country. The cumulative decline in teen smoking overall is quite dramatic. Over the last 6 years, the proportion of eighth-graders who reported ever having smoked has dropped from 49.2 percent to 31.4 percent.

The steady decrease in smoking rates among young Americans parallels several years in which increased proportions of teens said they believe there is a “great” health risk associated with cigarette smoking and expressed disapproval of pack-a-day smokers. Roughly 60 percent of 10th- and 12th-graders and 64 percent of 8th-graders agreed with the statement, “I think becoming a smoker reflects poor judgment.”

“Young people are getting the message, and increased awareness of the risks of smoking is being translated into better choices about behavior,” notes NIDA Acting Director Dr. Glen Hanson. “Smoking is the leading preventable cause of death and sickness in this country. Nearly all adults who smoke began before age 18, so every young person’s decision not to

Annual Prevalence of Teen Smoking, 1991-2002

Year	91	92	93	94	95	96	97	98	99	00	01	02
Lifetime (Have ever smoked)												
8th-graders	44.0	45.2	45.3	46.1	46.4	49.2*	47.3	45.7	44.1	40.5	36.6	31.4*
10th-graders	55.1	53.5	56.3	56.9	57.6	61.1	60.2	57.7	57.6	55.1	52.8	47.4
12th-graders	63.1	61.8	61.9	62.0	64.2	63.5	65.4	65.3	64.6	62.5	61.0	57.2
Current (Have smoked at least once in the past 30 days)												
8th-graders	14.3	15.5	16.7	18.6	19.1	21.0	19.4	19.1	17.5	14.6	12.2	10.7
10th-graders	20.8	21.5	24.7	25.4	27.9	30.4	29.8	27.6	25.7	23.9	21.3	17.7
12th-graders	28.3	27.8	29.9	31.2	33.5	34.0	36.5	35.1	34.6	31.4	29.5	26.7
Daily (Smoked at least one cigarette per day during the past month)												
8th-graders	7.2	7.0	8.3	8.8	9.3	10.4	9.0	8.8	8.1	7.4	5.5	5.1
10th-graders	12.6	12.3	14.2	14.6	16.3	18.3	18.0	15.8	15.9	14.0	12.2	10.1
12th-graders	18.5	17.2	19.0	19.4	21.6	22.2	24.6	22.4	23.1	20.6	19.0	16.9

*Bold black indicates highest level ever; bold blue indicates lowest level.

In 2002, the percentages of 8th-, 10th-, and 12th-grade students who have ever smoked, are current smokers, or who smoke daily reached the lowest levels reported since the Monitoring the Future survey began gathering smoking data for all three grades in 1991.

smoke represents a longer and more productive life.”

The 2002 survey included responses from roughly 15,000 8th-graders, 14,000 10th-graders, and 13,000 seniors. Students were asked about lifetime use (Have you ever smoked a cigarette?), current use (Have you smoked at all in the past 30 days?), and daily use (Have you smoked at least once per day for the past 30 days?) of cigarettes. Students also were asked if they believed smoking one or more packs of cigarettes per day involved “no risk,” “slight risk,” “moderate risk,” or “high risk” and if they “disapprove,” “strongly disapprove,” or “don’t disapprove” of people smoking one or more packs of cigarettes per day. **NN**

For More Information

Detailed information about patterns of use of tobacco, alcohol, and illicit drugs by teenage Americans since 1975 is available at the Monitoring the Future Web site: <http://monitoringthefuture.org>. Additional information about smoking and nicotine addiction can be found on NIDA’s Web site: www.drugabuse.gov.

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