

Research Report

SERIES

TOBACCO Addiction

Tobacco use kills nearly half a million Americans each year, with one in every six U.S. deaths the result of smoking. Smoking harms nearly every organ of the body, causing many diseases and compromising smokers' health in general. Nicotine, a component of tobacco, is the primary reason that tobacco is addictive, although cigarette smoke contains many other dangerous chemicals, including tar, carbon monoxide, acetaldehyde, nitrosamines, and more.

An improved overall understanding of addiction and of nicotine as an addictive drug has been instrumental in developing medications and behavioral treatments for tobacco addiction. For example, the nicotine patch and gum, now readily available at drugstores and supermarkets nationwide, have proven effective for smoking cessation when combined with behavioral therapy.

Advanced neuroimaging technologies further assist this mission by allowing researchers to observe changes in brain function that result from smoking tobacco. Researchers have also identified new roles for genes that predispose people to tobacco addiction and predict their response to smoking cessation treatments. These findings—and many other recent research accomplishments—are affording us unique opportunities to discover, develop, and disseminate new treatments for tobacco addiction, as well as scientifically based prevention programs to help curtail the public health burden that tobacco use represents.

We hope this Research Report, summarizing the latest scientific information about tobacco addiction, will help readers understand its harmful effects as well as identify best practices for its prevention and treatment.

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What is the extent and impact of tobacco use?

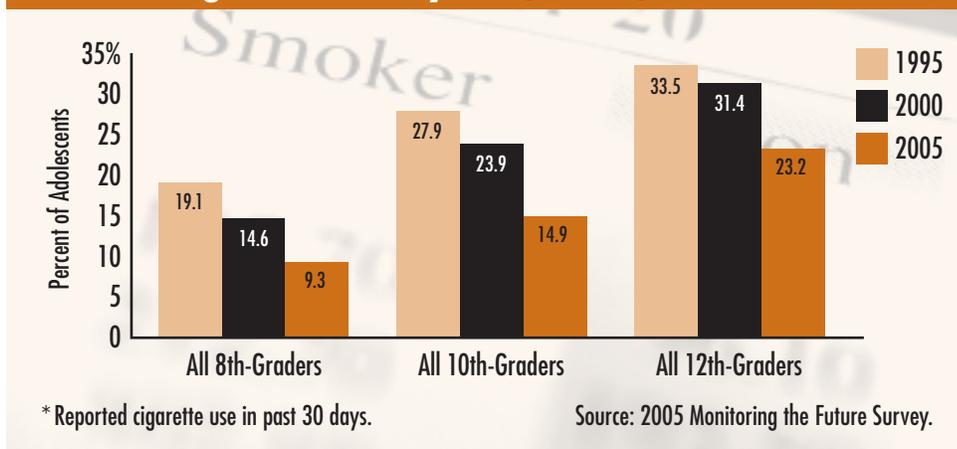
According to the 2004 National Survey on Drug Use and Health, an estimated 70.3 million Americans age 12 or older reported current use of tobacco—59.9 million (24.9 percent of the population) were current cigarette smokers, 13.7 million (5.7 percent) smoked cigars, 1.8 million (0.8 percent) smoked pipes, and 7.2 million (3.0 percent) used smokeless tobacco, confirming that tobacco is one of the most widely abused substances in the United States. While these numbers are still

unacceptably high, they represent a decrease of almost 50 percent since peak use in 1995.

NIDA's 2005 Monitoring the Future Survey of 8th-, 10th-, and 12th-graders, used to track drug use patterns and attitudes, has also shown a striking decrease in smoking trends among the Nation's youth. The latest results indicate that about 9 percent of 8th-graders, 15 percent of 10th-graders, and 23 percent of 12th-graders had used cigarettes in the 30 days prior to the survey. Despite cigarette use being at the lowest levels of the survey since a peak in the mid-1990s, the past few years indicate a clear slowing of this decline. And while perceived risk and disapproval of

from the director

Current* Cigarette Use by 8th-, 10th-, and 12th-Graders



smoking had been on the rise, recent years have shown the rate of change to be dwindling. In fact, current use, perceived risk, and disapproval leveled off among 8th-graders in 2005, suggesting that renewed efforts are needed to ensure that teens understand the harmful consequences of smoking.

Moreover, the declining prevalence of cigarette smoking among the general U.S. population is not reflected in patients with mental illnesses. For them, it remains substantially higher, with the incidence of smoking in patients suffering from post-traumatic stress disorder, bipolar disorder, major depression, and other mental illness twofold to fourfold higher than the general population, and smoking incidence among people with schizophrenia as high as 90 percent.

Tobacco use is the leading preventable cause of death in the United States. The impact of tobacco use in terms of morbidity and mortality costs to society is staggering. Economically, more than \$75 billion of total U.S. healthcare costs each year is attributable directly to smoking. However, this cost is well below the total cost to society because it does not include burn care from smoking-related fires, perinatal care for low birth-weight infants of mothers who smoke, and medical care costs associated with disease caused by secondhand smoke. In addition to healthcare costs, the costs of lost productivity due to smoking effects are estimated at \$82 billion per year, bringing a conservative estimate of the economic burden of smoking to more than \$150 billion per year.



How does tobacco deliver its effects?

There are more than 4,000 chemicals found in the smoke of tobacco products. Of these, nicotine, first identified in the early 1800s, is the primary reinforcing component of tobacco that acts on the brain.

Cigarette smoking is the most popular method of using tobacco; however, there has also been a recent increase in the sale and consumption of smokeless tobacco products, such as snuff and chewing tobacco. These smokeless products also contain nicotine, as well as many toxic chemicals.

The cigarette is a very efficient and highly engineered drug-delivery system. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of nicotine per cigarette. When tobacco is smoked, nicotine rapidly reaches peak levels in the bloodstream and enters the brain. A typical smoker will take 10 puffs on a cigarette over a period of 5 minutes that the

cigarette is lit. Thus, a person who smokes about 1-1/2 packs (30 cigarettes) daily gets 300 “hits” of nicotine to the brain each day. In those who typically do not inhale the smoke—such as cigar and pipe smokers and smokeless tobacco users—nicotine is absorbed through the mucosal membranes and reaches peak blood levels and the brain more slowly.

Immediately after exposure to nicotine, there is a “kick” caused in part by the drug’s stimulation of the adrenal glands and resulting discharge of epinephrine (adrenaline). The rush of adrenaline stimulates the body and causes a sudden release of glucose, as well as an increase in blood pressure, respiration, and heart rate. Nicotine also suppresses insulin output from the pancreas, which means that smokers are always slightly hyperglycemic (i.e., they have elevated blood sugar levels). The calming effect of nicotine reported by many users is usually associated with a decline in withdrawal effects rather than direct effects of nicotine.

Is nicotine addictive?

Yes. Most smokers use tobacco regularly because they are addicted to nicotine. Addiction is characterized by compulsive drug seeking and use, even in the face of negative health consequences. It is well documented that most smokers identify tobacco use as harmful and express a desire to reduce or stop using it, and nearly 35 million of them want to quit each year. Unfortunately, only about 6 percent of people who try to quit are successful for more than a month.

Research has shown how nicotine acts on the brain to produce a number of effects. Of primary importance to its addictive nature are findings that nicotine activates reward pathways—the brain circuitry that regulates feelings of pleasure. A key brain chemical involved in mediating the desire to consume drugs is the neurotransmitter dopamine, and research has shown that nicotine increases levels of dopamine in the reward circuits. This reaction is similar to that seen with other drugs of abuse, and is thought to underlie the pleasurable sensations experienced by many smokers. Nicotine's pharmacokinetic properties also enhance its abuse potential. Cigarette smoking produces a rapid distribution of nicotine to the brain, with drug levels peaking within 10 seconds of inhalation. However, the acute effects of nicotine dissipate in a few minutes, as do the associated feelings of reward, which causes the smoker to continue dosing to maintain the drug's pleasurable effects and prevent withdrawal.

Nicotine withdrawal symptoms include irritability, craving, cognitive and attentional deficits, sleep disturbances, and increased appetite. These symptoms may begin within a few hours after the last cigarette, quickly driving people back to tobacco use. Symptoms peak within the first few days of smoking cessation and may subside within a few weeks. For some people, however, symptoms may persist for months.

While withdrawal is related to the pharmacological effects of nicotine, many behavioral factors can also affect the severity of withdrawal symptoms. For some people, the feel, smell, and sight of a cigarette and the ritual of obtaining, handling, lighting, and smoking the cigarette are all associated with the pleasurable effects of smoking and can make withdrawal or craving worse. While nicotine gum and patches may alleviate the pharmacological aspects of withdrawal, cravings often persist. Other forms of nicotine replacement, such as inhalers, attempt to address some of these other issues, while behavioral therapies can help smokers identify environmental triggers of withdrawal and craving so they can employ strategies to prevent or circumvent these symptoms and urges.

Are there other chemicals that may contribute to tobacco addiction?

Yes, research is showing that nicotine may not be the only psychoactive ingredient in tobacco. Using advanced neuroimaging technology, scientists can see the dramatic effect of cigarette

smoking on the brain and are finding a marked decrease in the levels of monoamine oxidase (MAO), an important enzyme that is responsible for the breakdown of dopamine. This change is likely caused by some tobacco smoke ingredient other than nicotine, since we know that nicotine itself does not dramatically alter MAO levels. The decrease in two forms of MAO (A and B) results in higher dopamine levels and may be another reason that smokers continue to smoke—to sustain the high dopamine levels that lead to the desire for repeated drug use.

Recently, NIDA-funded researchers have shown in animals that acetaldehyde, another chemical constituent of tobacco smoke, dramatically increases the reinforcing properties of nicotine and may also contribute to tobacco addiction. The investigators further report that this effect is age-related, with adolescent animals displaying far more sensitivity to this reinforcing effect, suggesting that the brains of adolescents may be more vulnerable to tobacco addiction.

What are the medical consequences of tobacco use?

Cigarette smoking kills an estimated 440,000 U.S. citizens each year—more than alcohol, cocaine, heroin, homicide, suicide, car accidents, fire, and AIDS combined. Since 1964, more than 12 million Americans have died prematurely from smoking, and another 25 million U.S. smokers alive today will most likely die of a smoking-related illness.

Cigarette smoking harms every organ in the body. It has been conclusively linked to leukemia, cataracts, and pneumonia, and accounts for about one-third of all cancer deaths. The overall rates of death from cancer are twice as high among smokers as nonsmokers, with heavy smokers having rates that are four times greater than those of nonsmokers. Foremost among the cancers caused by tobacco use is lung cancer—cigarette smoking has been linked to about 90 percent of all lung cancer cases, the number-one cancer killer of both men and women. Smoking is also associated with cancers of the mouth, pharynx, larynx, esophagus, stomach, pancreas, cervix, kidney, ureter, and bladder.

In addition to cancer, smoking causes lung diseases such as chronic bronchitis and emphysema, and it has been found to exacerbate asthma symptoms in adults and children. More than 90 percent of all deaths from chronic obstructive pulmonary diseases are attributable to cigarette smoking. It has also been well documented that smoking substantially increases the risk of heart disease, including stroke, heart attack, vascular disease, and aneurysm. It is estimated that smoking accounts for approximately 21 percent of deaths from coronary heart disease each year.

Exposure to high doses of nicotine, such as those found in some insecticide sprays, can be extremely toxic as well, causing vomiting, tremors, convulsions, and death. In fact, one drop of pure nicotine can kill a person. Nicotine poisoning has been

reported from accidental ingestion of insecticides by adults and ingestion of tobacco products by children and pets. Death usually results in a few minutes from respiratory failure caused by paralysis.

While we often think of medical consequences that result from direct use of tobacco products, passive or secondary smoke also increases the risk for many diseases. Environmental tobacco smoke is a major source of indoor air contaminants; secondhand smoke is estimated to cause approximately 3,000 lung cancer deaths per year among nonsmokers and contributes to more than 35,000 deaths related to cardiovascular disease. Exposure to tobacco smoke in the home is also a risk factor for new cases and increased severity of childhood asthma and has been associated with sudden infant death syndrome. Additionally, dropped cigarettes are the leading cause of residential fire fatalities, leading to more than 1,000 deaths each year.

WARNING: There is no safe tobacco product. The use of any tobacco product—including cigarettes, cigars, pipes, and spit tobacco; mentholated, “low tar,” “naturally grown” or “additive free”—can cause cancer and other adverse health effects.

Are there safe tobacco products?

The adverse health effects of tobacco use are well known, yet many people do not want to quit or have difficulty quitting. As a result, there has been a recent surge in the development of tobacco products that claim to reduce exposure to harmful tobacco constituents or

to have fewer health risks than conventional products. These “potentially reduced exposure products” (or PREPs), which include cigarettes and smokeless tobacco (e.g., snuff, tobacco lozenges), have not yet been evaluated sufficiently to determine whether they are indeed associated with reduced risk of disease. Recent studies indicate that the levels of carcinogens in these PREPs range from relatively low to comparable to conventional tobacco products. These studies conclude that medicinal nicotine (found in the nicotine patch and gum) is a safer alternative than these modified tobacco products.

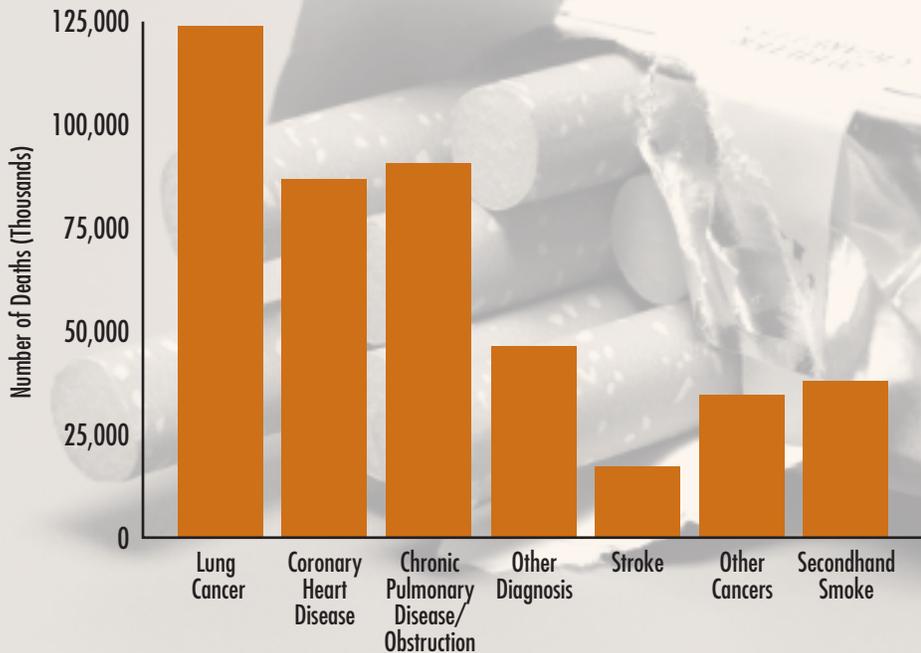
Smoking and pregnancy—What are the risks?

In the United States, it is estimated that 18 percent of pregnant women smoke during their pregnancies. Carbon monoxide and nicotine from tobacco

smoke may interfere with the oxygen supply to the fetus. Nicotine also readily crosses the placenta, with concentrations in the fetus reaching as much as 15 percent higher than maternal levels. Nicotine

concentrates in fetal blood, amniotic fluid, and breast milk. Combined, these factors can have severe consequences for the fetuses and infants of smoking mothers. Smoking during pregnancy caused an estimated 910 infant deaths annually from 1997 through 2001, and neonatal care costs related to smoking are estimated to be more than \$350 million per year.

Approximately 440,000 Annual Deaths Are Attributable to Cigarette Smoking



Source: CDC, *MMWR* 2005. 54(25):625–628

The adverse effects of smoking during pregnancy can include fetal growth retardation and decreased birth weights. The decreased birth weights seen in infants of mothers who smoke reflect a dose-dependent relationship—the more the woman smokes during pregnancy, the greater the reduction of infant birth weight. These newborns also display signs of stress and drug withdrawal consistent with what has been reported in infants exposed to other drugs. In some cases, smoking during pregnancy may be associated with spontaneous abortions, sudden infant death syndrome, as well as learning and behavioral problems in children. In addition, smoking more than a pack a day during pregnancy nearly doubles the risk that the affected child will become addicted to tobacco if that child starts smoking.

Are there gender differences in tobacco smoking?

Several avenues of research now indicate that men and women differ in their smoking behavior. For instance, women smoke fewer cigarettes per day, tend to use cigarettes with lower nicotine content, and do not inhale as deeply as men. However, it is unclear whether this is due to differences in sensitivity to nicotine or other factors that affect women differently, such as social factors or the sensory aspects of smoking.

The number of smokers in the United States declined in the 1970s and 1980s, remained relatively stable throughout the 1990s, and declined further through the early 2000s. Because this decline in smoking was greater among men

than women, the prevalence of smoking is only slightly higher for men today than it is for women. Several factors appear to be contributing to this narrowing gender gap, including increased initiation of smoking among female teens and women being less likely than men to quit.

Large-scale smoking cessation trials show that women are less likely to initiate quitting and may be more likely to relapse if they do quit. In cessation programs using nicotine replacement methods, such as the patch or gum, the nicotine does not seem to reduce craving as effectively for women as for men. Other factors that may contribute to women's difficulty with quitting are that withdrawal may be more intense for women or that women are more concerned about weight gain.

Although postcessation weight gain is typically modest (about 5–10 pounds), concerns about this may be an obstacle to treatment success. In fact, NIDA research has found that when women's weight concerns were addressed during cognitive-behavioral therapy, they were more successful at quitting than women who were in a program designed only to attenuate postcessation weight gain. Other NIDA researchers have found that medications used for smoking cessation, such as bupropion and naltrexone, can also attenuate postcessation weight gain and could become an additional strategy for enhancing treatment success.

It is important for treatment professionals to be aware that standard regimens may have to be adjusted to compensate for gender differences in nicotine sensitivity and in other related factors that contribute to continued smoking.

Smoking and adolescence

There are nearly 4 million American adolescents who have used a tobacco product in the past month. Nearly 90 percent of smokers start smoking by age 18, and of smokers under 18 years of age, more than 6 million will die prematurely from a smoking-related disease.

Tobacco use in teens is not only the result of psychosocial influences, such as peer pressure; recent research suggests that there may be biological reasons for this period of increased vulnerability. Indeed, even intermittent smoking can result in the development of tobacco addiction in some teens. Animal models of teen smoking provide additional evidence of an increased vulnerability. Adolescent rats are more susceptible to the reinforcing effects of nicotine than adult rats, and take more nicotine when it is available than do adult animals.

Adolescents may also be more sensitive to the reinforcing effects of nicotine in combination with other chemicals found in cigarettes, thus increasing susceptibility to tobacco addiction. As mentioned above, acetaldehyde increases nicotine's addictive properties in adolescent, but not adult, animals. That is, adolescent animals performing a task to receive nicotine showed greater response rates to nicotine when combined with acetaldehyde. NIDA continues to actively support research aimed at increasing our understanding of why and how adolescents become addicted, and to develop prevention, intervention, and treatment strategies to meet the specific needs of teens.

Numerous Forms of Treatment Are Available:

- Behavioral Therapy
- Nicotine Replacement
 - Patch
 - Gum
 - Nasal Spray
- Other Medications

Are there effective treatments for tobacco addiction?

Yes, extensive research has shown that treatments for tobacco addiction do work. Although some smokers can quit without help, many individuals need assistance in quitting. This is particularly important because smoking cessation can have immediate health benefits. For example, within 24 hours of quitting, blood pressure and chances of heart attack decrease. Long-term benefits of smoking cessation include decreased risk of stroke, lung and other cancers, and coronary heart disease. A 35-year-old man who quits smoking will, on average, increase his life expectancy by 5.1 years.

Nicotine Replacement Treatments

Nicotine replacement therapies (NRTs), such as nicotine gum and the transdermal nicotine patch, were the first pharmacological treatments approved by the Food and Drug Administration (FDA) for use in smoking cessation therapy. NRTs are used (in conjunction with behavioral support) to relieve withdrawal symptoms—

they produce less severe physiological alterations than tobacco-based systems and generally provide users with lower overall nicotine levels than they receive with tobacco. An added benefit is that these forms of nicotine have little abuse potential since they do not produce the pleasurable effects of tobacco products—nor do they contain the carcinogens and gases associated with tobacco smoke. Behavioral treatments, even beyond what is recommended on packaging labels, have been shown to enhance the effectiveness of NRTs and improve long-term outcomes.

The FDA's approval of nicotine gum in 1984 marked the availability (by prescription) of the first NRT on the U.S. market. In 1996, the FDA approved Nicorette gum for over-the-counter (OTC) sales. Whereas nicotine gum provides some smokers with the desired control over dose and the ability to relieve cravings, others are unable to tolerate the taste and chewing demands. In 1991 and 1992, the FDA approved four transdermal nicotine patches, two of which became OTC products in 1996. In 1996 a nicotine nasal spray, and in 1998 a nicotine inhaler, also became available by prescription, thus meeting the needs of many additional tobacco users. All the NRT products—gum, patch, spray, and inhaler—appear to be equally effective.

Additional Medications

Although the major focus of pharmacological treatments for tobacco addiction has been nicotine replacement, other treatments are also being studied. For example, the antidepressant bupropion was approved by the FDA in 1997 to help people quit smoking, and

is marketed as Zyban. Varenicline tartrate (Chantix) is a new medication that recently received FDA approval for smoking cessation. This medication, which acts at the sites in the brain affected by nicotine, may help people quit by easing withdrawal symptoms and blocking the effects of nicotine if people resume smoking.

Several other nonnicotine medications are being investigated for the treatment of tobacco addiction, including other antidepressants and an antihypertensive medication, among others. Scientists are also investigating the potential of a vaccine that targets nicotine for use in relapse prevention. The nicotine vaccine is designed to stimulate the production of antibodies that would block access of nicotine to the brain and prevent nicotine's reinforcing effects.

Behavioral Treatments

Behavioral interventions play an integral role in smoking cessation treatment, either in conjunction with medication or alone. They employ a variety of methods to assist smokers in quitting, ranging from self-help materials to individual cognitive-behavioral therapy. These interventions teach individuals to recognize high-risk smoking situations, develop alternative coping strategies, manage stress, improve problemsolving skills, as well as increase social support. Research has also shown that the more therapy is tailored to a person's situation, the greater the chances are for success.

Traditionally, behavioral approaches were developed and delivered through formal settings, such as smoking-cessation clinics and community and public health settings. Over the past decade,

however, researchers have been adapting these approaches for mail, telephone, and Internet formats, which can be more acceptable and accessible to smokers who are trying to quit. In 2004, the U.S. Department of Health and Human Services (HHS) established a national toll-free number, 800-QUIT-NOW (800-784-8669), to serve as a single access point for smokers seeking information and assistance in quitting. Callers to the number are routed to their state's smoking cessation quitline or, in states that have not established quitlines, to one maintained by the National Cancer Institute. In addition, a new HHS Web site (www.smoke-free.gov) offers online advice and downloadable information to make cessation easier.

Quitting smoking can be difficult. While people can be helped during the time an intervention is delivered, most intervention programs are short-term (1–3 months). Within 6 months, 75–80 percent of people who try to quit smoking relapse. Research has now shown that extending treatment beyond the typical duration of a smoking cessation program can produce quit rates as high as 50 percent at 1 year.

Where can I get further scientific information about tobacco addiction?

To learn more about tobacco and other drugs of abuse, visit the National Institute on Drug Abuse Web site at www.drugabuse.gov or call the National Clearinghouse for Alcohol and Drug Information at 800-729-6686.

Materials on the health effects of cigarettes and tobacco products and other drug abuse topics are available on the NIDA Web site (www.drugabuse.gov), and can be ordered free of charge in English and Spanish from NCADI at www.health.org.

Nicotine and tobacco information can be accessed also through these other Web sites:

NICOTINE AND TOBACCO WEB SITES

Centers for Disease Control and Prevention:
www.cdc.gov/tobacco

National Cancer Institute:
www.cancer.gov

U.S. Department of Health & Human Services: www.smokefree.gov

Society for Research on Nicotine and Tobacco: www.srnt.org

NicNet: www.nicnet.org

The Robert Wood Johnson Foundation:
www.rwjf.org

Join Together Online: www.quitnet.org

American Legacy Foundation:
www.americanlegacy.org

NIDA Web Sites

www.drugabuse.gov

www.steroidabuse.gov

www.clubdrugs.gov

www.hiv.drugabuse.gov

www.inhalant.drugabuse.gov

NCADI

Phone No.: 800-729-6686

Glossary

Addiction: A chronic, relapsing disease characterized by compulsive drug seeking and abuse and by long-lasting neurochemical and molecular changes in the brain.

Adrenal glands: Glands located above each kidney that secrete hormones, e.g., adrenaline.

Craving: A powerful, often uncontrollable desire for drugs.

Dopamine: A neurotransmitter present in regions of the brain that regulate movement, emotion, motivation, and feelings of pleasure.

Emphysema: A lung disease in which tissue deterioration results in increased air retention and reduced exchange of gases. The result is difficulty breathing and shortness of breath.

Hyperglycemic: The presence of an abnormally high concentration of glucose in the blood.

Neurotransmitter: A chemical that acts as a messenger to carry signals or information from one nerve cell to another.

Nicotine: An alkaloid derived from the tobacco plant that is responsible for smoking's psychoactive and addictive effects.

Pharmacokinetics: The pattern of absorption, distribution, and excretion of a drug over time.

Rush: A surge of euphoria that rapidly follows administration of some drugs.

Tobacco: A plant widely cultivated for its leaves, which are used primarily for smoking; the *N. tabacum* species is the major source of tobacco products.

Withdrawal: A variety of symptoms that occur after chronic use of an addictive drug is reduced or stopped.

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Access information on the Internet

- **What's new on the NIDA Web site**
- **Information on drugs of abuse**
- **Publications and communications (including NIDA Notes)**
- **Calendar of events**
- **Links to NIDA organizational units**
- **Funding information (including program announcements and deadlines)**
- **International activities**
- **Links to related Web sites (access to Web sites of many other organizations in the field)**