

BI 358 Discussion Session 2

:30 **I. Group Discussion:** DLN 2-2 thru 2-6 *Cannibas in the Clinic: The Medical Marijuana Debate.*
University of Utah, Genetic Science Learning Center, 2014
<http://learn.genetics.utah.edu/content/addiction/cannabis/>

:35 **II. Class Convenes:** w/group summary statements.

:40 **III. Regroup** (new groups!) for DLN review
Try to incorporate general model of addiction after
D.O. Norris Simplified Homeostatic Model.

#1 Alcohol DLN 2-7 thru 2-12

#2 Cocaine DLN 2-13 thru 2-20

#3 Heroin DLN 2-21 thru 2-28

#4 Marijuana DLN 2-29 thru 2-44

#5 Methamphetamine DLN 2-45 thru 2-54

#6 Tobacco-Nicotine DLN 2-55 thru 2-66

:10 **IV. Informal Group Overhead Presentations**



Paper Topic + 4 copies of Brief Outline due next T!

Be sure to visit the fabulous University of Utah website
<http://learn.genetics.utah.edu/content/addiction/mouse/>

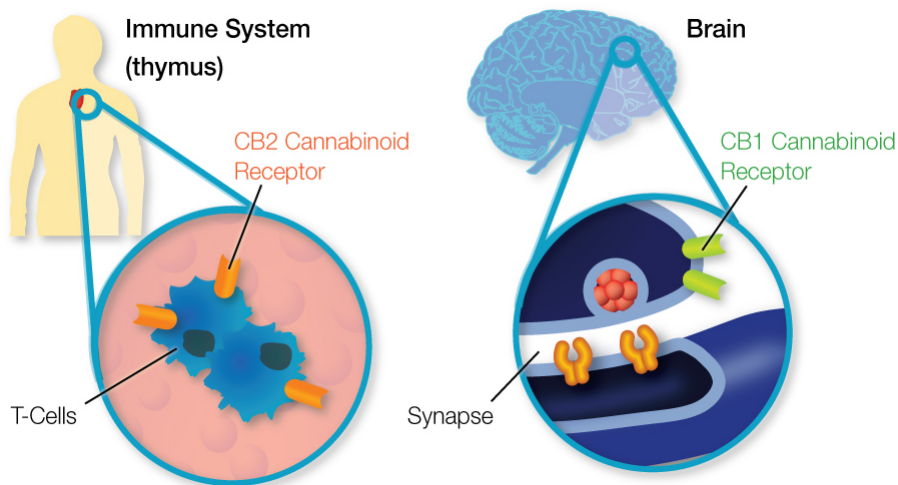
Cannabis in the Clinic: The Medical Marijuana Debate

Until its prohibition in 1937, extract of *Cannabis sativa* (marijuana) was one of the top three most prescribed medicines in the US. When it became illegal, its use as a medicine became restricted. Despite these regulations, research on the medical use of marijuana continued.

In recent years, when some states decided to legalize smoked marijuana for certain patients, medical marijuana became a subject of contentious debate. Should patients be allowed to grow their own plants? Might medical use inevitably lead to recreational use?



The Endocannabinoid System

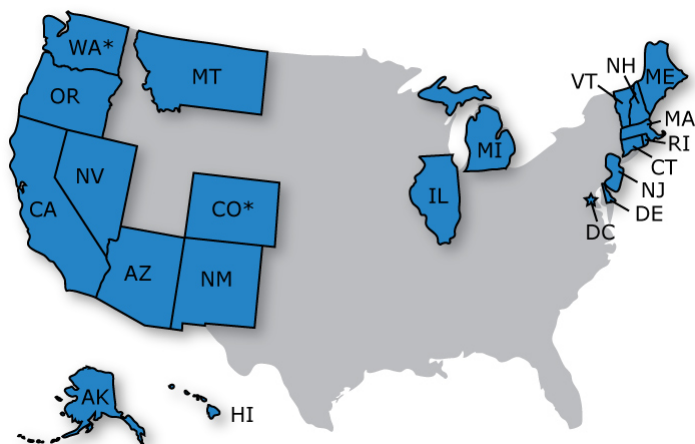


We have two types of cannabinoid receptors: CB1 receptors are expressed on the surface of neurons, and CB2 receptors are expressed on cells of the immune system.

The active compounds in marijuana are similar to a class of molecules in our bodies called endocannabinoids. The endocannabinoid system influences our immune system, protects nerve cells from premature death, and influences mood, memory, appetite, sleep, sensation, and movement. Both endocannabinoids and the compounds in marijuana bind to proteins called cannabinoid receptors in the brain and throughout the body.

"Endocannabinoids regulate every one of the systems in our bodies." --Dr. Robert Melamede

Defining Medical Marijuana



As of October, 2013, 20 states plus Washington, DC, have legalized medical marijuana. Two states (*) also allow recreational use. The trend is moving toward legalization. (The Wikipedia page Medical cannabis in the United States has up-to-date legal information.)

Each state has its own regulations to control details such as allowable quantities and registration requirements. However, in June of 2005, the Supreme Court ruled that individuals in all states can still be prosecuted under federal law, under which medical marijuana remains illegal under the Controlled Substances Act

"There are different kinds of pain." --Dr. Robert Melamede

In 1970, Congress classified cannabis and THC (one of the active compounds in cannabis) as Schedule I drugs under the Controlled Substances Act. Schedule I drugs are defined by Congress as having no medicinal value. The one exception to this classification allows for use in FDA-approved research programs.

Who can benefit?

Research suggests that there are conditions for which medical marijuana may be an effective treatment:

- Cancer - Relieves nausea during chemotherapy treatment, may prevent the spread of some cancers.

- HIV/AIDS - Increases appetite in patients experiencing severe weight loss, eases neurological symptoms.
 - Neurological disorders (including spinal cord injury and multiple sclerosis) - Reduces pain and spasticity resulting from nerve damage.
 - Inflammatory pain - Cannabinoids seem to be more effective than opiates in treating long-term, chronic pain. (Opiates are better for treating short-term acute pain.)
 - Autoimmune diseases (such as arthritis) - Suppresses the immune system, decreasing pain and inflammation.
-

Cannabinoid Delivery Methods

The active compounds in marijuana are available in several forms and can be administered in a variety of ways. Each delivery method has benefits and disadvantages.

Smoking

- (+) Delivers all of the plant's active compounds.
- (+) Easy to regulate dose (patients smoke until symptoms are eased, but are not intoxicated).
- (-) No standardization. Amounts of active ingredients may vary.
- (-) Burning marijuana produces toxins which can cause emphysema and lung cancer.
- (-) Illegal in most states.

Marinol - Synthetic THC in pill form

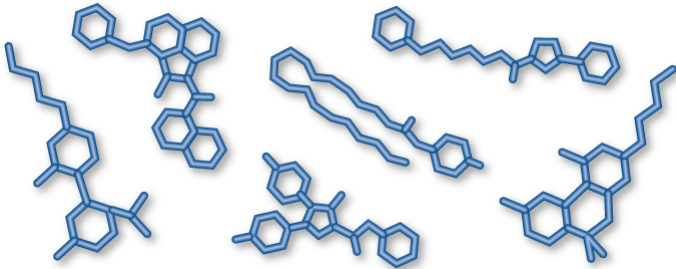
- (+) Legal in the US.
- (+) Delivers some of the benefits of the whole plant.
- (-) Difficult to control dose.
- (-) Contains only one of the plant's active compounds (THC).
- (-) Patients report fewer of the positive effects and more negative side effects.

Vaporizer

- (+) Converts the active compounds to inhalable form without releasing toxins.
- (+) Delivers all of the plant's active compounds.
- (+) Easy to control dose.
- (-) No standardization. Amounts of active ingredients may vary.
- (-) Illegal in most states.

Sativex (nabiximols) - Extract from plants delivered as a spray

- (+) Contains all of the plant's active compounds.
- (+) Concentrations of active ingredients are standardized.
- (+) Relatively easy to regulate dose.
- (+) Legally approved for the medical treatment of Multiple Sclerosis.
- (-) Legal in a limited number of countries.



Marijuana contains approximately 66 active compounds with different properties, collectively called cannabinoids. Scientists are studying cannabinoids to understand their individual and combined effects and their potential benefits.

"Studies show that Sativex (marijuana extract) is not as addicting as legal prescription medications such as opiates." --Dr. William Notcutt, Director of Sativex trials

Social Implications



Some argue that Congress should change marijuana's classification under the Controlled Substances Act. If it were no longer a Schedule I drug, its medicinal benefits could be recognized legally. But if medical marijuana were legalized, there could be repercussions outside the realm of medicine.

Opponents worry that legalizing medical marijuana might lead teens to believe that marijuana is safe for recreational use and increase availability of the drug. On the other hand, some supporters think changing the perception of marijuana from a party drug to a medication might make it less attractive to teens wanting to defy or rebel.

Legal Implications

Legalized medical marijuana also presents lawmakers with challenges. How would federal, state, and local governments control and regulate the production, distribution, and sale of medical marijuana? Who would define what is recreational versus medical use of the drug, and how would that be enforced?



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TRANSLATE





U.S. Department of Health
& Human Services

National Institutes of Health

National Institute on Alcohol Abuse
and Alcoholism

ALCOHOL ALERT

Number 77

April 2009

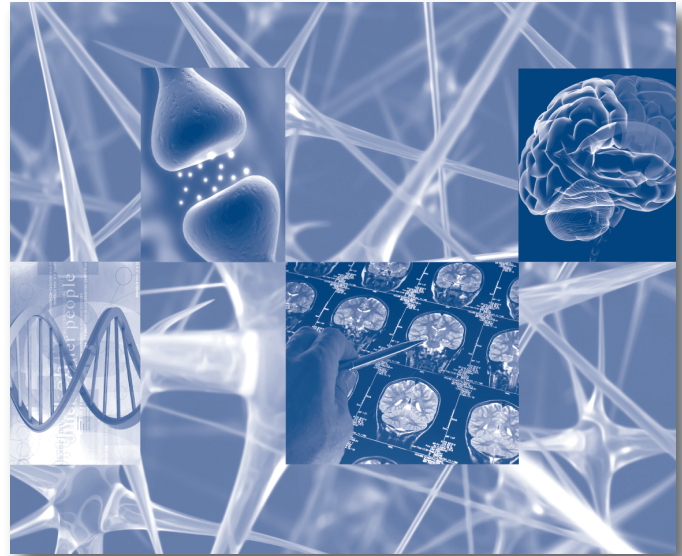
NEUROSCIENCE: PATHWAYS TO ALCOHOL DEPENDENCE

Why does drinking alcohol have such profound effects on thought, mood, and behavior? And why does alcohol dependence develop and persist in some people and not in others? Scientists are addressing these questions and others through neuroscience—the study of the brain, where both alcohol intoxication and dependence begin. Through neuroscience research, scientists are gaining a better understanding of how alcohol changes the brain and how those changes in turn influence certain behaviors.

To function normally, the brain must maintain a careful balance of chemicals called neurotransmitters—small molecules involved in the brain's communication system that ultimately help regulate the body's function and behavior. Just as a heavy weight can tip a scale, alcohol intoxication can alter the delicate balance among different types of neurotransmitter chemicals and can lead to drowsiness, loss of coordination, and euphoria—hallmarks of alcohol intoxication.

Remarkably, with ongoing exposure to alcohol, the brain starts to adapt to these chemical changes. When alcohol is present in the brain for long periods—as with long-term heavy drinking—the brain seeks to compensate for its effects. To restore a balanced state, the function of certain neurotransmitters begins to change so that the brain can perform more normally in the presence of alcohol. These long-term chemical changes are believed to be responsible for the harmful effects of alcohol, such as alcohol dependence.

“When alcohol is present in the brain for long periods—as with long-term heavy drinking—the brain seeks to compensate for its effects.”



Today, thanks to rapidly advancing technology, researchers know more than ever about how alcohol affects the brain and how the brain responds and adapts to these effects. This *Alcohol Alert* summarizes some of what we know about alcohol's short- and long-term effects on the brain and how breakthroughs in neuroscience are leading to better treatments for alcohol-related problems.

HOW ALCOHOL CHANGES THE BRAIN: TOLERANCE AND WITHDRAWAL

As the brain adapts to alcohol's presence over time, a heavy drinker may begin to respond to alcohol differently than someone who drinks only moderately. Some of these changes may be behind alcohol's effects, including alcohol tolerance (i.e., having to drink more in order to become intoxicated) (1) and alcohol withdrawal symptoms. These effects are associated with alcohol dependence.

When the brain is exposed to alcohol, it may become tolerant—or insensitive—to alcohol's effects. Thus, as a person

continues to drink heavily, he or she may need more alcohol than before to become intoxicated. As tolerance increases, drinking may escalate, putting a heavy drinker at risk for a number of health problems—including alcohol dependence.

Even as the brain becomes tolerant to alcohol, other changes in the brain may increase some people's sensitivity to alcohol. Desire for alcohol may transition into a pathological craving for these effects. This craving is strongly associated with alcohol dependence (1).

Other changes in the brain increase a heavy drinker's risk for experiencing alcohol withdrawal—a collection of symptoms that can appear when a person with alcohol dependence suddenly stops drinking. Withdrawal symptoms can be severe, especially during the 48 hours immediately follow-

ing a bout of drinking. Typical symptoms include profuse sweating, racing heart rate, and feelings of restlessness and anxiety (2). Research shows that alcohol-dependent people may continue drinking to avoid experiencing withdrawal. Feelings of anxiety associated with alcohol withdrawal can persist long after the initial withdrawal symptoms have ceased, and some researchers believe that—over the long term—this anxiety is a driving force behind alcohol-use relapse (3).

THE BRAIN'S UNIQUE COMMUNICATION SYSTEM

Tolerance and withdrawal are tangible evidence of alcohol's influence on the brain. Scientists now understand some of the mechanisms that lead to these changes—changes that begin with the brain's unique communication system.

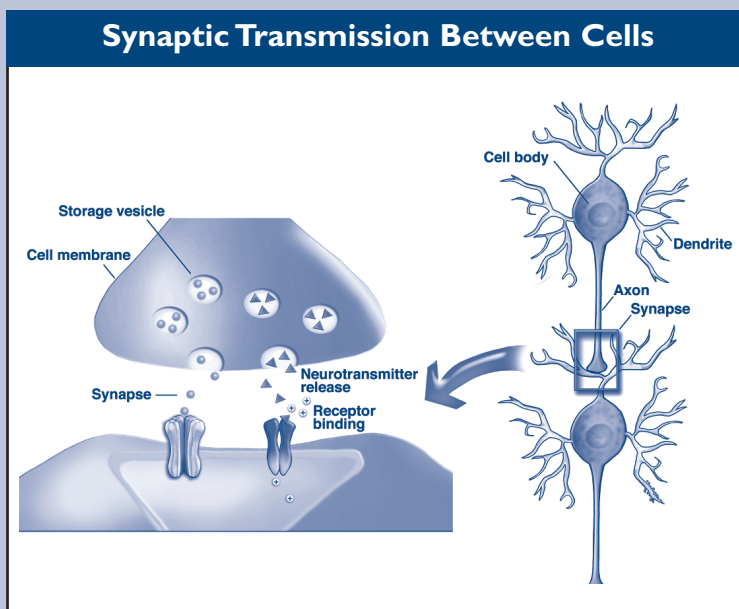
NEURONS AND SYNAPTIC TRANSMISSION

The brain transmits information through a system of interconnected nerve cells known as neurons. Signals travel rapidly along chains of neurons using a combination of electrical and chemical processes. These signals cause many of alcohol's effects on behaviors, such as tolerance, craving, and addiction.

Signals travel from one neuron to the next through a process known as synaptic transmission. Synaptic transmission is made possible by the neuron's unique structure. In addition to a main cell body, neurons have two types of specialized thin branches: axons and dendrites. Axons transmit messages from one neuron to the next, and dendrites receive those messages from nearby neurons. Individual neurons are separated by tiny gaps known as synapses.

Messages travel from one neuron to the next across synaptic gaps and bind to special docking molecules on the receiving neuron's dendrites. These docking molecules are known as neurotransmitter receptors. When a neurotransmitter binds to a receptor, it changes the activity of the receiving neuron.

Depending on the situation, these changes might make the neuron either more likely or less likely to pass on, or "fire," the signal to the next neuron. If the signal is fired, it travels down the axon, sparking the release of more neurotransmitters into the next synapse and passing the signal along to the dendrites of the next neuron. If a signal is not fired, the signal stops.



SOURCE: Lovinger, D.M. Communication networks in the brain: Neurons, receptors, neurotransmitters, and alcohol. *Alcohol Research & Health* 31(3):196–214, 2008.

The brain communicates through a complex system of electrical and chemical signals. These signals are vital to brain function, sending messages throughout the brain, which, in turn, regulate every aspect of the body's function. Neurotransmitter chemicals play a key role in this signal transmission (4).

Under normal circumstances, the brain's balance of neurotransmitters allows the body and brain to function unimpaired. Alcohol can cause changes that upset this balance, impairing brain function. For example, the brain balances the activity of inhibitory neurotransmitters, which work to delay or stop nerve signals, with that of excitatory neurotransmitters, which work to speed up these signals. Alcohol can slow signal transmission in the brain, contributing to some of the effects associated with alcohol intoxication, including sleepiness and sedation.

As the brain grows used to alcohol, it compensates for alcohol's slowing effects by increasing the activity of excitatory neurotransmitters, speeding up signal transmission. In this way, the brain attempts to restore itself to a normal state in the presence of alcohol. If the influence of alcohol is suddenly removed (that is, if a long-term heavy drinker stops drinking suddenly), the brain may have to readjust once again: this may lead to the unpleasant feelings associated with alcohol withdrawal, such as experiencing "the shakes" or increased anxiety.

NEUROTRANSMITTERS: A KEY TO EFFECTIVE MEDICATIONS FOR ALCOHOLISM

As researchers learn more about how neurotransmitters are involved in addiction, they can develop more effective medications that target specific neurotransmitter systems.

Unfortunately, there is no "magic bullet" for treating alcohol-related problems. It is unclear why some people respond well to certain medications, but others do not. However, exciting new research is helping scientists learn more about how alcohol affects different people. A handful of medications are now available to treat alcohol problems, many of which aim to alter

the short- or long-term effects of alcohol by either interfering with or imitating the actions of key neurotransmitters.

The table on page 4 provides information on some of the drugs used to treat alcohol withdrawal and dependence as well as brief descriptions of the neurotransmitter systems the drugs target. Scientists still are seeking to understand the details of how some of these medications work in the brain, but studies suggest that, in some people, they can be helpful in treating alcoholism and its consequences.

NEW STRATEGIES FOR STUDYING ALCOHOL AND THE BRAIN

Powerful imaging methods now allow researchers to study how alcohol affects different brain systems and structures. Some of these methods include positron emission tomography (PET), event-related potentials (ERPs), and magnetic resonance imaging and magnetic resonance spectroscopy (MRI/MRS). These methods are especially useful because they allow researchers to see, in real time, how alcohol changes the human brain. These imaging techniques—when used with alcoholics, nonalcoholics, and children of alcoholics—may help identify genetic risk factors for alcoholism (5).

PET is being used to track the changes that alcohol use causes in specific neurotransmitter systems—changes that may be the cause of alcohol's short-term pleasurable effects (i.e., intoxication) and long-term detrimental effects (i.e., alcohol dependence) (6). PET technology allows researchers to see how these molecules behave. For example, researchers are using PET to track the activity of dopamine, a neurotransmitter believed to contribute to alcoholism. With this information, researchers can identify specific parts of the dopamine system that could be targeted for the development of medications to treat alcoholism (6).

Using ERP, researchers have identified markers that appear in the brains of alcoholics and in children of alcoholics (a population that is at high risk for developing alcoholism) (7; for a review, see 8). A marker is a distinct characteristic that can be associated with a certain group of people. Such markers may be useful for identifying people who are at risk

for alcoholism. For example, scientists have found that certain electrical currents in the brain (as measured by a brainwave called P300) are different in people who are at risk for alcoholism. Research shows that alcoholics have a blunted P300 brainwave; that is, the peak of the brainwave is much lower than in people without an alcohol use disorder. Moreover, this difference in P300 peak is evident in children of alcoholics even before they have taken their first drink. Certain markers linked to alcoholism also are

“As researchers learn more about how neurotransmitters are involved in addiction, they can develop more effective medications that target specific neurotransmitter systems.”

MEDICATIONS FOR ALCOHOLISM

Food and Drug Administration Approved Medications	Treatment Use	Target Neurotransmitters	Effect
Benzodiazepines (Valium® and Xanax®)	Treating alcohol withdrawal	GABA (γ-aminobutyric acid)	Increases GABA activity, curbing the brain's "excitability" during its withdrawal from alcohol, allowing the brain to restore its natural balance.
Disulfiram (Antabuse®)	Preventing alcohol consumption	Main effect on alcohol metabolism rather than in the brain	Increases the concentration of acetaldehyde, a toxic byproduct that occurs when alcohol is broken down (i.e., metabolized) in the body. Excess amounts of this byproduct cause unpleasant symptoms, such as nausea and flushing of the skin.
Naltrexone (ReVia®, Vivitrol®, Naltrel®)	Reducing/stopping drinking	Opioids	Blocks opioid receptors involved in the pleasant sensations associated with drinking.
Acamprosate (Campral®)	Enhancing abstinence	Glutamate	Thought to dampen glutamate activity and may reduce some of the hyper-excitability associated with alcohol withdrawal.

Promising Medications*	Original Use	Target Neurotransmitters	Potential Use
Topiramate (Topamax®)	Treating seizures	GABA and glutamate	Appears effective in reducing drinking in alcohol-dependent patients.
Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine [Prozac®], sertraline [Zoloft®], and others)	Treating depression and anxiety	Serotonin	SSRIs have shown mixed results for treating alcoholics with depression. May reduce drinking in patients who developed alcohol dependence later in life.
Ondansetron (Zofran®)	Preventing nausea and vomiting	Serotonin	May reduce drinking in patients who developed alcohol dependence early in life.
Baclofen (Kemstro®, Lioresal®)	Treating muscle spasms	GABA	May have beneficial effects in encouraging abstinence, especially in alcoholic patients with liver cirrhosis.
Quetiapine (Seroquel®)	Sometimes used in treating psychiatric disorders	Dopamine and serotonin	Early-stage trials indicate quetiapine might be effective in increasing rates of abstinence, and to be especially useful in patients with severe alcoholism or in those who developed alcohol dependence early in life.

NOTE: *Not yet approved for use in the treatment of alcohol use disorders.

SOURCES: Lovinger, D.M. Communication networks in the brain: Neurons, receptors, neurotransmitters, and alcohol. *Alcohol Research & Health* 31(3):196–214, 2008. Krishnan-Sarin, S.; O'Malley, S.; and Krystal, J.H. Treatment implications: Using neuroscience to guide the development of new pharmacotherapies for alcoholism. *Alcohol Research & Health* 31(4):400–407, 2008.

New Technology to Map Alcohol's Effects

With magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS), researchers use a powerful magnetic field to generate a highly detailed “map” of the brain. For example, one technique, known as functional MRI (fMRI), allows researchers to “see” blood flow to specific regions in the brain and, thus, to identify which regions of the brain currently are active. Using this technique, researchers are exploring how alcohol affects brain function and how brain function changes as alcohol dependence develops over time (9).

found with other mental health disorders, including drug use disorders, antisocial personality disorder, conduct disorder, and attention deficit hyperactivity disorder (for a review, see 8), suggesting that there may be a genetic connection among all of these disorders.

In addition to imaging studies, researchers also are using animals to study alcoholism. The results of these studies can help researchers better understand how to treat alcoholism in humans. In particular, animal models help scientists study the genetic links involved in alcoholism. Researchers can “turn off” genes that may be involved in alcohol addiction in laboratory animals, giving them insight into how these genes affect an animal’s behavior (10). For example, an animal model could show whether an animal will still seek alcohol once a specific gene has been turned off. Researchers also are able to work with small clusters of cells from animal brains and to study alcohol’s effects on a cellular level (11).

Animal studies allow researchers to explore how alcohol damages the brain and how the brain begins to recover from this damage with abstinence from drinking. Studies in rats show that heavy episodic drinking (i.e., “binge drinking”) can injure the brain by causing the death of neurons and other components (12). These brain injuries may cause some of the changes in thought and behavior that are associated with alcohol dependence in humans (13). Animal studies

suggest that the brain can recover at least partially from this damage. One method being investigated is the use of neural stem cells, which, over time, may help to rewire new neurons and repair damage to the brain’s communication system (14).

CONCLUSION

Neuroscience is showing that the pathways of addiction are based in the brain. Using advanced techniques such as imaging methods and studies with animal models, researchers are learning more about how alcohol interacts with the brain’s communication system in different people. Innovative technology also is helping identify the changes that occur in the brain’s structure and function as a result of drinking, and how alcohol disrupts the brain’s delicate chemical balance. This information may help scientists understand why and how alcoholism develops in different populations and ultimately result in more effective and targeted therapies for alcohol abuse and dependence.

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Resources

Source material for this *Alcohol Alert* originally appeared in *Alcohol Research & Health*, Volume 31, Number 3, 2008 and *Alcohol Research & Health*, Volume 31, Number 4, 2008.

- ▶ *Alcohol Research and Health 31(3): Neuroscience: Pathways to Alcohol Dependence Part I—Overview of the Neurobiology of Dependence.* The first issue in this special two-part series introduces what we know about alcohol's effects on the brain, and how these effects might lead to dependence. Articles explore the brain's complex communication systems, and how short- and long-term alcohol use can affect these systems. A special section highlights emerging technologies, such as brain imaging and animal studies, which are helping researchers to understand even more about alcohol's effects on the brain.
- ▶ *Alcohol Research and Health 31(4): Neuroscience: Pathways to Alcohol Dependence Part II—Neuroadaptation, Risk, and Recovery.* The second issue in this series describes how the brain's own adaptations to the presence of alcohol may play a key role in alcohol dependence, and how neuroscience is helping researchers target medications to help people at risk for alcohol use disorders. Other articles show how changes in the brain may lead to tolerance, withdrawal, and relapse to drinking.
- ▶ For these and other resources, visit NIAAA's Web site, www.niaaa.nih.gov



Full text of this publication is available on NIAAA's World Wide Web site at www.niaaa.nih.gov.

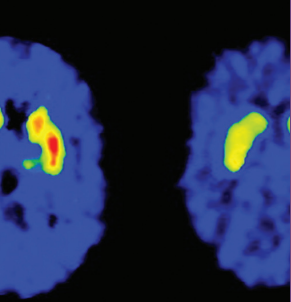
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Cocaine's stimulant and addictive effects explained. See page 2.

Research Report Series

from the director:

Cocaine abuse and addiction continue to plague our Nation. In 2008, almost 15 percent of Americans had tried cocaine, with 6 percent having tried it by their senior year of high school. Recent discoveries about the inner workings of the brain and the harmful effects of cocaine offer us unprecedented opportunities for addressing this persistent public health problem.

Genetic studies continue to provide critical information about hereditary influences on the risk of addiction to psychoactive substances, including cocaine. But genetic risk is far less rigid than previously thought. More recent epigenetic research has begun to shed light on the power of environmental factors (e.g., nutrition, chronic stress, parenting style) to influence gene expression and thus, genetic risk. Furthermore, sophisticated imaging technologies have allowed scientists to visualize the brain changes that result from chronic drug exposure or that occur when an addicted person is exposed to drug-associated "cues" that can trigger craving and lead to relapse. By mapping genetic factors, epigenetic mechanisms, and brain regions responsible for the multiple effects of cocaine, we are gaining fundamental insights that can help us identify new targets for treating cocaine addiction.

NIDA remains vigilant in its quest for more effective strategies to address the serious public health issues linked to cocaine abuse. We not only support a wide range of basic and clinical research, but also facilitate the translation of these research findings into real-world settings. To this end, we strive to keep the public informed of the latest scientific advances in the field of addiction. We hope that this compilation of scientific information on cocaine abuse will inform readers and bolster our efforts to tackle the personal and social devastation caused by drug abuse and addiction.

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse



Cocaine

What Is Cocaine?

Cocaine is a powerfully addictive stimulant that directly affects the brain. Cocaine was labeled the drug of the 1980s and 1990s because of its extensive popularity and use during that period. However, cocaine is not a new drug. In fact, it is one of the oldest known psychoactive substances. Coca leaves, the source of cocaine, have been chewed and ingested for thousands of years, and the purified chemical, cocaine hydrochloride, has been an abused substance for more than 100 years. In the early 1900s, for example, purified cocaine was the main active ingredient in most of the tonics and elixirs

continued inside

that were developed to treat a wide variety of illnesses.

Pure cocaine was originally extracted from the leaf of the *Erythroxylon* coca bush, which grew primarily in Peru and Bolivia. After the 1990s, and following crop reduction efforts in those countries, Colombia became the nation with the largest cultivated coca crop. Today, cocaine is a Schedule II drug, which means that it has high potential for abuse but can be administered by a doctor for legitimate medical uses, such as local anesthesia for some eye, ear, and throat surgeries.

Cocaine is generally sold on the street as a fine, white, crystalline powder and is also known as “coke,” “C,” “snow,” “flake,” or “blow.” Street dealers generally dilute it with inert substances such as cornstarch, talcum powder, or sugar, or with active drugs such as procaine (a

chemically related local anesthetic) or amphetamine (another stimulant). Some users combine cocaine with heroin—in what is termed a “speedball.”

There are two chemical forms of cocaine that are abused: the water-soluble hydrochloride salt and the water-insoluble cocaine base (or freebase). When abused, the hydrochloride salt, or powdered form of cocaine, can be injected or snorted. The base form of cocaine has been processed with ammonia or sodium bicarbonate (baking soda) and water, and then heated to remove the hydrochloride to produce a smokable substance. The term “crack,” which is the street name given to freebase cocaine, refers to the crackling sound heard when the mixture is smoked.

Cocaine use ranges from occasional to repeated or compulsive use, with a variety of patterns between these extremes. Other than medical uses, there is no safe way to use cocaine. Any route of administration can lead to absorption of toxic amounts of cocaine, possible acute cardiovascular or cerebrovascular emergencies, and seizures—all of which can result in sudden death.

How Does Cocaine Produce Its Effects?

Research has led to a clear understanding of how cocaine produces its pleasurable effects and why it is so addictive. Scientists have discovered regions within the brain that are stimulated by all types of reinforcing stimuli such as food, sex, and many drugs of abuse. One neural system that appears to be most affected by cocaine originates in a region of the midbrain called the ventral tegmental area (VTA). Nerve fibers originating in the VTA extend to a region known as the nucleus accumbens, one of the brain’s key areas involved in reward. Animal studies show that rewards increase levels of the brain chemical (or neurotransmitter) dopamine, thereby increasing neural activity in the nucleus accumbens. In the normal communication process, dopamine is released by a neuron into the synapse (the small gap between two neurons), where it binds to specialized proteins (called dopamine receptors) on the neighboring neuron and sends a signal to that neuron. Dopamine is then

How Is Cocaine Abused?

The principal routes of cocaine administration are oral, intranasal, intravenous, and inhalation. Snorting, or intranasal administration, is the process of inhaling cocaine powder through the nostrils, where it is absorbed into the bloodstream through the nasal tissues. The drug also can be rubbed onto mucous tissues. Injecting, or intravenous use, releases the drug directly into the bloodstream and heightens the intensity of its effects. Smoking involves inhaling cocaine vapor or smoke into the lungs, where absorption into the bloodstream is as rapid as by injection. This rather immediate and euphoric effect is one of the reasons that crack became enormously popular in the mid-1980s.



Coca bush



removed from the synapse to be recycled for further use. Drugs of abuse can interfere with this normal communication process. For example, scientists have discovered that cocaine acts by blocking the removal of dopamine from the synapse, which results in an accumulation of dopamine and an amplified signal

to the receiving neurons (see image on page 4, “Cocaine in the brain”). This is what causes the initial euphoria commonly reported by cocaine abusers.

small amounts, cocaine usually makes the user feel euphoric, energetic, talkative, and mentally alert, especially to the sensations of sight, sound, and touch. It can also temporarily decrease the need for food and sleep. Some users find that the drug helps them perform simple physical and intellectual tasks more quickly, although others experience the opposite effect.

What Are the Short-Term Effects of Cocaine Use?

Cocaine’s effects appear almost immediately after a single dose and disappear within a few minutes to an hour. Taken in

The duration of cocaine’s euphoric effects depend upon the route of administration. The faster the drug is absorbed, the more intense the resulting high, but also

What Is the Scope of Cocaine Use in the United States?

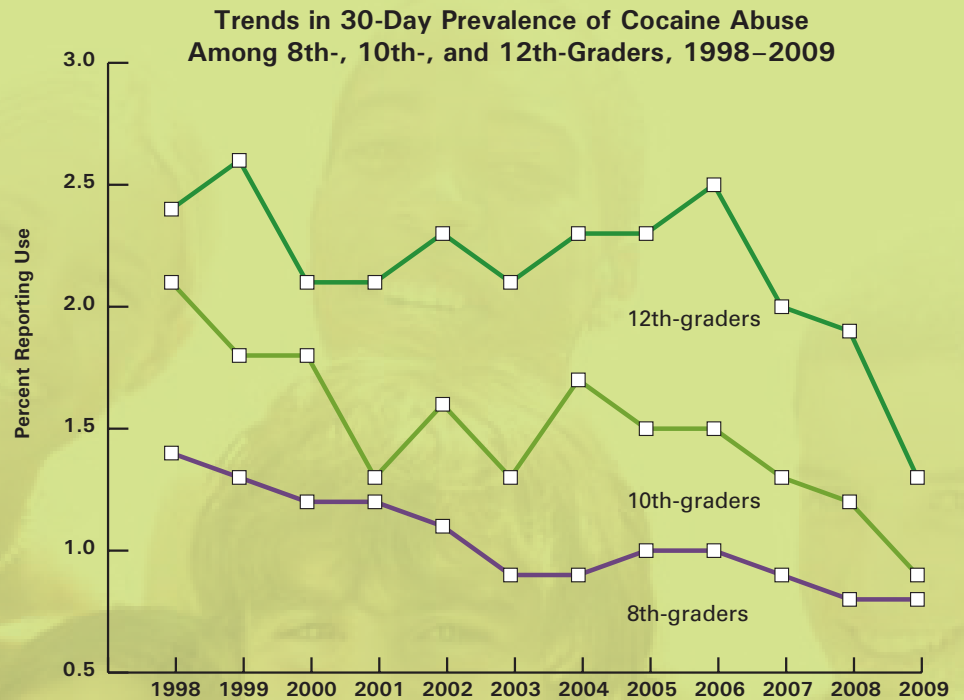
The National Survey on Drug Use and Health (NSDUH) estimates that in 2008 there were 1.9 million current (past month) cocaine users, of which approximately 359,000 were current crack users. Adults aged 18 to 25 years have a higher rate of current cocaine use than any other age group, with 1.5 percent of young adults reporting past-month cocaine use. Overall, men report higher rates of current cocaine use than women.

The 2009 Monitoring the Future survey, which annually surveys teen attitudes and drug use, reports a significant decline in 30-day prevalence of powder cocaine use among 8th-, 10th-, and 12th-graders from peak use in the late 1990s, as well as significant declines in past-month use among 10th- and 12th-graders from 2008 to 2009.

Repeated cocaine use can produce addiction and other adverse health consequences. In 2008, according

to the NSDUH, about 1.4 million Americans met the *Diagnostic and Statistical Manual of Mental Disorders* criteria for dependence or abuse of cocaine (in any form) in the past 12 months. Further, data from the 2008 Drug Abuse Warning Network (DAWN) report showed that cocaine was involved

in 482,188 of the nearly 2 million visits to emergency departments for drug misuse or abuse. This translates to almost one in four drug misuse or abuse emergency department visits (24 percent) that involved cocaine.



Source: University of Michigan, 2009 Monitoring the Future Survey.

the shorter the duration. The high from snorting is relatively slow to arrive, but it may last from 15 to 30 minutes; in contrast, the effects from smoking are more immediate but may last only 5 to 10 minutes.

The short-term physiological effects of cocaine use include constricted blood vessels; dilated pupils; and increased body temperature, heart rate, and blood pressure. Large amounts of cocaine may intensify the user's high but can also lead to bizarre, erratic, and violent behavior. Some cocaine users report feelings of restlessness, irritability, anxiety, panic, and paranoia. Users may also experience tremors, vertigo, and muscle twitches.

There also can be severe medical complications associated with cocaine abuse. Some of the most frequent are cardiovascular effects, including disturbances in heart rhythm and heart attacks; neurological effects, including strokes, seizures, headaches, and coma; and gastrointestinal complications, including abdominal pain and nausea. In rare instances, sudden death can occur on the first use of cocaine or unexpectedly thereafter. Cocaine-related deaths are often a result of cardiac arrest or seizures followed by respiratory arrest.

In addition, research has also revealed a potentially dangerous interaction between cocaine and alcohol. This mixture is the most common two-drug combination that results in drug-related death.

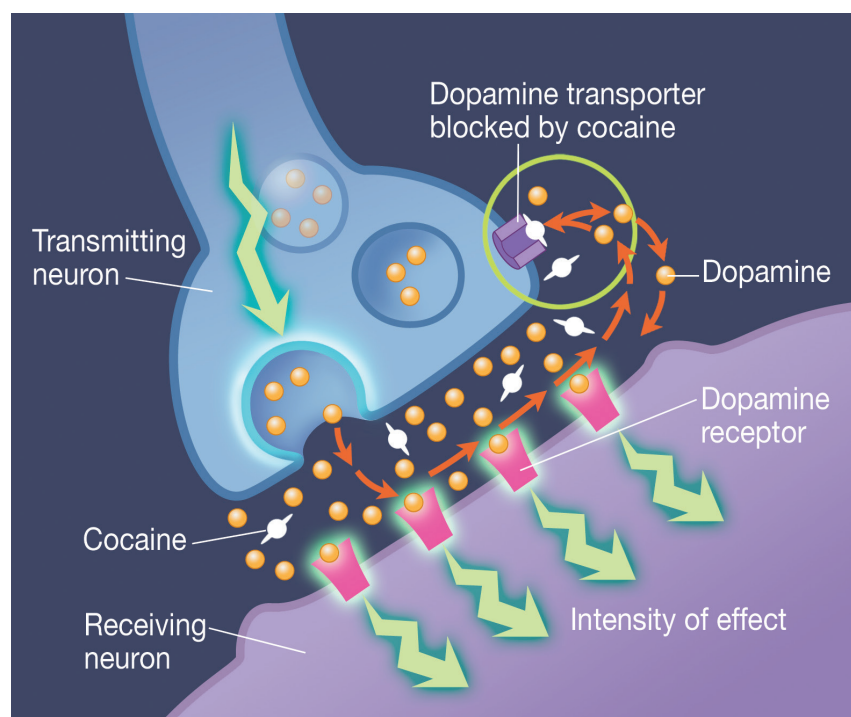
What Are the Long-Term Effects of Cocaine Use?

Cocaine is a powerfully addictive drug. Thus, it is unlikely that an individual will be able to reliably predict or control the extent to which he or she will continue to want or use the drug. And, if addiction takes hold, the risk for relapse is high even following long periods of abstinence. Recent studies have shown that during periods of abstinence, the memory of the cocaine experience or exposure to cues associated with drug use can trigger tremendous craving and relapse to drug use.

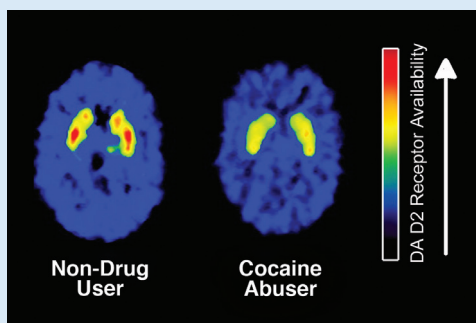
With repeated exposure to cocaine, the brain starts to adapt, and the reward pathway becomes less sensitive to natural reinforcers and to the drug itself. Tolerance may develop—this means that higher doses and/or more frequent use of cocaine is needed to register the same level of pleasure experienced during initial use. At the same time, users can also become more sensitive (sensitization) to cocaine's anxiety-producing, convulsant, and other toxic effects.

Users take cocaine in "binges," during which the cocaine is used repeatedly and at increasingly higher doses. This can lead to increased irritability, restlessness, panic attacks, and paranoia—even a full-blown psychosis, in which the individual loses touch with reality and experiences auditory hallucinations. With increasing dosages or frequency of use, the risk of adverse psychological or physiological effects increases.

Different routes of cocaine administration can produce different adverse effects. Regularly snorting cocaine, for example, can lead to loss of sense of smell; nosebleeds; problems with swallowing;



Cocaine in the brain—In the normal communication process, dopamine is released by a neuron into the synapse, where it can bind to dopamine receptors on neighboring neurons. Normally, dopamine is then recycled back into the transmitting neuron by a specialized protein called the dopamine transporter. If cocaine is present, it attaches to the dopamine transporter and blocks the normal recycling process, resulting in a buildup of dopamine in the synapse, which contributes to the pleasurable effects of cocaine.



Brain images showing decreased dopamine (D₂) receptors in the brain of a person addicted to cocaine versus a nondrug user. The dopamine system is important for conditioning and motivation, and alterations such as this are likely responsible, in part, for the diminished sensitivity to natural rewards that develops with addiction.

hoarseness; and an overall irritation of the nasal septum, which could result in a chronically inflamed, runny nose. Ingested cocaine can cause severe bowel gangrene due to reduced blood flow. Persons who inject cocaine have puncture marks called “tracks,” most commonly in their forearms, and may experience allergic reactions, either to the drug or to some additive in street cocaine, which in severe cases can result in death. Many chronic cocaine users lose their appetite and experience significant weight loss and malnourishment.

Are Cocaine Abusers at Risk for Contracting HIV/AIDS and Hepatitis?

Yes, cocaine abusers are at increased risk for contracting such infectious diseases as human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and viral hepatitis. This risk stems not only from sharing contaminated needles and drug paraphernalia but also from engaging in risky behaviors as a result of intoxication. Research has shown that drug intoxication and addiction can compromise judgment and decisionmaking,

and potentially lead to risky sexual encounters, needle sharing, and trading sex for drugs—by both men and women. In fact, some studies are showing that among drug abusers, those who do not inject drugs are contracting HIV at rates equal to those who do inject drugs, further highlighting the role of sexual transmission of HIV in this population.

Additionally, hepatitis C (HCV) has spread rapidly among injecting drug users. Risk begins with the first injection, and within 2 years, nearly 40 percent of injection drug users (IDUs) are exposed to HCV. By the time IDUs have been injecting for 5 years, their chances of being infected with HCV are between 50 and 80 percent. Although treatment for HCV is not effective for everyone and can have significant side effects, medical followup is essential for all those who are infected. There is no vaccine for the hepatitis C virus, and it is highly transmissible via injection; thus, HCV testing is recommended for any individual who has ever injected drugs.

What Treatments Are Effective for Cocaine Abusers?

In 2007, cocaine accounted for about 13 percent of all admissions to drug abuse treatment programs.

The majority of individuals (72 percent in 2007) who seek treatment for cocaine abuse smoke crack and are likely to be polydrug abusers, or users of more than one substance. The widespread abuse of cocaine has stimulated extensive efforts to develop treatment programs for cocaine. As with any drug addiction, this is a complex disease that involves biological changes in the brain as well as myriad social, familial, and other environmental problems. Therefore, treatment of cocaine addiction must be comprehensive, and strategies need to assess the neurobiological, social, and medical aspects of the patient’s drug abuse. Moreover, patients who have a variety of addictions often have other co-occurring mental disorders that require additional behavioral or pharmacological interventions.

Pharmacological Approaches

Presently, there are no FDA-approved medications to treat cocaine addiction. Consequently, NIDA is working aggressively to identify and test new medications to treat cocaine addiction safely and effectively. Several medications marketed for other diseases (e.g., vigabatrin, modafinil, tiagabine, disulfiram, and topiramate) show promise and have been reported to reduce cocaine use in controlled clinical trials. Among these, disulfiram (used to treat alcoholism) has produced the most consistent reductions in cocaine abuse. On the other hand, new knowledge of how the brain is changed by cocaine is directing attention to novel targets for medications development. Compounds that are currently being tested for addiction treatment take advantage of underlying cocaine-induced adaptations in the brain that disturb the balance between excitatory (glutamate) and inhibitory (gamma-aminobutyric acid) neurotransmission. Also,

What Are the Effects of Maternal Cocaine Use?

The full extent of the effects of prenatal cocaine exposure on a child is not completely known, but many scientific studies have documented that babies born to mothers who abuse cocaine during pregnancy are often prematurely delivered, have low birth weights and smaller head circumferences, and are shorter in length than babies born to mothers who do not abuse cocaine.

Nevertheless, it is difficult to estimate the full extent of the consequences of maternal drug abuse and to determine the specific hazard of a particular drug to the unborn child. This is because multiple factors—



such as the amount and number of *all* drugs abused, including nicotine; extent of prenatal care; possible neglect or abuse of the child; exposure to violence in the environment; socioeconomic conditions; maternal nutrition; other health conditions; and exposure to sexually transmitted diseases—can all interact to impact maternal, fetal, and child outcomes.

Some may recall that “crack babies,” or babies born to mothers who abused crack cocaine while pregnant, were at one time written off as a lost generation. They were predicted to suffer from severe, irreversible damage, including reduced intelligence and social skills. It was later found that this was a gross exaggeration. However, the fact that most of these children appear normal should not be overinterpreted to indicate that there is no cause for concern. Using sophisticated technologies, scientists are now finding that exposure to cocaine during fetal development may lead to subtle, yet significant, later deficits in some children, including deficits in some aspects of cognitive performance, information processing, and attention to tasks—abilities that are important for the realization of a child’s full potential.

dopamine D₃ receptors (a subtype of dopamine receptor) constitute a novel molecular target of high interest. Medications that act at these receptors are now being tested for safety in humans. Finally, a cocaine vaccine that prevents entry of cocaine into the brain holds great promise for reducing the risk of relapse. In addition to treatments for addiction, medical treatments are being developed to address the acute emergencies that result from cocaine overdose each year.

Behavioral Interventions

Many behavioral treatments for cocaine addiction have proven to be effective in both residential and outpatient settings. Indeed, behavioral therapies are often the only available and effective treatments for many drug problems, including stimulant addictions. However, the integration of behavioral and pharmacological treatments may ultimately prove to be the most effective approach.

Presently, there are no proven medications to treat cocaine addiction. Consequently, NIDA is working aggressively to identify and test new medications.

One form of behavioral therapy that is showing positive results in cocaine-addicted populations is contingency management, or motivational incentives (MI). MI may be particularly useful for helping patients achieve initial abstinence from cocaine and for helping patients stay in treatment. Programs use a voucher or prize-based system that rewards patients who abstain from cocaine and other drug use. On the basis of drug-free urine tests, the patients earn points, or chips, which can be exchanged for items that encourage healthy living, such as a gym membership,

movie tickets, or dinner at a local restaurant. This approach has recently been shown to be practical and effective in community treatment programs.

Cognitive-behavioral therapy (CBT) is an effective approach for preventing relapse. CBT is focused on helping cocaine-addicted individuals abstain—and remain abstinent—from cocaine and other substances. The underlying assumption is that learning processes play an important role in the development and continuation of cocaine abuse and addiction. These same learning processes can be harnessed to help individuals reduce drug use and successfully prevent relapse. This approach attempts to help patients recognize, avoid, and cope; that is, they recognize the situations in which they are most likely to use cocaine, avoid these situations when appropriate, and cope more effectively with a range of problems and problematic behaviors associated with drug abuse. This

therapy is also noteworthy because of its compatibility with a range of other treatments patients may receive.

Therapeutic communities (TCs), or residential programs, offer another alternative to persons in need of treatment for cocaine addiction. TCs usually require a 6- or 12-month stay and use the program's entire "community" as active components of treatment.

They can include onsite vocational rehabilitation and other supportive services and focus on successful re-integration of the individual into society.

Community-based recovery groups—such as Cocaine Anonymous—that use a 12-step program can also be helpful to people trying to sustain abstinence. Participants may benefit from the supportive fellowship and from

sharing with those experiencing common problems and issues.

It is important that patients receive services that match all of their treatment needs. For example, if a patient is unemployed, it may be helpful to provide vocational rehabilitation or career counseling along with addiction treatment. If a patient has marital problems, it may be important to offer couples counseling.

Glossary

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

Anesthetic: An agent that causes insensitivity to pain and is used for surgeries and other medical procedures.

Coca: The plant, *Erythroxylon*, from which cocaine is derived. Also refers to the leaves of this plant.

Crack: The slang term for a smokable form of cocaine.

Craving: A powerful, often uncontrollable, desire for drugs.

Dopamine: A brain chemical, classified as a neurotransmitter, found in regions of the brain that regulate movement, emotion, motivation, and pleasure.

Freebase: A solid, water-insoluble, and smokable form of cocaine that is produced when its hydrochloride salt form is processed with ammonia or sodium bicarbonate and water, then heated to remove the hydrochloride. (Also, see "crack.")

Frontal cortex: The front part of the brain involved with reasoning, planning, problemsolving, and other higher cognitive functions.

Gamma-aminobutyric acid (GABA): The main inhibitory neurotransmitter in the central nervous system. GABA provides the needed counterbalance to the actions of other systems, particularly the excitatory neurotransmitter glutamate.

Glutamate: An excitatory neurotransmitter found throughout the brain that influences the reward system and is involved in learning and memory, among other functions.

Hydrochloride salt: A powdered, water-soluble form of cocaine that can be injected or snorted.

Neuron: A nerve cell.

Nucleus accumbens: A brain region involved in motivation and reward. Nearly all drugs of abuse directly or indirectly increase dopamine in the nucleus accumbens, contributing to their addictive properties.

Polydrug user: An individual who uses more than one drug.

Rush: A surge of pleasure (euphoria) that rapidly follows the administration of some drugs.

Stimulant: A class of drugs that enhances the activity of monoamines (such as dopamine) in the brain, increasing arousal, heart rate, blood pressure, and respiration, and decreasing appetite; includes some medications used to treat attention-deficit hyperactivity disorder (e.g., methylphenidate and amphetamines), as well as cocaine and methamphetamine.

Tolerance: A condition in which higher doses of a drug are required to produce the same effect achieved during initial use.

Vertigo: The sensation of dizziness.

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Where can I get further information about cocaine?

To learn more about cocaine and other drugs of abuse, visit the NIDA Web site at www.drugabuse.gov or contact the *DrugPubs* Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

NATIONAL INSTITUTE ON DRUG ABUSE



RESEARCH DISSEMINATION CENTER

What's New on the NIDA Web Site

- Information on drugs of abuse and related health consequences
- NIDA publications, news, and events
- Resources for health care professionals
- 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)

NIDA Web Sites

www.drugabuse.gov
www.backtoschool.drugabuse.gov
www.teens.drugabuse.gov

For Physician Information



www.drugabuse.gov/nidamed

Other Web Sites

Information on cocaine abuse and addiction is also available through the following Web site:

- Substance Abuse and Mental Health Services Administration Health Information Network: www.samhsa.gov/shin



National Institute
on Drug Abuse

NIH Publication Number 10-4166
Printed May 1999, Revised November 2004,
Revised June 2009, Revised September 2010.

Feel free to reprint this publication.



How is heroin linked to prescription drug abuse?
See page 3.



National Institute on Drug Abuse

from the director:

Heroin is a highly addictive opioid drug, and its use has repercussions that extend far beyond the individual user. The medical and social consequences of drug use—such as hepatitis, HIV/AIDS, fetal effects, crime, violence, and disruptions in family, workplace, and educational environments—have a devastating impact on society and cost billions of dollars each year.

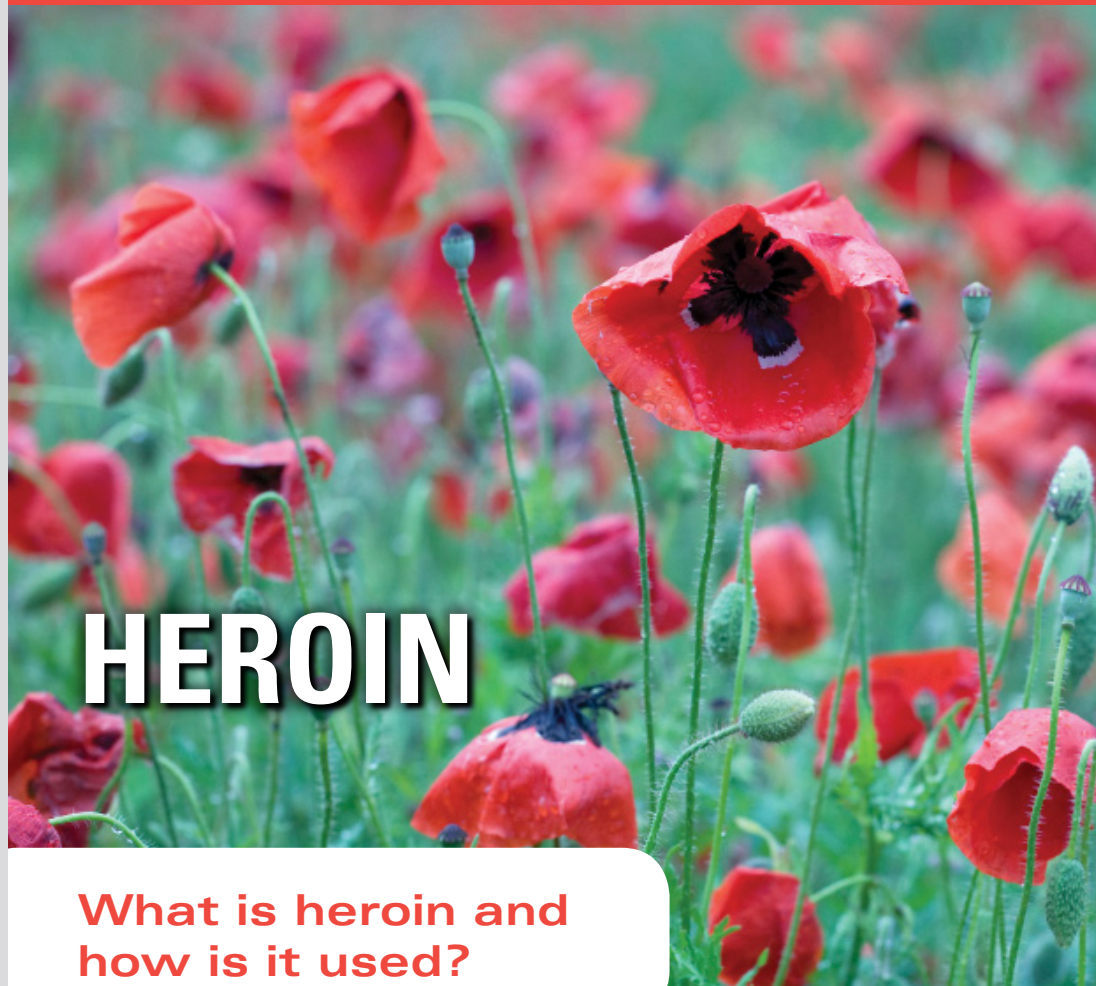
Although heroin use in the general population is rather low, the numbers of people starting to use heroin have been steadily rising since 2007.¹ This may be due in part to a shift from abuse of prescription pain relievers to heroin as a readily available, cheaper alternative²⁻⁵ and the misperception that highly pure heroin is safer than less pure forms because it does not need to be injected.

Like many other chronic diseases, addiction can be treated. Medications are available to treat heroin addiction while reducing drug cravings and withdrawal symptoms, improving the odds of achieving abstinence. There are now a variety of medications that can be tailored to a person's recovery needs while taking into account co-occurring health conditions. Medication combined with behavioral therapy is particularly effective, offering hope to individuals who suffer from addiction and for those around them.

The National Institute on Drug Abuse (NIDA) has developed this publication to provide an overview of heroin use and its consequences as well as treatment options available for those struggling with heroin addiction. We hope this compilation of scientific information on heroin will help to inform readers about the harmful effects of heroin as well as assist in prevention and treatment efforts.

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

Research Report Series

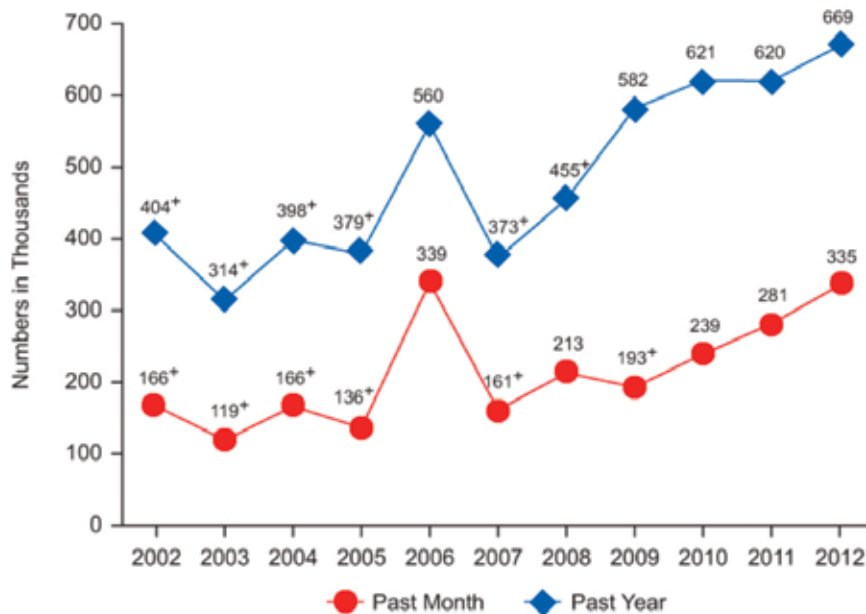


HEROIN

What is heroin and how is it used?

Heroin is an illegal, highly addictive drug processed from morphine, a naturally occurring substance extracted from the seed pod of certain varieties of poppy plants. It is typically sold as a white or brownish powder that is “cut” with sugars, starch, powdered milk, or quinine. Pure heroin is a white powder with a bitter taste that predominantly originates in South America and, to a lesser extent, from Southeast Asia, and dominates U.S. markets east of the Mississippi River.³ Highly pure heroin can be snorted or smoked and may be more appealing to new users because it eliminates the stigma associated with injection drug use. “Black tar” heroin is sticky like roofing tar or hard like coal and is predominantly produced in Mexico and sold in U.S. areas west of the Mississippi River.³ The dark color associated with black tar heroin results from crude processing methods that leave behind impurities. Impure heroin is usually dissolved, diluted, and injected into veins, muscles, or under the skin.

Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002-2012



Source: National Survey on Drug Use and Health: Summary of National Findings, 2012.

What is the scope of heroin use in the United States?

According to the National Survey on Drug Use and Health (NSDUH), in 2012 about 669,000 Americans reported using heroin in the past year,¹ a number that has been on the rise since 2007. This trend appears to be driven largely by young adults aged 18–25 among whom there have been the greatest increases. The number of people using heroin for the first time is unacceptably high, with 156,000 people starting heroin use in 2012, nearly double the number of people in 2006 (90,000). In contrast, heroin use has been declining among teens aged 12–17. Past-year heroin use among the Nation’s 8th-, 10th-, and 12th-graders is at its lowest levels in the history of the Monitoring the Future survey, at less than 1 percent of those surveyed in all 3 grades from 2005 to 2013.⁶

It is no surprise that with heroin use on the rise, more people are experiencing negative health effects that occur from repeated use. The number of people meeting

Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for dependence or abuse of heroin doubled from 214,000 in 2002 to 467,000 in 2012.¹ The recently released DSM-V no longer separates substance abuse from dependence, but instead provides criteria for opioid use disorders that range from mild to severe, depending on the number of symptoms a person has.⁷ Data on the scope and severity of opioid use disorders in the United States are not yet available for these new criteria.

The impact of heroin use is felt all across the United States, with heroin being identified as the most or one of the most important drug abuse issues affecting several local regions from coast to coast. The rising harm associated with heroin use at the community level was presented in a report produced by the NIDA Community Epidemiology Work Group (CEWG). The CEWG is comprised of researchers from major metropolitan areas in the United States and selected foreign countries and provides community-level surveillance of

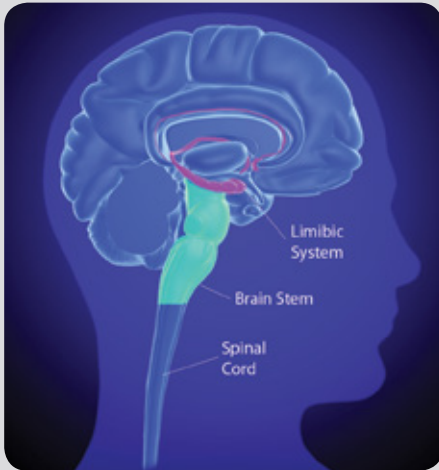
drug abuse and its consequences to identify emerging trends.³

Heroin use no longer predominates solely in urban areas. Several suburban and rural communities near Chicago and St. Louis report increasing amounts of heroin seized by officials as well as increasing numbers of overdose deaths due to heroin use. Heroin use is also on the rise in many urban areas among young adults aged 18–25.⁸ Individuals in this age group seeking treatment for heroin abuse increased from 11 percent of total admissions in 2008 to 26 percent in the first half of 2012.

What effects does heroin have on the body?

Heroin binds to and activates specific receptors in the brain called mu-opioid receptors (MORs). Our bodies contain naturally occurring chemicals called neurotransmitters that bind to these receptors throughout the brain and body to regulate pain, hormone release, and feelings of well-being.⁹ When MORs are activated in the reward center of the brain, they stimulate the release of the neurotransmitter dopamine, causing a sensation of pleasure.¹⁰ The consequences of activating opioid receptors with externally administered opioids such as heroin (versus naturally occurring chemicals within our bodies) depend on a variety of factors: how much is used, where in the brain or body it binds, how strongly it binds and for how long, how quickly it gets there, and what happens afterward.

The greatest increase in heroin use is seen in young adults aged 18-25.



Opioids Act on Many Places in the Brain and Nervous System

- Opioids can depress breathing by changing neurochemical activity in the brain stem, where automatic body functions such as breathing and heart rate are controlled.
- Opioids can increase feelings of pleasure by altering activity in the limbic system, which controls emotions.
- Opioids can block pain messages transmitted through the spinal cord from the body.

What are the immediate (short-term) effects of heroin use?

Once heroin enters the brain, it is converted to morphine and binds rapidly to opioid receptors.¹¹ Abusers typically report feeling a surge of pleasurable sensation—a “rush.” The intensity of the rush is a function of how much drug is taken and how rapidly the drug enters the brain and binds to the opioid receptors. With heroin, the rush is usually accompanied by a warm flushing of the skin, dry mouth, and a heavy feeling in the extremities, which may be accompanied by nausea, vomiting, and severe itching. After the initial effects, users usually will be drowsy for several hours; mental function is clouded; heart function slows; and breathing is also severely slowed, sometimes enough to be life-threatening. Slowed breathing can also lead to coma and permanent brain damage.¹²

What are the long-term effects of heroin use?

Repeated heroin use changes the physical structure¹³ and physiology of the brain, creating long-term imbalances in neuronal and hormonal systems that are not easily reversed.^{14,15} Studies have shown some deterioration of the brain’s white matter due to heroin use, which may affect decision-making abilities, the ability to regulate behavior, and responses to stressful situations.¹⁶⁻¹⁸ Heroin also produces profound degrees of tolerance and physical dependence. Tolerance occurs when more and more of the drug is required to achieve the same effects. With physical dependence, the body adapts to the presence of the drug and withdrawal symptoms occur if use is reduced abruptly. Withdrawal may occur within a few hours after the last time the drug is taken. Symptoms of withdrawal include restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps (“cold turkey”), and leg movements. Major withdrawal symptoms peak between 24–48 hours after the last dose of heroin and subside after about a week. However, some people have shown persistent withdrawal signs for many months. Finally, repeated heroin use often results in addiction—a chronic relapsing disease that goes beyond physical dependence and is characterized by uncontrollable drug-seeking no matter the consequences.¹⁹ Heroin is extremely addictive no matter how it is administered, although routes of administration that allow it to reach the brain the fastest (i.e., injection and smoking) increase the risk of addiction. Once a person becomes addicted to heroin, seeking and using the drug becomes their primary purpose in life.

How is heroin linked to prescription drug abuse?

Harmful health consequences resulting from the abuse of opioid medications that are prescribed for the treatment of pain, such as Oxycontin®, Vicodin®, and Demerol®, have dramatically increased in recent years. For example, unintentional poisoning deaths from prescription opioids quadrupled from 1999 to 2010 and now outnumber those from heroin and cocaine combined.²⁰ People often assume prescription pain relievers are safer than illicit drugs because they are medically

prescribed; however, when these drugs are taken for reasons or in ways or amounts not intended by a doctor, or taken by someone other than the person for whom they are prescribed, they can result in severe adverse health effects including addiction, overdose, and death, especially when combined with other drugs or alcohol. Research now suggests that abuse of these medications may actually open the door to heroin use. Nearly half



of young people who inject heroin surveyed in three recent studies reported abusing prescription opioids before starting to use heroin. Some individuals reported switching to heroin because it is cheaper and easier to obtain than prescription opioids.²⁻⁴

What are the medical complications of chronic heroin use?

No matter how they ingest the drug, chronic heroin users experience a variety of medical complications including insomnia and constipation. Lung complications (including various types of pneumonia and tuberculosis) may result from the poor health of the user as well as from heroin's effect of depressing respiration. Many experience mental disorders such as depression and antisocial personality disorder. Men often experience sexual dysfunction and women's menstrual cycles often become irregular. There are also specific consequences associated with different routes of administration. For example, people who repeatedly snort heroin can damage the mucosal tissues in their noses as well as perforate the nasal septum (the tissue that separates the nasal passages).

Medical consequences of chronic injection use include scarred and/or collapsed veins, bacterial infections of the blood vessels and heart valves, abscesses (boils), and other soft-tissue infections. Many of the additives in street heroin may include substances that do not readily dissolve and result in clogging the blood vessels that lead to the lungs, liver, kidneys, or brain. This can cause infection or even death of small patches of cells in vital organs. Immune reactions to these or other contaminants can cause arthritis or other rheumatologic problems.

Sharing of injection equipment or fluids can lead to some of the most severe consequences of heroin abuse—infections with hepatitis B and C, HIV, and a host of other blood-borne viruses, which drug abusers can then pass on to their sexual partners and children.

Short- and Long-Term Effects of Heroin Use

Short-Term Effects

- "Rush"
- Depressed respiration
- Clouded mental functioning
- Nausea and vomiting
- Suppression of pain
- Spontaneous abortion

Long-Term Effects

- Addiction
- Infectious disease (e.g., HIV, hepatitis B and C)
- Collapsed veins
- Bacterial infections
- Abscesses
- Infection of heart lining and valves
- Arthritis and other rheumatologic problems
- Liver and kidney disease

Why does heroin use create special risk for contracting HIV/AIDS and hepatitis B and C?



Heroin use increases the risk of being exposed to HIV, viral hepatitis, and other infectious agents through contact with infected blood or body fluids (e.g., semen, saliva) that results from the sharing of syringes and injection paraphernalia that have been used by infected individuals or through unprotected sexual contact with an

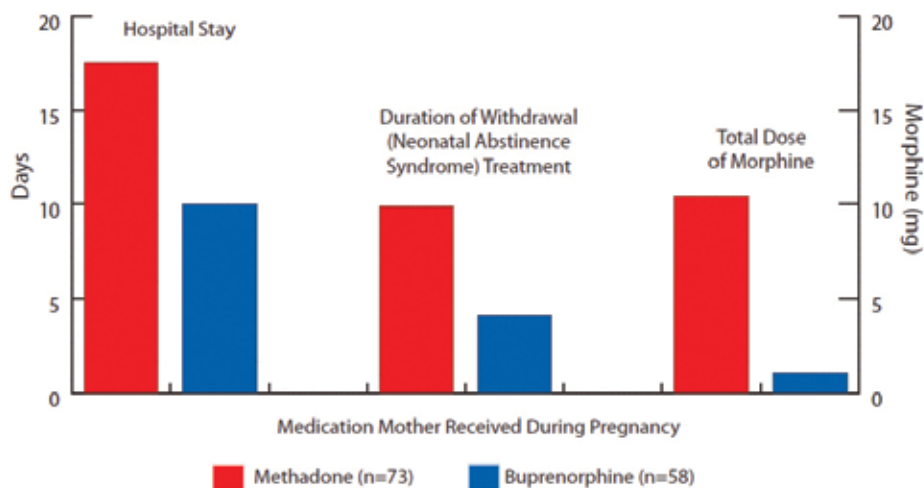
infected person. Snorting or smoking does not eliminate the risk of infectious disease like hepatitis and HIV/AIDS because people under the influence of drugs still engage in risky sexual and other behaviors that can expose them to these diseases.

Injection drug users (IDUs) are the highest-risk group for acquiring hepatitis C (HCV) infection and continue to drive the escalating HCV epidemic: Each IDU infected with HCV is likely to infect 20 other people.²¹ Of the 17,000 new HCV infections occurring in the United States in 2010, over half (53 percent) were among IDUs.²² Hepatitis B (HBV) infection in IDUs was reported to be as high as 20 percent in the United States in 2010,²³ which is particularly disheartening since an effective vaccine that protects against

HBV infection is available. There is currently no vaccine available to protect against HCV infection.

Drug use, viral hepatitis and other infectious diseases, mental illnesses, social dysfunctions, and stigma are often co-occurring conditions that affect one another, creating more complex health challenges that require comprehensive treatment plans tailored to meet all of a patient's needs. For example, NIDA-funded research has found that drug abuse treatment along with HIV prevention and community-based outreach programs can help people who use drugs change the behaviors that put them at risk for contracting HIV and other infectious diseases. They can reduce drug use and drug-related risk behaviors such as needle

Mothers' Buprenorphine Treatment During Pregnancy Benefits Infants



A NIDA-funded clinical trial found buprenorphine to be a safe and effective alternative to methadone for treating opioid dependence during pregnancy. Buprenorphine was also found to be effective in reducing neonatal abstinence syndrome in newborns born to opioid-dependent mothers.

sharing and unsafe sexual practices and, in turn, reduce the risk of exposure to HIV/AIDS and other infectious diseases. Only through coordinated utilization of effective antiviral therapies coupled with treatment for drug abuse and mental illness can the health of those suffering from these conditions be restored.

How does heroin use affect pregnant women?

Heroin use during pregnancy can result in neonatal abstinence syndrome (NAS). NAS occurs when heroin passes through the placenta to the fetus during pregnancy, causing the baby to become dependent along with the mother. Symptoms include excessive crying, fever, irritability, seizures, slow weight gain, tremors, diarrhea, vomiting, and possibly death. NAS requires hospitalization and treatment with medication (often morphine) to relieve symptoms; the medication is gradually tapered off until the baby adjusts to being opioid-free. Methadone maintenance combined with prenatal care and a comprehensive drug treatment program can improve many of the outcomes associated with untreated heroin use for both the infant and mother, although infants exposed to methadone during



pregnancy typically require treatment for NAS as well.

A recent NIDA-supported clinical trial demonstrated that buprenorphine treatment of opioid-dependent mothers is safe for both the unborn child and the mother. Once born, these infants require less morphine and shorter hospital stays as compared to infants born of mothers on methadone maintenance treatment.²⁴ Research also indicates that buprenorphine combined with naloxone (compared to a morphine taper) is equally safe for treating babies born with NAS, further reducing side effects experienced by infants born to opioid-dependent mothers.^{25,26}

What can be done for a heroin overdose?

Overdose is a dangerous and deadly consequence of heroin use. A large dose of heroin depresses heart rate and breathing to such an extent that a user cannot survive without medical help. Naloxone (e.g., Narcan[®]) is an opioid receptor antagonist medication that can eliminate all signs of opioid intoxication to reverse an opioid overdose. It works by rapidly binding to opioid receptors, preventing heroin from activating them.²⁷ Because of the huge increase in overdose deaths from prescription opioid abuse, there has been greater demand for opioid overdose prevention services. Naloxone that can be used by nonmedical personnel has been shown to be cost-effective and save lives.²⁸ In April 2014, the U.S. Food and Drug Administration (FDA) approved a naloxone hand-held auto-injector called Evzio, which rapidly delivers a single dose of naloxone into the muscle or under the skin, buying time until medical assistance can arrive. Since Evzio can be used by family members or caregivers, it greatly expands access to naloxone.²⁹ NIDA and the FDA are working with drug manufacturers to support the development of nasal spray formulations of this live-saving medication.

In addition, the Substance Abuse and Mental Health Services Administration (SAMHSA) released an Opioid Overdose Prevention Toolkit in August 2013 that provides helpful information necessary to develop policies and practices to prevent opioid-related overdoses and deaths. The kit provides material tailored for first responders, treatment providers, and individuals recovering from an opioid overdose.

What are the treatments for heroin addiction?

A variety of effective treatments are available for heroin addiction, including both behavioral and pharmacological (medications). Both approaches help to restore a degree of normalcy to brain function and behavior, resulting in increased employment rates and lower risk of HIV and other diseases and criminal behavior. Although behavioral and pharmacologic treatments can be extremely useful when utilized alone, research shows that for some people, integrating both types of treatments is the most effective approach.

Pharmacological Treatment (Medications)

Scientific research has established that pharmacological treatment of opioid addiction increases retention in treatment programs and decreases drug use, infectious disease transmission, and criminal activity.

When people addicted to opioids first quit, they undergo withdrawal symptoms (pain, diarrhea, nausea, and vomiting), which may be severe. Medications can be helpful in this detoxification stage to ease craving and other physical symptoms, which often prompt a person to relapse. While not a treatment for addiction itself, detoxification is a useful first step when it is followed by some form of evidence-based treatment.

Medications developed to treat opioid addiction work through the same opioid receptors as the addictive drug, but are safer and less likely to produce the harmful behaviors that characterize addiction. Three types of medications include: (1) agonists, which activate opioid receptors; (2) partial agonists,

which also activate opioid receptors but produce a smaller response; and (3) antagonists, which block the receptor and interfere with the rewarding effects of opioids. A particular medication is used based on a patient's specific medical needs and other factors. Effective medications include:

- Methadone (Dolophine® or Methadose®) is a slow-acting opioid agonist. Methadone is taken orally so that it reaches the brain slowly, dampening the “high” that occurs with other routes of administration while preventing withdrawal symptoms. Methadone has been used since the 1960s to treat heroin addiction and is still an excellent treatment option, particularly for patients who do not respond well to other medications. Methadone is only available through approved outpatient treatment programs, where it is dispensed to patients on a daily basis.
- Buprenorphine (Subutex®) is a partial opioid agonist. Buprenorphine relieves drug cravings without producing the “high” or dangerous side effects of other opioids. Suboxone® is a novel formulation of buprenorphine that is taken orally or sublingually and contains naloxone (an opioid antagonist) to prevent attempts to get high by injecting the medication. If an addicted patient were to inject Suboxone, the naloxone would induce withdrawal symptoms, which are averted when taken orally as prescribed. FDA approved buprenorphine in 2002, making it the first medication eligible to be prescribed by certified physicians through the Drug

Addiction Treatment Act. This approval eliminates the need to visit specialized treatment clinics, thereby expanding access to treatment for many who need it. In February 2013, FDA approved two generic forms of Suboxone, making this treatment option more affordable.

- Naltrexone (Depade® or Revia®) is an opioid antagonist. Naltrexone blocks the action of opioids, is not addictive or sedating, and does not result in physical dependence; however, patients often have trouble complying with the treatment, and this has limited its effectiveness. An injectable long-acting formulation of naltrexone (Vivitrol®) recently received FDA approval for treating opioid addiction. Administered once a month, Vivitrol® may improve compliance by eliminating the need for daily dosing.

Behavioral Therapies

The many effective behavioral treatments available for heroin addiction can be delivered in outpatient and residential settings. Approaches such as contingency management and cognitive-behavioral therapy have been shown to effectively treat heroin addiction, especially when applied in concert with medications. Contingency management uses a voucher-based system in which patients earn “points” based on negative drug tests, which they can exchange for items that encourage healthy living. Cognitive-behavioral therapy is designed to help modify the patient's expectations and behaviors related to drug use and to increase skills in coping with various life stressors. An important task is to match the best treatment approach to meet the particular needs of the patient.



Glossary

Addiction: A chronic, relapsing disease, characterized by compulsive drug seeking and use accompanied by neurochemical and molecular changes in the brain.

Agonist: A chemical compound that mimics the action of a natural neurotransmitter and binds to the same receptor on nerve cells to produce a biological response.

Antagonist: A drug that binds to the same nerve cell receptor as the natural neurotransmitter but does not activate the receptor, instead blocking the effects of another drug.

Buprenorphine: A partial opioid agonist for the treatment of opioid addiction that relieves drug cravings without producing the “high” or dangerous side effects of other opioids.

Craving: A powerful, often uncontrollable desire for drugs.

Detoxification: A process of allowing the body to rid itself of a drug while managing the symptoms of withdrawal; often the first step in a drug treatment program.

Methadone: A long-acting opioid agonist medication shown to be effective in treating heroin addiction.

Naloxone: An opioid receptor antagonist that rapidly binds to opioid receptors, blocking heroin from activating them. An appropriate dose of naloxone acts in less than 2 minutes and completely eliminates all signs of opioid intoxication to reverse an opioid overdose.

Naltrexone: An opioid antagonist medication that can only be used after a patient has completed detoxification. Naltrexone is not addictive or sedating and does not result in physical dependence; however, poor patient compliance has limited its effectiveness. A new, long-acting form of naltrexone called Vivitrol® is now available that is injected once per month, eliminating the need for daily dosing, improving patient compliance.

Neonatal abstinence syndrome (NAS): NAS occurs when heroin from the mother passes through the placenta into the baby’s bloodstream during pregnancy, allowing the baby to become addicted along with the mother. NAS requires hospitalization and treatment with medication (often a morphine taper) to relieve symptoms until the baby adjusts to becoming opioid-free.

Opioid: A natural or synthetic psychoactive chemical that binds to opioid receptors in the brain and body. Natural opioids include morphine and heroin (derived from the opium poppy) as well as opioids produced by the human body (e.g., endorphins); semi-synthetic or synthetic opioids include analgesics such as oxycodone, hydrocodone, and fentanyl.

Opioid use disorder: A problematic pattern of opioid drug use, leading to clinically significant impairment or distress that includes cognitive, behavioral, and physiological symptoms as defined by the new Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria. Diagnosis of an opioid use disorder can be mild, moderate, or severe depending on the number of symptoms a person experiences. Tolerance or withdrawal symptoms that occur during medically supervised treatment are specifically excluded from an opioid use disorder diagnosis.

Partial agonist: A substance that binds to and activates the same nerve cell receptor as a natural neurotransmitter but produces a diminished biological response.

Physical dependence: An adaptive physiological state that occurs with regular drug use and results in a withdrawal syndrome when drug use is stopped; usually occurs with tolerance.

Rush: A surge of euphoric pleasure that rapidly follows administration of a drug.

Tolerance: A condition in which higher doses of a drug are required to produce the same effect as during initial use; often leads to physical dependence.

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

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Where can I get further information about heroin?

To learn more about heroin and other drugs of abuse, visit the NIDA Web site at www.drugabuse.gov or contact the *DrugPubs* Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

NATIONAL INSTITUTE ON DRUG ABUSE



RESEARCH DISSEMINATION CENTER

What's on the NIDA Web Site

- Information on drugs of abuse and related health consequences
- NIDA publications, news, and events
- Resources for health care professionals
- 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)

NIDA Web Sites

www.drugabuse.gov
www.teens.drugabuse.gov
www.drugabuse.gov/drugs-abuse/heroin
www.easyread.drugabuse.gov
www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide

For Physician Information

NIDAMED

www.drugabuse.gov/nidamed

Other Web Sites

Information on heroin and addiction is also available through these other Web sites:

- Medication-Assisted Treatment for Opioid Addiction
www.drugabuse.gov/publications/topics-in-brief/medication-assisted-treatment-opioid-addiction
- Prescription Drugs
www.drugabuse.gov/drugs-abuse/prescription-drugs
- Medication-Assisted Treatment for Opioid Addiction
www.samhsa.gov/samhsaNewsLetter/Volume_17_Number_5/TreatingOpioidAddiction.aspx



National Institute
on Drug Abuse

NIH Publication Number 15-0165

Published October 1997, Revised May 2005. Revised February 2014, Revised April 2014. Revised November 2014.

Feel free to reprint this publication.



How does marijuana use affect school, work, and social life? See page 7.



National Institute on Drug Abuse

from the director:

Changes in marijuana policies across states legalizing marijuana for medical and/or recreational use suggest that marijuana is gaining greater acceptance in our society. Thus, it is particularly important for people to understand what is known about both the adverse health effects and the potential therapeutic benefits linked to marijuana.

Because marijuana impairs short-term memory and judgment and distorts perception, it can impair performance in school or at work and make it dangerous to drive an automobile. It also affects brain systems that are still maturing through young adulthood, so regular use by teens may have a negative and long-lasting effect on their cognitive development, putting them at a competitive disadvantage and possibly interfering with their well-being in other ways. Also, contrary to popular belief, marijuana can be addictive, and its use during adolescence may make other forms of drug abuse or addiction more likely.

Whether smoking or otherwise consuming marijuana has therapeutic benefits that outweigh its health risks is still an open question that science has not resolved. Although many states now permit dispensing marijuana for medicinal purposes and there is mounting anecdotal evidence for the efficacy of marijuana-derived compounds, there are currently no FDA-approved indications for “medical marijuana.” However, safe medicines based on cannabinoid chemicals derived from the marijuana plant have been available for decades and more are being developed.

This Research Report is intended as a useful summary of what the most up-to-date science has to say about marijuana and its effects on those who use it—both young and old.

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

Research Report Series



Marijuana

What is marijuana?

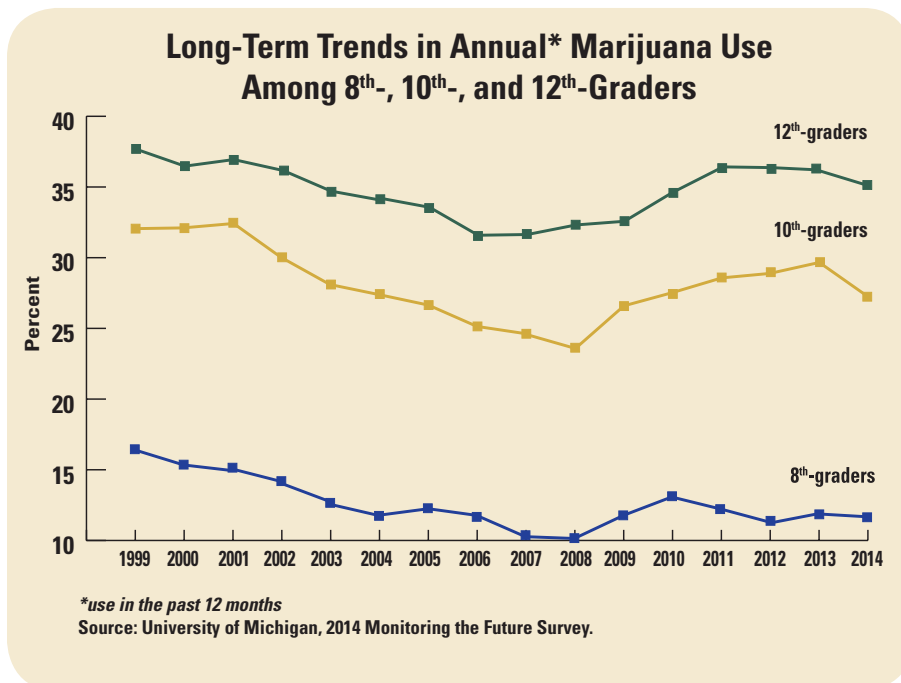
Marijuana—also called *weed*, *herb*, *pot*, *grass*, *bud*, *ganja*, *Mary Jane*, and a vast number of other slang terms—is a greenish-gray mixture of the dried, shredded leaves and flowers of *Cannabis sativa*—the hemp plant. Some users smoke marijuana in hand-rolled cigarettes called *joints*; many use pipes, water pipes (sometimes called *bongs*), or marijuana cigars called *blunts* (often made by slicing open cigars and replacing some or all of the tobacco with marijuana).¹ Marijuana can also be used to brew tea and, particularly when it is sold or consumed for medicinal purposes, is frequently mixed into foods (“edibles”) such as brownies, cookies, or candies. In addition, concentrated resins containing high doses of marijuana’s active ingredients, including honey-like “hash oil,” waxy “budder,” and hard amber-like “shatter,” are increasingly popular among both recreational and medical users.

The main *psychoactive* (mind-altering) chemical in marijuana, responsible for most of the intoxicating effects sought by recreational users, is delta-9-tetrahydro-cannabinol (THC). The chemical is found in resin produced by the leaves and buds primarily of the female cannabis plant. The plant also contains more than 500 other chemicals, including over 100 compounds that are chemically related to THC, called *cannabinoids*.²

What is the scope of marijuana use in the United States?

Marijuana is the most commonly used illicit drug (19.8 million past-month users) according to the 2013 National Survey on Drug Use and Health (NSDUH).³ That year, marijuana was used by 81.0 percent of current illicit drug users (defined as having used a drug at some time in the 30 days before the survey) and was the only drug used by 64.7 percent of them.

Marijuana use is widespread among adolescents and young adults. According to the Monitoring the Future survey—an annual survey of drug use and attitudes among the Nation’s middle and high school students—most measures of marijuana use by 8th-, 10th-, and 12th-graders have held steady in



the past few years following several years of increase in the previous decade. Teens’ perceptions of the risks of marijuana use have steadily declined over the past decade, possibly related to increasing public debate about legalizing or loosening restrictions on marijuana for medicinal and recreational use. In 2014, 11.7 percent of 8th-graders reported marijuana use in the past year and 6.5 percent were current users. Among 10th-graders, 27.3 percent had used marijuana in the past year and 16.6 percent were current users. Rates of use among 12th-graders were higher still: 35.1 percent had used marijuana during the year prior to the survey and 21.2 percent were current users; 5.8 percent said they used marijuana daily or near-daily.⁴

Medical emergencies possibly related to marijuana use have also increased. The Drug Abuse Warning Network (DAWN), a system for monitoring the health impact of drugs, estimated that in 2011, there were nearly 456,000 drug-related emergency department visits in the United States in which marijuana use was mentioned in the medical record (a 21 percent increase over 2009). About two-thirds of patients were male and 13 percent were between the ages of 12 and 17.⁵ It is unknown whether this increase is due to increased use, increased *potency* of marijuana (amount of THC it contains), or other factors. It should be noted, however, that mentions of marijuana in medical records do not necessarily indicate that these emergencies were directly related to marijuana intoxication.



What are marijuana effects?

- When marijuana is smoked, THC and other chemicals in the plant pass from the lungs into the bloodstream, which rapidly carries them throughout the body and to the brain. The user begins to experience their effects almost immediately (see “**How does marijuana produce its effects?**”). Many users experience a pleasant euphoria and sense of relaxation. Other common effects, which may vary dramatically among different users, include heightened sensory perception (e.g., brighter colors), laughter, altered perception of time, and increased appetite.
- If marijuana is consumed in foods or beverages, these effects are somewhat delayed—usually appearing after 30 minutes to 1 hour—because the drug must first pass through the digestive system. Eating or drinking marijuana delivers significantly less THC into the bloodstream than smoking an equivalent amount of the plant. Because of the delayed effects, users may inadvertently consume more THC than they intend to.
- Pleasant experiences with marijuana are by no means universal. Instead of relaxation and euphoria, some users experience anxiety, fear, distrust, or panic. These effects are more common when too much is taken, the marijuana has an unexpectedly high potency, or a user is inexperienced. People who have taken large doses of marijuana may experience an acute psychosis, which includes hallucinations, delusions, and a loss of the sense of personal identity. These unpleasant but temporary reactions are distinct from longer-lasting psychotic disorders, such as schizophrenia, that may be associated with the use of marijuana in vulnerable individuals. (See “**Is there a link between marijuana use and mental illness?**”)

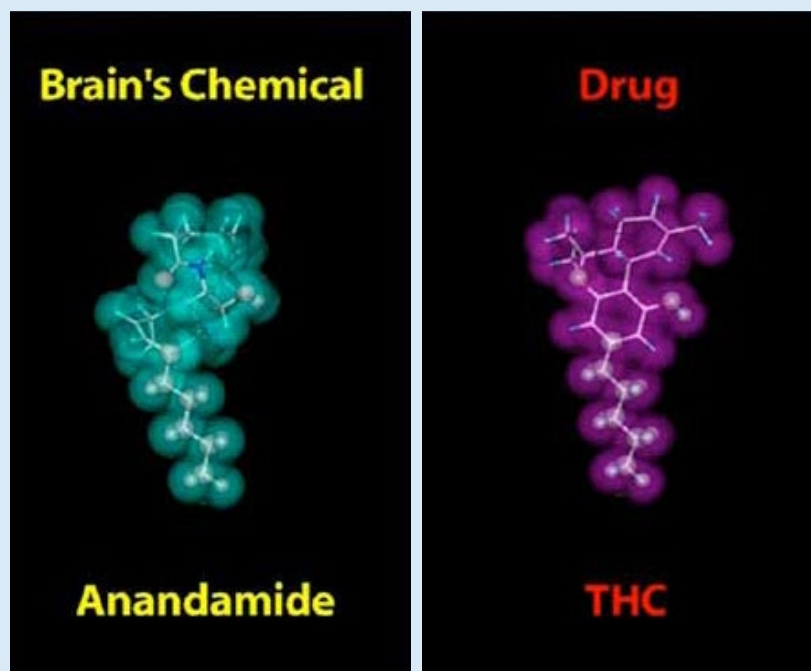
Although detectable amounts of THC may remain in the body for days or even weeks after use, the noticeable effects of smoked marijuana generally last from 1 to 3 hours and those of marijuana consumed in food or drink may last for many hours.

How does marijuana produce its effects?

THC and other cannabinoid chemicals in marijuana are similar to cannabinoid chemicals that naturally occur in the body. These *endogenous cannabinoids* (such as anandamide; see figure below) function as *neurotransmitters* because they send chemical messages between nerve cells (*neurons*) throughout the nervous system. They affect brain areas

that influence pleasure, memory, thinking, concentration, movement, coordination, and sensory and time perception. Because of this similarity, THC is able to attach to molecules called *cannabinoid receptors* on neurons in these brain areas and activate them, disrupting various mental and physical functions and causing the effects described earlier. The neural communication network that uses these cannabinoid neurotransmitters, known as the *endocannabinoid system*, plays a critical role in the nervous system’s normal functioning, so interfering with it can have profound effects.

For example, THC is able to alter the functioning of the hippocampus (see “**Marijuana, Memory, and the Hippocampus**”) and orbitofrontal cortex, brain areas that enable a person to form new memories and shift their attentional focus. As a result,



THC’s chemical structure is similar to the brain chemical anandamide. Similarity in structure allows drugs to be recognized by the body and to alter normal brain communication

Marijuana users who have taken large doses of the drug may experience an acute psychosis, which includes hallucinations, delusions, and a loss of the sense of personal identity.

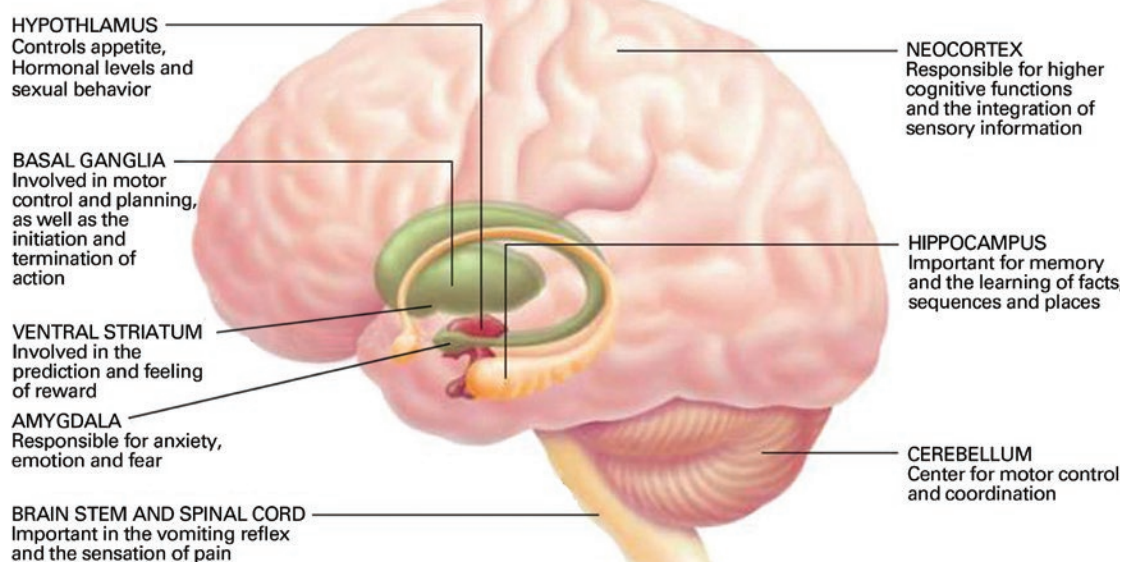
using marijuana causes impaired thinking and interferes with a user's ability to learn and to perform complicated tasks. THC also disrupts functioning of the cerebellum and basal ganglia, brain areas that regulate balance, posture, coordination, and reaction time. This is the reason people who have used marijuana may not be able to drive a car safely (see “Does marijuana use affect driving?”) and may be impaired at playing sports or other physical activities.

THC, acting through cannabinoid receptors, also activates the brain's reward system, which includes regions that govern the response to healthy pleasurable behaviors like sex and eating. Like most other drugs of abuse, THC stimulates neurons in the reward system to release the signaling chemical *dopamine* at levels higher than typically observed in response to natural stimuli. This flood of dopamine contributes to the pleasurable “high” that recreational marijuana users seek.

Does marijuana use affect driving?

Marijuana significantly impairs judgment, motor coordination, and reaction time, and studies have found a direct relationship between blood THC concentration and impaired driving ability.^{6,7} Marijuana is the illicit drug most frequently found in the blood of drivers who have been involved in accidents, including fatal ones⁸ (although it is important to note that marijuana can remain detectable in body fluids for days or even weeks after acute intoxication). A meta-analysis of multiple studies found that the risk of being involved in an accident roughly doubles after marijuana use.⁹

Marijuana's Effects on the Brain



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When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.

Accident-involved drivers with THC in their blood, particularly higher levels, are three to seven times more likely to be responsible for the accident than drivers who had not used drugs or alcohol. The risk associated with marijuana in combination with alcohol appears to be greater than that for either drug by itself.⁷

Is marijuana addictive?

Yes. Over time, overstimulation of the endocannabinoid system by marijuana use can cause changes in the brain that lead to *addiction*, a condition in which a person cannot stop using a drug even though it interferes with many aspects of his or her life. It is estimated that 9 percent of people who use marijuana will become dependent on it.^{10,11} The number goes up to about 17 percent in those who start using young (in their teens) and to 25 to 50 percent among daily users.^{12,13} According to the 2013 NSDUH, marijuana accounted for 4.2 million of the estimated 6.9 million Americans dependent on or abusing illicit drugs.³

Marijuana addiction is linked to a mild withdrawal syndrome. Frequent marijuana users often report irritability, mood and sleep difficulties, decreased appetite, cravings, restlessness, and/or various forms of physical discomfort that peak within the first week after quitting and last up to 2 weeks.^{14,15}

Rising Potency

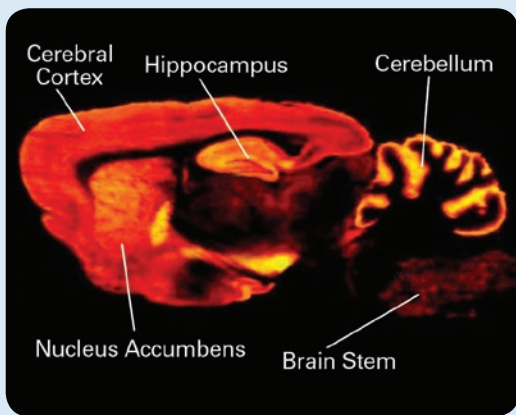
Marijuana potency, as detected in confiscated samples, has steadily increased over the past few decades.² In the early 1990s, the average THC content in confiscated cannabis samples was roughly 3.7 percent for marijuana and 7.5 percent for sinsemilla (a higher potency marijuana from specially tended female plants). In 2013, it was 9.6 percent for marijuana and 16 percent for sinsemilla.¹⁶ Also, newly popular methods of smoking or eating THC-rich hash oil extracted from the marijuana plant (a practice called “dabbing”) may deliver very high levels of THC to the user. The average marijuana extract contains over 50 percent THC, with some samples exceeding 80 percent. These trends raise concerns that the consequences of marijuana use could be worse than in the past, particularly among new users or in young people, whose brains are still developing (see “What are marijuana’s long-term effects on the brain?”).

Researchers do not yet know the full extent of the consequences when the body and brain (especially the developing brain) are exposed to high concentrations of THC or whether the recent increases in emergency department visits by people testing positive for marijuana are related to rising potency. The extent to which marijuana users adjust for increased potency by using less or by smoking it differently is also unknown. Recent studies suggest that experienced users may adjust the amount they smoke and how much they inhale based on the believed strength of the marijuana they are using, but are not able to fully compensate for variations in potency.^{17,18}

What are marijuana’s long-term effects on the brain?

Substantial evidence from animal research and a growing number of studies in humans indicate that marijuana exposure during development can cause long-term or possibly permanent adverse changes in the brain. Rats exposed to THC before birth, soon after birth, or during adolescence show notable problems with specific learning and memory tasks later in

life.^{19–21} Cognitive impairments in adult rats exposed to THC during adolescence are associated with structural and functional changes in the hippocampus.^{22–24} Studies in rats also show that adolescent exposure to THC is associated with an altered reward system, increasing the likelihood that an animal will self-administer other drugs (e.g., heroin) when given an opportunity (see “**Is marijuana a gateway drug?**”). Imaging studies in human adolescents show that regular marijuana users display impaired neural connectivity in specific brain regions involved in a broad range



Distribution of cannabinoid receptors in the rat brain. Brain image reveals high levels (shown in orange and yellow) of cannabinoid receptors in many areas, including the cortex, hippocampus, cerebellum, and nucleus accumbens (ventral striatum).

Marijuana, Memory, and the Hippocampus

Memory impairment from marijuana use occurs because THC alters how information is processed in the hippocampus, a brain area responsible for memory formation.

Most of the evidence supporting this assertion comes from animal studies. For example, rats exposed to THC in utero, soon after birth, or during adolescence, show notable problems with specific learning/memory tasks later in life. Moreover, cognitive impairment in adult rats is associated with structural

and functional changes in the hippocampus from THC exposure during adolescence.

As people age, they lose neurons in the hippocampus, which decreases their ability to learn new information. Chronic THC exposure may hasten age-related loss of hippocampal neurons. In one study, rats exposed to THC every day for 8 months (approximately 30 percent of their life-span) showed a level of nerve cell loss (at 11 to 12 months of age) that equaled that of unexposed animals twice their age.

of executive functions like memory, learning, and impulse control compared to non-users.²⁵

The latter findings may help explain the results of a large longitudinal study conducted in New Zealand, which found that frequent and persistent marijuana use starting in adolescence was associated with a loss of an average of 8 IQ points measured in mid-adulthood.²⁶ Significantly, in that study, those who used marijuana heavily as teenagers and quit using as adults did not recover the lost IQ points. Users who only began using marijuana heavily in adulthood did not lose IQ points. These results suggest that marijuana has its strongest long-term impact on young users whose brains are still busy building new connections and maturing in other ways. The endocannabinoid system is known to play an important role in the proper formation of synapses (the connections between neurons) during early brain development,

and a similar role has been proposed for the refinement of neural connections during adolescence. If confirmed by future research, this may be one avenue by which marijuana use during adolescence produces its long-term effects.²⁷

The ability to draw definitive conclusions about marijuana's long-term impact on the human brain from past studies is often limited by the fact that study participants use multiple substances, and there is often limited data about the participants' health or mental functioning prior to the study. Over the next decade, the National Institutes of Health is planning to fund a major longitudinal study that will track a large sample of young Americans from late childhood (before first use of drugs) to early adulthood. The study will use neuroimaging and other advanced tools to clarify precisely how and to what extent marijuana and other substances, alone and in combination, affect adolescent brain development.

Is marijuana a gateway drug?

Early exposure to cannabinoids in adolescent rodents decreases the reactivity of brain dopamine reward centers later in adulthood.²⁸ To the extent that these findings generalize to humans, this could help explain early marijuana initiates' increased vulnerability for drug abuse and addiction to other substances of abuse later in life that has been reported by most epidemiological studies.²⁹ It is also consistent with animal experiments showing THC's ability to "prime" the brain for enhanced responses to other drugs.³⁰ For example, rats previously administered THC show heightened behavioral response not only when further exposed to THC but also when exposed to other drugs such as morphine—a phenomenon called *cross-sensitization*.³¹

These findings are consistent with the idea of marijuana as a “gateway drug.” However, most people who use marijuana do not go on to use other, “harder” substances. Also, cross-sensitization is not unique to marijuana. Alcohol and nicotine also prime the brain for a heightened response to other drugs³² and are, like marijuana, also typically used before a person progresses to other, more harmful substances.

It is important to note that other factors besides biological mechanisms, such as a person’s social environment, are also critical in a person’s risk for drug use. An alternative to the gateway-drug hypothesis is that people who are more vulnerable to drug-taking are simply more likely to start with readily available substances like marijuana, tobacco, or alcohol, and their subsequent social interactions with other drug users increases their chances of trying other drugs. Further research is needed to explore this question.

How does marijuana use affect school, work, and social life?

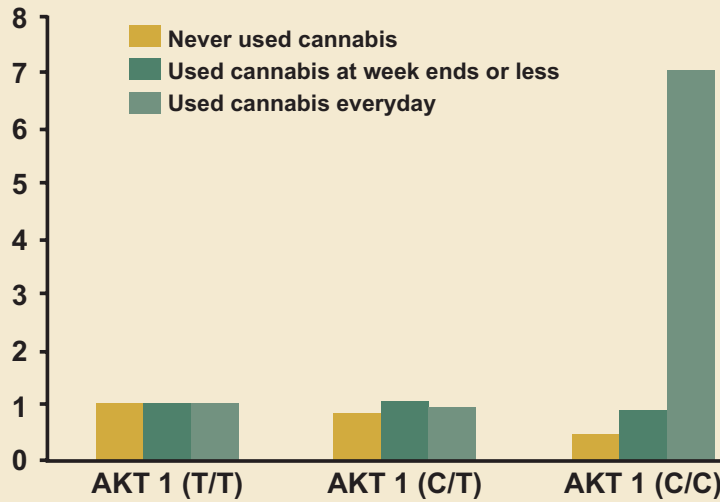
Research has shown that marijuana’s negative effects on attention, memory, and learning can last for days or weeks after the acute effects of the drug wear off, depending on the user’s history with the drug.³³ Consequently, someone who smokes marijuana daily may be functioning at a reduced intellectual level most or all of the time. Considerable evidence suggests that students who smoke marijuana have poorer educational outcomes than their

nonsmoking peers. For example, a review of 48 relevant studies found marijuana use to be associated with reduced educational attainment (i.e. reduced chances of graduating).³⁴ A recent analysis using data from three large studies in Australia and New Zealand found that adolescents who used marijuana regularly were significantly less likely than their non-using peers to finish high school or obtain a degree. They also had a much higher chance of later developing dependence, using other drugs, and attempting suicide.³⁵ Several studies have also linked heavy marijuana use to lower income, greater welfare dependence, unemployment, criminal behavior, and lower life satisfaction.^{36,37}

To what degree marijuana use is directly causal in these associations remains an open question requiring further research. It is possible that other factors independently predispose people to both marijuana use and various negative life outcomes such as school dropout.³⁸ That said, marijuana users themselves report a perceived influence of their marijuana use on poor outcomes on a variety of life satisfaction and achievement measures. One study, for example, compared current and former long-term, heavy users of marijuana with a control group who reported smoking marijuana at least once in their lives but not more than 50 times.³⁹ All participants had similar



AKT1 Gene Variants and Psychosis



Whether adolescent marijuana use can contribute to developing psychosis later in adulthood appears to depend on whether a person already has a genetically based vulnerability to the disorder. The AKT1 gene governs an enzyme that affects brain signaling involving the neurotransmitter dopamine. Altered dopamine signaling is known to be involved in schizophrenia. AKT1 can take one of three forms in a specific region of the gene implicated in susceptibility to schizophrenia: T/T, C/T, and C/C. Daily users of marijuana (green bars) with the C/C variant have a seven times higher risk of developing psychosis than infrequent marijuana users or nonusers. The risk for psychosis among those with the T/T variant was unaffected by whether they used marijuana.

Source: Di Forti et al. Biol Psychiatry. 2012.

education and income backgrounds, but significant differences were found in their educational attainment: Fewer of the heavy cannabis users completed college and more had yearly household incomes less than \$30,000. When asked how marijuana affected their cognitive abilities, career achievements, social lives, and physical and mental health, the majority of heavy users reported that marijuana had negative effects in all these areas of their lives.

Studies have also suggested specific links between marijuana use and adverse consequences in the workplace, such as increased risk for injury or accidents.⁴⁰ One study among postal workers found that employees who tested positive for marijuana on a pre-employment urine drug test had 55 percent more industrial accidents, 85 percent more injuries, and 75 percent greater absenteeism compared with those who tested negative for marijuana use.⁴¹

Is there a link between marijuana use and mental illness?

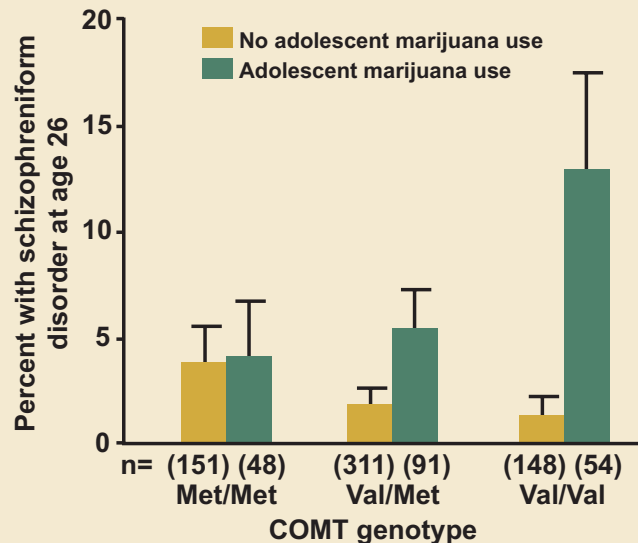
Several studies have linked marijuana use to increased risk for mental illnesses, including psychosis (schizophrenia), depression, and anxiety, but whether and to what extent it actually causes these conditions is not always easy to determine.¹⁹ The amount of drug used, the age at first use, and genetic vulnerability have all been shown to influence this relationship. The strongest evidence to date concerns the link between marijuana use and psychotic disorders in those with a preexisting genetic or other vulnerability.⁴² Recent research (see **AKT1 Gene Variations and Psychosis**) has found that marijuana users who carry a specific variant of the *AKT1* gene, which codes for an enzyme that affects dopamine signaling in the *striatum*, are at increased risk of developing psychosis. The *striatum* is an area of the brain that becomes activated and flooded with dopamine when certain stimuli are present. One study found that the risk for those with this variant was seven times higher for daily marijuana users compared with infrequent- or non-users.⁴³

Another study found an increased risk of psychosis among adults who had used marijuana in adolescence and also carried a specific variant of the gene for catechol-O-methyltransferase (COMT), an enzyme that degrades neurotransmitters such as dopamine

and norepinephrine.⁴⁴ (see **Genetic Variations in COMT Influences the Harmful Effects of Abused Drugs**). Marijuana use has also been shown to worsen the course of illness in patients who already have schizophrenia. As mentioned previously, marijuana can also produce a brief psychotic reaction in non-schizophrenic users, especially at high doses, although this fades as the drug wears off.

Other, less consistent associations have been reported between marijuana use and depression, anxiety, suicidal thoughts among teens, and personality disorders. Marijuana has also been associated with an *amotivational syndrome*, defined as a diminished or absent drive to engage in typically rewarding activities. Because of the role of the endocannabinoid system in regulating mood and reward, it is logical to hypothesize the existence of such a link underpinned by brain changes, but more research is needed to confirm and better understand it.

Genetic Variation in COMT Influences the Harmful Effects of Abused Drugs



The influence of adolescent marijuana use on adult psychosis is affected by genetic variables. This figure shows that variations in a gene can affect the likelihood of developing psychosis in adulthood, following exposure to cannabis in adolescence. The COMT gene governs an enzyme that breaks down dopamine, a brain chemical involved in schizophrenia. It comes in two forms: “Met” and “Val.” Individuals with one or two copies of the Val variant have a higher risk of developing schizophrenic-type disorders if they used cannabis during adolescence (dark bars). Those with only the Met variant were unaffected by cannabis use.⁷

Source: Caspi et al. *Biol Psychiatry*. 2005.

Adverse Consequences of Marijuana Use

Acute (present during intoxication)

- Impaired short-term memory
- Impaired attention, judgment, and other cognitive functions
- Impaired coordination and balance
- Increased heart rate
- Anxiety, paranoia
- Psychosis (uncommon)

Persistent (lasting longer than intoxication, but may not be permanent)

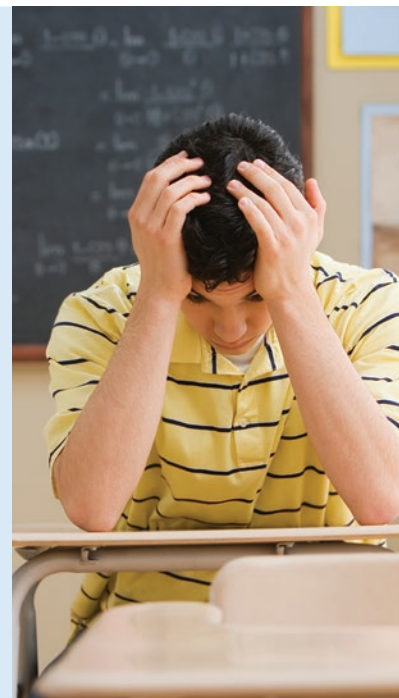
- Impaired learning and coordination
- Sleep problems



Long-term (cumulative effects of repeated use)

- Potential for addiction
- Potential loss of IQ
- Increased risk of chronic cough, bronchitis
- Increased risk of schizophrenia in vulnerable people*
- Potentially increased risk of anxiety, depression, and amotivational syndrome*

*These are often reported co-occurring symptoms/disorders with chronic marijuana use. However, research has not yet determined whether marijuana is causal or just associated with these mental problems.





What are marijuana's effects on general physical health?

Within a few minutes after inhaling marijuana smoke, a person's heart rate speeds up, the breathing passages relax and become enlarged, and blood vessels in the eyes expand, making the eyes look bloodshot (red). The heart rate—normally 70 to 80 beats per minute—may increase by 20 to

50 beats per minute or may even double in some cases. Taking other drugs with marijuana can amplify this effect.

Limited evidence suggests that a person's risk of heart attack during the first hour after smoking marijuana is nearly five times his or her usual risk.⁴⁵ This observation could be partly explained by marijuana raising blood pressure (in some cases) and heart rate and reducing the blood's capacity to carry oxygen.⁴⁶ Marijuana may also cause *orthostatic hypotension*

(head rush or dizziness on standing up), possibly raising danger from fainting and falls. Tolerance to some cardiovascular effects often develops with repeated exposure.⁴⁷ These health effects need to be examined more closely, particularly given the increasing use of “medical marijuana” by people with health issues and older adults who may have increased baseline vulnerability due to age-related cardiovascular risk factors (see “**Marijuana as Medicine**”).

Marijuana smoke, like tobacco smoke, is an irritant to the throat and lungs and can cause a heavy cough during use. It also contains toxic gases and particles that can damage the lungs. Marijuana smoking is associated with large airway inflammation, increased airway resistance, and lung hyperinflation, and regular marijuana smokers report more symptoms of chronic bronchitis than non-smokers.⁴⁸ Smoking marijuana may also reduce the respiratory system's immune response, increasing the likelihood of the user acquiring respiratory infections, including pneumonia.⁴⁹ One study found that frequent marijuana smokers used more sick days than other people, often because of respiratory illnesses.⁵⁰

Whether smoking marijuana causes lung cancer, as cigarette smoking does, is less certain. Although marijuana smoke contains *carcinogenic* (cancer-causing) combustion products, evidence for a link between marijuana use and lung cancer has thus far been inconclusive.⁵¹ The very different ways marijuana and tobacco are used, including factors like how frequently they are smoked during the day and how long the smoke is



held in the lungs, as well as the fact that many people use both substances make determining marijuana's precise contribution to lung cancer risk, if any, difficult to establish. This is an area that will require more research.

However, a few studies have shown a clear link between marijuana use in adolescence and increased risk for an aggressive form of testicular cancer (non-seminomatous testicular germ cell tumor) that predominantly strikes young adult males.^{52,53} The early onset of testicular cancers compared to lung and most other cancers indicates that, whatever the nature of marijuana's contribution, it may accumulate over just a few years of use.

Can marijuana use during pregnancy harm the baby?

Animal research suggests that the body's endocannabinoid system plays a role in the control of brain maturation, particularly in the development of emotional responses. Thus THC exposure very early in life may negatively affect brain development. Research in rats suggests that exposure to even low concentrations of THC late in pregnancy could have profound and long-lasting consequences for both

Marijuana as Medicine

The potential medicinal properties of marijuana and its components have been the subject of research and heated debate for decades. THC itself has proven medical benefits in particular formulations. There are two FDA-approved, THC-based medications, dronabinol (Marinol®) and nabilone (Cesamet®), prescribed for the treatment of nausea in patients undergoing cancer chemotherapy and to stimulate appetite in patients with wasting syndrome due to AIDS.

In addition, several other marijuana-based medications have been approved or are undergoing clinical trials. Nabiximols (Sativex®), which is currently available in the United Kingdom, Canada, and several European countries for treating the spasticity and neuropathic pain that may accompany multiple sclerosis, combines THC with another chemical found in marijuana called cannabidiol (CBD). CBD does not have the rewarding properties of THC, and anecdotal reports indicate it may have promise for the treatment of seizure disorders, among other conditions. A CBD-based medication called Epidiolex is currently being tested in the United States for the treatment of two forms of severe childhood epilepsy, Dravet syndrome and Lennox-Gastaut syndrome.

Medications like these, which use purified chemicals derived from or based on those in the marijuana plant, are generally considered by researchers to be more promising therapeutically than use of the whole marijuana plant or its crude extracts. Development of drugs from botanicals such as the marijuana plant poses numerous challenges. Botanicals may contain hundreds of unknown, active chemicals, and it can be difficult to develop a product with accurate and consistent doses of these chemicals. Use of marijuana as medicine also poses other problems such as the adverse health effects of smoking and THC-induced cognitive impairment. Nevertheless, a growing number of states have legalized dispensing of marijuana or its extracts to people with a range of medical conditions.

An additional concern with "medical marijuana" is that little is known about the long-term impact of marijuana use by people with health- and/or age-related vulnerabilities to whom it is dispensed—such as older adults or people with cancer, AIDS, cardiovascular disease, multiple sclerosis, or other neurodegenerative diseases. Further research will be needed to determine whether people whose health has been compromised by disease or its treatment (e.g., chemotherapy) are at greater risk for adverse health outcomes from marijuana use.

brain and behavior of offspring.⁵⁴ Human studies have shown that some babies born to women who used marijuana during their pregnancies respond differently to visual stimuli, tremble more, and have a high-pitched cry, which could indicate problems with neurological development.^{55,56} In school, children prenatally exposed to marijuana are more likely to show gaps in problem-solving skills, memory, and the ability to remain attentive.^{57,58} More research is needed, however, to disentangle marijuana's specific effects from other environmental factors, including maternal nutrition, exposure to nurturing/neglect, and use of other substances by mothers.⁵⁹ Establishing marijuana's effects on prenatal development is important, because roughly half of U.S. pregnancies are unplanned, with the rate considerably higher for teens and young adults,⁶⁰ so many women may use marijuana without knowing they are pregnant.



Available Treatments for Marijuana Use Disorders

Marijuana addiction appears to be very similar to other substance use disorders, although the long-term clinical outcomes may be less severe. On average, adults seeking treatment for marijuana use disorders have used marijuana nearly every day for more than 10 years and have attempted to quit more than six times.⁶¹ People with marijuana use disorders, especially adolescents, often also suffer from other psychiatric disorders (comorbidity).⁶² They may also abuse or be addicted to other substances, such as cocaine or alcohol. Available studies indicate that effectively treating the mental health disorder with standard treatments involving medications and behavioral therapies may help reduce marijuana use, particularly among heavy users and those with more chronic mental disorders. The following behavioral treatments have shown promise:

- **Cognitive-behavioral therapy:** A form of psychotherapy that teaches people strategies to identify and correct problematic behaviors in order to enhance self-control, stop drug use, and address a range of other problems that often co-occur with them.
- **Contingency management:** A therapeutic management approach based on frequent monitoring of the target behavior and the provision (or removal) of tangible, positive rewards when the target behavior occurs (or does not).
- **Motivational enhancement therapy:** A systematic form of intervention designed to produce rapid, internally motivated change; the therapy does not attempt to treat the person, but rather mobilize their own internal resources for change and engagement in treatment.

Currently, no medications are indicated for the treatment of marijuana use disorder, but research is active in this area. Because sleep problems feature prominently in marijuana withdrawal, some studies are examining the effectiveness of medications that aid in sleep. Medications that have shown promise in early studies or small clinical trials include the sleep aid zolpidem (Ambien®), an anti-anxiety/anti-stress medication called buspirone (BuSpar®), and an anti-epileptic drug called gabapentin (Horizant®, Neurotin®) that may improve sleep and, possibly, executive function. Other agents being studied include the nutritional supplement N-acetylcysteine and chemicals called FAAH inhibitors, which may reduce withdrawal by inhibiting the breakdown of the body's own cannabinoids. Future directions include the study of substances called *allosteric modulators* that interact with cannabinoid receptors to inhibit THC's rewarding effects.

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Where can I get further information about marijuana?

To learn more about marijuana and other drugs of abuse, visit the NIDA Web site at www.drugabuse.gov or contact the DrugPubs Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

NATIONAL INSTITUTE ON DRUG ABUSE



RESEARCH DISSEMINATION CENTER

NIDA'S website includes:

- Information on drugs of abuse and related health consequences
- NIDA publications, news, and events
- Resources for researchers, health care professionals, educators, and patients and families.
- Information on NIDA research studies and clinical trials.
- Funding information (including program announcements and deadlines)
- International activities
- Links to related websites (access to websites of many other organizations in the field)
- Information in Spanish (en español)

NIDA websites and webpages

www.drugabuse.gov
www.teens.drugabuse.gov
www.easyread.drugabuse.gov
www.drugabuse.gov/drugs-abuse/marijuana
www.hiv.drugabuse.gov
www.researchstudies.drugabuse.gov
www.irp.drugabuse.gov

For Physician Information

NIDAMED 

www.drugabuse.gov/nidamed

Other websites

Information on marijuana is also available through the

- Substance Abuse and Mental Health Services Administration
www.samhsa.gov
- Drug Enforcement Administration:
www.dea.gov
- Monitoring the Future:
www.monitoringthefuture.org/
- The Partnership at Drug Free.org:
www.drugfree.org/drug-guide



National Institute
on Drug Abuse

NIH Publication Number 15-3859

Printed October 2002, Reprinted March 2003, Printed July 2005, Revised September 2010,
Revised July 2012, Revised December 2014.

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What are the long-term effects of methamphetamine abuse?
See page 4.

from the director:

The abuse of methamphetamine—a potent and highly addictive stimulant—remains an extremely serious problem in the United States. According to data from the 2012 National Survey on Drug Use and Health (NSDUH), over 12 million people (4.7 percent of the population) have tried methamphetamine at least once. NSDUH also reports that approximately 1.2 million people used methamphetamine in the year leading up to the survey.

The consequences of methamphetamine abuse are terrible for the individual—psychologically, medically, and socially. Abusing the drug can cause memory loss, aggression, psychotic behavior, damage to the cardiovascular system, malnutrition, and severe dental problems. Methamphetamine abuse has also been shown to contribute to increased transmission of infectious diseases, such as hepatitis and HIV/AIDS.

Beyond its devastating effects on individual health, methamphetamine abuse threatens whole communities, causing new waves of crime, unemployment, child neglect or abuse, and other social ills. A 2009 report from the RAND Corporation noted that methamphetamine abuse cost the Nation approximately \$23.4 billion in 2005.

But the good news is that methamphetamine abuse can be prevented and addiction to the drug can be treated. People can and do recover over time if they have ready access to effective treatments that address the multitude of problems resulting from their abuse of methamphetamine.

The primary goals of the National Institute on Drug Abuse (NIDA) are to apply what our scientists learn from drug abuse research to develop new treatment approaches and enhance existing ones, and to bring these effective treatments to the communities that need them.

In this newly updated Research Report, we provide an overview of the latest scientific information on methamphetamine. Our intent is to illustrate for readers the damaging effects of methamphetamine abuse and to inform them about effective prevention and treatment interventions.

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

Research Report Series

Methamphetamine

What is Methamphetamine?

Methamphetamine is a powerful, highly addictive stimulant that affects the central nervous system. Also known as meth, chalk, ice, and crystal, among many other terms, it takes the form of a white, odorless, bitter-tasting crystalline powder that easily dissolves in water or alcohol.

Methamphetamine was developed early in the 20th century from its parent drug, amphetamine, and was used originally in nasal decongestants and bronchial inhalers. Like amphetamine, methamphetamine causes increased activity and talkativeness, decreased appetite, and a pleasurable sense of well-being or euphoria. However, methamphetamine differs from amphetamine in that, at comparable doses, much greater amounts of the drug get into the brain, making it a more potent stimulant. It also has longer-lasting and more harmful effects on the central nervous system. These characteristics make it a drug with high potential for widespread abuse.

Methamphetamine has been classified by the U.S. Drug Enforcement Administration as a Schedule II stimulant, which makes it legally available only through a nonrefillable prescription. Medically it may be indicated for the treatment of attention deficit hyperactivity disorder (ADHD) and as a short-term component of weight-loss treatments, but these uses are limited and it is rarely prescribed; also, the prescribed doses are far lower than those typically abused.

continued inside

What is the scope of methamphetamine abuse in the United States?

According to the 2012 National Survey on Drug Use and Health (NSDUH), approximately 1.2 million people (0.4 percent of the population) reported using methamphetamine in the past year, and 440,000 (0.2 percent) reported using it in the past month. This represents a decrease from previous years: In 2006 731,000 (0.3 percent) reported past-month use. In 2012, there were 133,000 new users of methamphetamine age 12 or older—the same as the previous year but continuing a general downward trend across the past decade. The average age of new methamphetamine users in 2012 was 19.7 years old.

The 2012 Monitoring the Future (MTF) survey of adolescent drug use and attitudes reported that about 1 percent of 8th, 10th, and 12th graders had used methamphetamine within the past year. These data indicate that 10th and 12th graders are using methamphetamine less than they did 5 years ago, but that use by 8th graders has not dropped significantly in that time. Overall, however, use of methamphetamine by adolescents has declined significantly since 1999, when this drug was first added to the survey.

According to the Drug Abuse Warning Network (DAWN), which collects information on drug-related episodes from hospital emergency departments (EDs) throughout the Nation, methamphetamine accounted for about 103,000 ED visits in 2011; it was the fourth most mentioned illicit drug in ED visits following cocaine, marijuana, and heroin. While still high, this number represents a decrease from the 132,576 ED visits for methamphetamine abuse measured in 2004.

The Treatment Episode Data Set (TEDS) provides information on admissions to substance abuse treatment facilities that are licensed or certified by State substance abuse agencies. According to TEDS data, nationwide treatment admissions for methamphetamine abuse dropped from 8.1 percent in 2005 to 5.6 percent in 2011. The majority of primary methamphetamine admissions were male (53 percent), and about two-thirds (68 percent) were non-Hispanic Whites.



While national trends are showing declines, methamphetamine abuse continues to exhibit regional variability. The strongest effects are felt in the West and parts of the Midwest, according to the National Institute on Drug Abuse’s (NIDA’s) Community Epidemiology Work Group (CEWG), a network of researchers that provides information about the nature and patterns of drug abuse across the United States. For example, in the first half of 2012, methamphetamine ranked first in drug-related treatment admissions in Hawaii and San Diego, second in San Francisco, and third in Denver and Phoenix.

How is methamphetamine abused?

Methamphetamine comes in several forms and can be smoked, inhaled (snorted), injected, or orally ingested. The preferred method of abusing the drug varies by geographical region and has changed over time. Smoking methamphetamine is currently the most common way of ingesting it, according to CEWG data.

Smoking or injecting methamphetamine puts the drug very quickly into the bloodstream and brain, causing an immediate, intense “rush” and amplifying the drug’s addiction potential and adverse health consequences. The rush, or “flash,” lasts only a few minutes and is described as extremely pleasurable. Snorting or oral ingestion produces euphoria—a high, but not an intense rush. Snorting produces effects within 3 to 5 minutes, and oral ingestion produces effects within 15 to 20 minutes.

As with many stimulants, methamphetamine is most often abused in a “binge and crash” pattern. Because the pleasurable effects of methamphetamine disappear even before the drug concentration in the blood falls significantly, users try to maintain the high by taking more of the drug. In some cases, abusers indulge in a form of binging known as a “run,” foregoing food and sleep while continuing to take the drug for up to several days.

How Is Methamphetamine Manufactured?

Most of the methamphetamine abused in this country is manufactured in “superlabs” here or, usually, in Mexico. But the drug is also easily made in small clandestine laboratories, with relatively inexpensive over-the-counter ingredients such as pseudoephedrine, a common ingredient in cold medications. To curb production of methamphetamine, Congress passed the Combat Methamphetamine Epidemic Act in 2005, which requires that pharmacies and other retail stores keep logs of purchases of products containing pseudoephedrine and limits the amount of those products an individual can purchase per day. A few States have even made pseudoephedrine available only with a prescription. Mexico has also tightened its restrictions on this and other methamphetamine precursor chemicals. But manufacturers adapt to these restrictions via small- or large-scale “smurfing”

operations: obtaining pseudoephedrine from multiple sources, below the legal thresholds, using multiple false identifications. Manufacturers in Mexico are also increasingly using a different production process (called P2P, from the precursor chemical phenyl-2-propanone) that does not require pseudoephedrine.

Methamphetamine production also involves a number of other easily obtained chemicals that are hazardous, such as acetone, anhydrous ammonia (fertilizer), ether, red phosphorus, and lithium. Toxicity from these chemicals can remain in the environment around a methamphetamine production lab long after the lab has been shut down, causing a wide range of damaging effects to health. Because of these dangers, the U.S. Environmental Protection Agency has provided guidance on cleanup and remediation of methamphetamine labs.

How is methamphetamine different from other stimulants, such as cocaine?

The methamphetamine molecule is structurally similar to amphetamine and to the neurotransmitter dopamine, a brain chemical that plays an important role in the regulation of reward, but it is quite different from cocaine. Although these stimulants have similar behavioral and physiological effects, there are some major differences in the basic mechanisms of how they work.

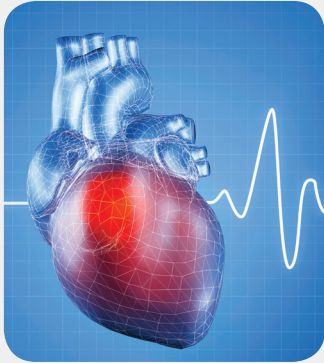
In contrast to cocaine, which is quickly removed from and almost completely metabolized in

the body, methamphetamine has a much longer duration of action, and a larger percentage of the drug remains unchanged in the body. Methamphetamine therefore remains in the brain longer, which ultimately leads to prolonged stimulant effects. Although both methamphetamine and cocaine increase levels of dopamine, administration of methamphetamine in animal studies leads to much higher levels of dopamine, because nerve cells respond differently to the two drugs. Cocaine prolongs dopamine

actions in the brain by blocking the re-absorption (re-uptake) of the neurotransmitter by signaling nerve cells. At low doses, methamphetamine also blocks the re-uptake of dopamine, but it also increases the release of dopamine, leading to much higher concentrations in the synapse (the gap between neurons), which can be toxic to nerve terminals.

Figure 1. Methamphetamine versus Cocaine

Methamphetamine	Cocaine
Stimulant	Stimulant and local anesthetic
Man-made	Plant-derived
Smoking produces a long-lasting high	Smoking produces a brief high
50% of the drug is removed from the body in 12 hours	50% of the drug is removed from the body in 1 hour
Increases dopamine release and blocks dopamine re-uptake	Blocks dopamine re-uptake
Limited medical use for ADHD, narcolepsy, and weight loss	Limited medical use as a local anesthetic in some surgical procedures



Short-Term Effects May Include:

- Increased attention
- Decreased fatigue
- Increased activity and wakefulness
- Decreased appetite
- Euphoria and rush
- Increased respiration
- Rapid/irregular heartbeat
- Hyperthermia

Long-Term Effects May Include:

- Addiction
- Psychosis, including:
 - paranoia
 - hallucinations
 - repetitive motor activity
- Changes in brain structure and function
- Deficits in thinking and motor skills
- Increased distractibility
- Memory loss
- Aggressive or violent behavior
- Mood disturbances
- Severe dental problems
- Weight loss

What are the immediate (short-term) effects of methamphetamine abuse?

As a powerful stimulant, methamphetamine, even in small doses, can increase wakefulness and physical activity and decrease appetite. Methamphetamine can also cause a variety of cardiovascular problems, including rapid heart rate, irregular heartbeat, and increased blood pressure. Hyperthermia (elevated body temperature) and convulsions may occur with methamphetamine overdose and, if not treated immediately, can result in death.

Most of the pleasurable effects of methamphetamine are believed to result from the release of very high levels of dopamine in the brain. Dopamine is involved in motivation, the experience of pleasure, and motor function, and most drugs of abuse work in part by affecting levels of this neurotransmitter. The elevated release of dopamine produced by methamphetamine is also thought to contribute to the drug's harmful effects on terminals of dopamine-producing neurons in the brain.

What are the long-term effects of methamphetamine abuse?

Long-term methamphetamine abuse has many negative consequences, including addiction. Addiction is a chronic, relapsing disease, characterized by compulsive drug seeking and use and accompanied by functional and molecular changes in the brain.

As is the case with many drugs, tolerance to methamphetamine's pleasurable effects develops when it is taken repeatedly. Abusers often need to take higher doses of the drug, take it more frequently, or change how they take it in an effort to get the desired effect. Chronic methamphetamine abusers may develop difficulty feeling any pleasure other than that provided by the drug, fueling further abuse. Withdrawal from methamphetamine occurs when a chronic abuser stops taking the drug; symptoms of withdrawal include depression, anxiety, fatigue, and an intense craving for the drug.

In addition to being addicted to methamphetamine, chronic abusers may exhibit symptoms that can include significant anxiety, confusion, insomnia, mood disturbances, and violent behavior. They also may display a number of psychotic features,

including paranoia, visual and auditory hallucinations, and delusions (for example, the sensation of insects creeping under the skin). Psychotic symptoms can sometimes last for months or years after a person has quit abusing methamphetamine, and stress has been shown to precipitate spontaneous recurrence of methamphetamine psychosis in formerly psychotic methamphetamine abusers.

These and other problems reflect significant changes in the brain caused by abuse of methamphetamine. Neuroimaging studies have demonstrated alterations in the activity of the dopamine system that are associated with reduced motor speed and impaired verbal learning. Studies in chronic methamphetamine abusers have also revealed severe structural and functional changes in areas of the brain associated with emotion and memory, which may account for many of the emotional and cognitive problems observed in chronic methamphetamine abusers.

Methamphetamine abuse also has been shown to have negative effects on non-neural brain cells

called microglia. These cells support brain health by defending the brain against infectious agents and removing damaged neurons. Too much activity of the microglial cells, however, can assault healthy neurons. A study using brain imaging found more than double the levels of microglial cells in former methamphetamine abusers compared to people with no history of methamphetamine abuse, which could explain some of the neurotoxic effects of methamphetamine.

Some of the neurobiological effects of chronic methamphetamine abuse appear to be at least partially reversible. In the aforementioned study, abstinence from methamphetamine resulted in less excess microglial activation over time, and abusers who had remained methamphetamine-free for 2 years exhibited microglial activation levels similar to the study's control subjects. Another neuroimaging study showed neuronal recovery in some brain regions following prolonged abstinence (14 but not 6 months). This recovery was associated with improved performance on motor and verbal memory tests. But function in other brain regions did not recover even after 14 months of abstinence, indicating that some methamphetamine-induced changes are very long lasting. Moreover, methamphetamine use can increase one's risk of stroke, which can cause irreversible damage to the brain. A recent study even showed higher incidence of Parkinson's disease among past users of methamphetamine.

In addition to the neurological and behavioral consequences of methamphetamine abuse, long-term users also suffer physical effects, including weight loss, severe tooth decay and tooth loss ("meth mouth"), and skin sores. The dental problems may be caused by a combination of poor nutrition and dental hygiene as well as dry mouth and teeth grinding caused by the drug. Skin sores are the result of picking and scratching the skin to get rid of insects imagined to be crawling under it.

BRAIN RECOVERY WITH PROLONGED ABSTINENCE



Recovery of Brain Dopamine Transporters in Chronic Methamphetamine (METH) Abusers

Methamphetamine abuse greatly reduces the binding of dopamine to dopamine transporters (highlighted in red and green) in the striatum, a brain area important in memory and movement. With prolonged abstinence, dopamine transporters in this area can be restored.

What are the risks of methamphetamine abuse during pregnancy?



Our knowledge of the effects of methamphetamine abuse during pregnancy is limited because studies of this issue have used small samples and have not been able to account for the possibility that mothers used other drugs besides methamphetamine. But the available research points to increased rates of premature delivery, placental abruption (separation of the placental lining from the uterus), and

various effects on babies prenatally exposed to methamphetamine, including small size, lethargy, and heart and brain abnormalities. A large ongoing NIDA-funded study is examining developmental outcomes in children born to mothers who abused methamphetamine. Thus far, researchers have found neurobehavioral problems such as decreased arousal and increased stress and subtle but significant attention impairments in these children.

Are people who abuse methamphetamine at risk for contracting HIV/AIDS and hepatitis B and C?

Methamphetamine abuse raises the risk of contracting or transmitting HIV and hepatitis B and C—not only for individuals who inject the drug but also for noninjecting methamphetamine abusers. Among injecting drug users, HIV and other infectious diseases are spread primarily through the re-use or sharing of contaminated syringes, needles, or related paraphernalia. But regardless of how methamphetamine is taken, its intoxicating effects can alter judgment and inhibition and lead people to engage in unsafe behaviors like unprotected sex.

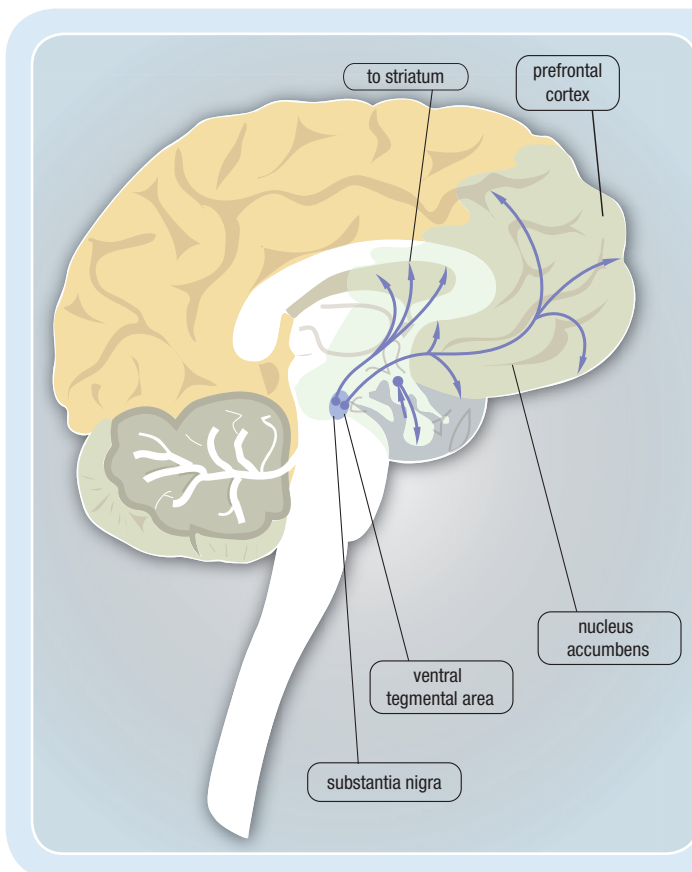
Methamphetamine abuse is associated with a culture of risky sexual behavior, both among men who have sex with men and in heterosexual populations, a link that may be attributed to the fact that methamphetamine and related stimulants can increase libido.

(Although paradoxically, long-term methamphetamine abuse may be associated with decreased sexual functioning, at least in men.) The combination of injection practices and sexual risk-taking may result in HIV becoming a greater problem among methamphetamine abusers than among other drug abusers, and some epidemiologic reports are already showing this trend. For example, while the link between HIV infection and methamphetamine abuse has not yet been established for heterosexuals, data show an association between methamphetamine abuse and the spread of HIV among men who have sex with men.

Methamphetamine abuse may also worsen the progression of HIV disease and its consequences. In animal studies, methamphetamine has been shown to increase viral replication. Clinical

studies in humans suggest that current methamphetamine users taking highly active antiretroviral therapy (HAART) to treat HIV may be at greater risk of developing AIDS than non-users, possibly as a result of poor medication adherence. Methamphetamine abusers with HIV also have shown greater neuronal injury and cognitive impairment due to HIV, compared with those who do not abuse the drug.

NIDA-funded research has found that, through drug abuse treatment, prevention, and community-based outreach programs, drug abusers can change their HIV risk behaviors. Drug abuse and drug-related risk behaviors, such as needle sharing and unsafe sexual practices, can be reduced significantly, thus decreasing the risk of exposure to HIV and other infectious diseases. Therefore, drug abuse treatment *is* HIV prevention.



Dopamine Pathways

In the brain, dopamine plays an important role in the regulation of reward and movement. As a major chemical messenger in the reward pathway, dopamine is manufactured in nerve cell bodies located within a group of neurons called the ventral tegmental area and is released in the nucleus accumbens, sometimes called the “pleasure center” because of its role in producing rewarding feelings, as well as in the prefrontal cortex, which is responsible for higher cognitive functions like decision-making and self-control. Dopamine’s regulation of motor functions is linked to a separate pathway: Cell bodies in the substantia nigra manufacture and release dopamine into the striatum, which is involved in executing and inhibiting movements and reward-seeking behavior.



What treatments are effective for people who abuse methamphetamine?

The most effective treatments for methamphetamine addiction at this point are behavioral therapies, such as cognitive-behavioral and contingency-management interventions. For example, the Matrix Model, a 16-week comprehensive behavioral treatment approach that combines behavioral therapy, family education, individual counseling, 12-Step support, drug testing, and encouragement for non-drug-related activities, has been shown to be effective in reducing methamphetamine abuse. Contingency management interventions, which provide tangible incentives in exchange for engaging in treatment and maintaining abstinence, have also been shown to be effective. Motivational Incentives for Enhancing Drug Abuse Recovery (MIEDAR), an incentive-

based method for promoting cocaine and methamphetamine abstinence, has demonstrated efficacy in methamphetamine abusers through NIDA's National Drug Abuse Clinical Trials Network.

Although medications have proven effective in treating some substance use disorders, there are currently no medications that counteract the specific effects of methamphetamine or that prolong abstinence from and reduce the abuse of methamphetamine by an individual addicted to the drug. NIDA has made research in the development of medications to treat addiction to stimulants and other drugs a priority, however. One approach being tried is to target the activity of glial cells. A drug called AV411 (ibudilast) that suppresses the neuroinflammatory

actions of glial cells has been shown to inhibit methamphetamine self-administration in rats and is now being fast-tracked in clinical trials to establish its safety and effectiveness in humans with methamphetamine addiction. Also under study are approaches that use the body's immune system to neutralize the drug in the bloodstream before it reaches the brain. These approaches include injecting a user with anti-methamphetamine antibodies or with vaccines that would stimulate the body to produce its own such antibodies. Researchers have begun a clinical study to establish the safety of an anti-methamphetamine monoclonal antibody known as mAb7F9 in human methamphetamine users.

Glossary

Addiction: A chronic, relapsing disease characterized by compulsive drug seeking and use despite serious adverse consequences, and by long-lasting changes in the brain.

Anesthetic: An agent that causes insensitivity to pain and is used for surgeries and other medical procedures.

Attention deficit hyperactivity disorder (ADHD):

A disorder that typically presents in early childhood, characterized by inattention, hyperactivity, and impulsivity.

Central nervous system (CNS): The brain and spinal cord.

Craving: A powerful, often uncontrollable desire for drugs.

Dopamine: A brain chemical, classified as a neurotransmitter, found in regions that regulate movement, emotion, motivation, and pleasure.

Neurotransmitter: A chemical produced by neurons that carry messages from one nerve cell to another.

Psychosis: A mental disorder characterized by delusional or disordered thinking detached from reality; symptoms often include hallucinations.

Rush: A surge of pleasure (euphoria) that rapidly follows the administration of some drugs.

Stimulants: A class of drugs that enhance the activity of monoamines (such as dopamine and norepinephrine) in the brain, increasing arousal, heart rate, blood pressure, and respiration, and decreasing appetite; includes some medications used to treat attention deficit hyperactivity disorder (e.g., methylphenidate and amphetamines), as well as cocaine and methamphetamine.

Tolerance: A condition in which higher doses of a drug are required to produce the same effect achieved during initial use; often associated with physical dependence.

Toxic: Causing temporary or permanent effects detrimental to the functioning of a body organ or group of organs.

Withdrawal: Symptoms that occur after chronic use of a drug is reduced abruptly or stopped.

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Where can I get further information about methamphetamine?

To learn more about methamphetamine and other drugs of abuse, visit the NIDA Web site at www.drugabuse.gov or contact the *DrugPubs* Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

NATIONAL INSTITUTE ON DRUG ABUSE



RESEARCH DISSEMINATION CENTER

What's on the NIDA Web Site

- Information on drugs of abuse and related health consequences
- NIDA publications, news, and events
- Resources for health care professionals
- 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)

NIDA Web Sites

www.drugabuse.gov
www.backtoschool.drugabuse.gov
www.smoking.drugabuse.gov
www.hiv.drugabuse.gov
www.marijuana-info.org
www.clubdrugs.gov
www.steroidabuse.gov
www.teens.drugabuse.gov
www.inhalants.drugabuse.gov

Other Web Sites

Information on drug abuse and other mental illnesses is also available through these other Web sites:

- National Institute of Mental Health: www.nimh.nih.gov
- National Institute on Alcohol Abuse and Alcoholism: www.niaaa.nih.gov
- Substance Abuse and Mental Health Services Administration Publications Ordering: www.store.samhsa.gov/home



NIH Publication Number 13-4210 • Revised September 2013
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What are the medical consequences of tobacco use? See page 4.

Research Report Series

from the director:

Tobacco use kills approximately 440,000 Americans each year, with one in every five U.S. deaths the result of smoking. Smoking harms nearly every organ in the body, causes many diseases, and compromises 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 make it possible for researchers to observe changes in brain function that result from smoking tobacco. Researchers are now also identifying genes that predispose people to tobacco addiction and predict their response to smoking cessation treatments. These findings—and many other recent research accomplishments—present 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 will help readers understand the harmful effects of tobacco use and identify best practices for the prevention and treatment of tobacco addiction.

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse



Tobacco/ Nicotine

What Are the Extent and Impact of Tobacco Use?

According to the 2010 National Survey on Drug Use and Health, an estimated 69.6 million Americans aged 12 or older reported current use of tobacco—58.3 million (23.0 percent of the population) were current cigarette smokers, 13.2 million (5.2 percent) smoked cigars, 8.9 million (3.5 percent) used smokeless tobacco, and 2.2 million (0.8 percent) smoked pipes, confirming that tobacco is one of the most widely abused substances in the United States. Although the numbers of people who smoke are still unacceptably high, according to the Centers for Disease Control and Prevention there has been a decline of almost 50 percent since 1965.

continued inside

NIDA's 2011 Monitoring the Future survey of 8th-, 10th-, and 12th-graders, which is 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 6 percent of 8th-graders, 12 percent of 10th-graders, and 19 percent of 12th-graders had used cigarettes in the 30 days prior to the survey—the lowest levels in the history of the survey.

The declining prevalence of cigarette smoking among the general U.S. population, however, is not reflected in patients with mental illnesses. The rate of smoking in patients suffering from post-traumatic stress disorder, bipolar

disorder, major depression, and other mental illnesses is twofold to fourfold higher than in the general population; and among people with schizophrenia, smoking rates as high as 90 percent have been reported.

Tobacco use is the leading preventable cause of death in the United States. The impact of tobacco use in terms of morbidity and mortality to society is staggering.

Economically, more than \$96 billion of total U.S. healthcare costs each year are attributable directly to smoking. However, this is well below the total cost to society because it does not include burn care from smoking-related fires, perinatal care for low-birthweight 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 \$97 billion per year, bringing a conservative estimate of the economic burden of smoking to more than \$193 billion per year.

How Does Tobacco Deliver Its Effects?

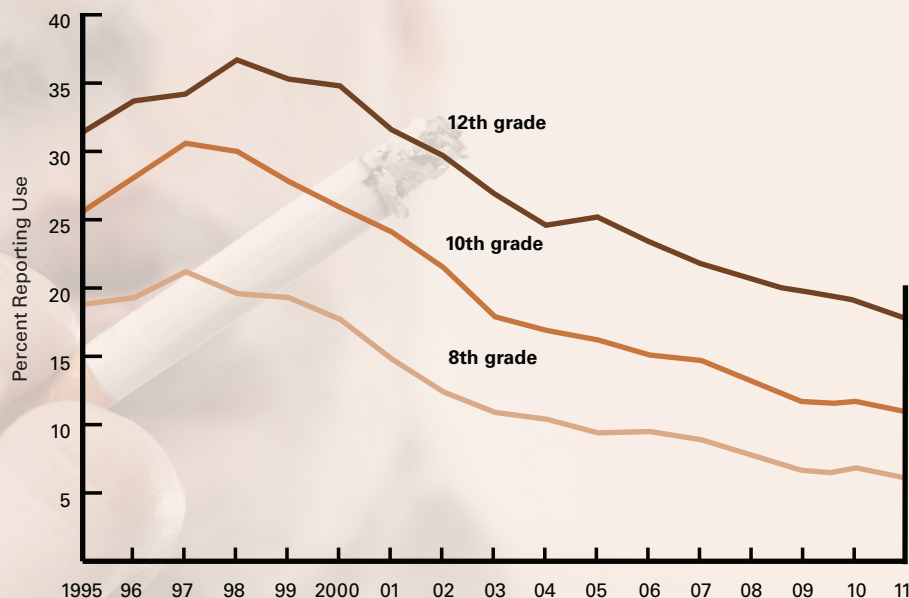
There are more than 7,000 chemicals found in the smoke of tobacco products. Of these, nicotine, first identified in the early 1800s, is the primary reinforcing component of tobacco.

Cigarette smoking is the most popular method of using tobacco; however, many people also use 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 1–2 milligrams 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 1½ packs (30 cigarettes) daily gets 300 “hits” of nicotine to the brain each day. In those who typically

Trends in Prevalence of Cigarette Use for 8th-, 10th-, and 12th-Graders

Percentage of Students Using Cigarettes Over a 30-Day Period, 1995–2011



Source: University of Michigan, 2011 Monitoring the Future Survey.

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 an increase in blood pressure, respiration, and heart rate.

Is Nicotine Addictive?

Yes. Most smokers use tobacco regularly because they are addicted to nicotine. Addiction is characterized by compulsive drug-seeking and abuse, 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, more than 85 percent of those who try to quit on their own relapse, most within a week.

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. For many tobacco users, long-term brain changes induced by continued nicotine exposure result in addiction.

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 quickly, 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, depression, anxiety, cognitive and attention 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 usually subside within a few weeks. For some people, however, symptoms may persist for months.

Although 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. Nicotine replacement therapies such as gum, patches, and inhalers may help alleviate the pharmacological aspects of withdrawal; however,



Tobacco plants

Most smokers identify tobacco use as harmful and express a desire to reduce or stop using it, and nearly 35 million want to quit each year.

cravings often persist. Behavioral therapies can help smokers identify environmental triggers of craving so they can employ strategies to prevent or circumvent these symptoms and urges.

Nicotine replacement therapies such as gum, patches, and inhalers may help alleviate the pharmacological aspects of withdrawal.

Are There Other Chemicals That May Contribute to Tobacco Addiction?

Yes, research is showing that nicotine may not be the only ingredient in tobacco that affects its addictive potential. 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 ingredient in tobacco smoke other than nicotine, because 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.

Animal studies by NIDA-funded researchers have shown that acetaldehyde, another chemical found in 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:

adolescent animals display far more sensitivity to this reinforcing effect, which suggests that the brains of adolescents may be more vulnerable to tobacco addiction.

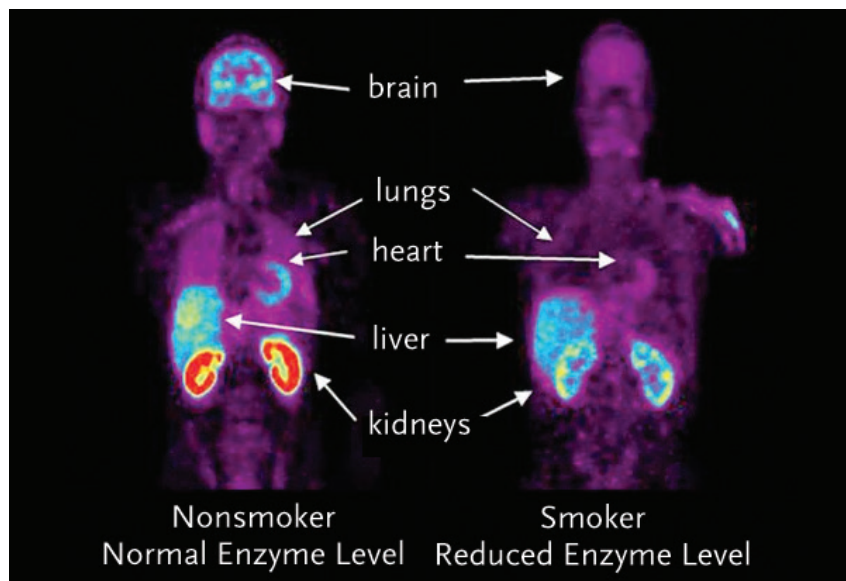
What Are the Medical Consequences of Tobacco Use?

Cigarette smoking kills an estimated 440,000 U.S. citizens each year—more than alcohol, illegal drug use, homicide, suicide, car accidents, and AIDS combined. Between 1964 and 2004, more than 12 million Americans 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 nearly every organ in the body. It has been conclusively linked to 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 cases of lung cancer, 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, bladder, and acute myeloid leukemia.

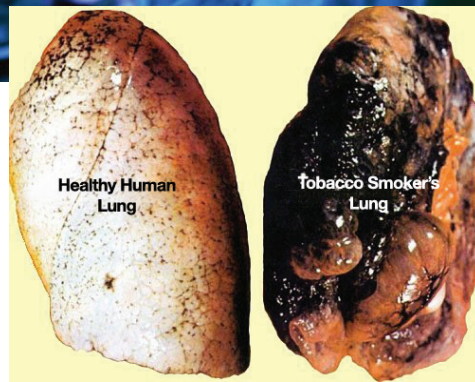
In addition to cancer, smoking causes lung diseases such as chronic bronchitis and emphysema, and it has been found to exacerbate asthma symptoms in adults and children. About 90 percent of all deaths from chronic obstructive pulmonary diseases are attributable to cigarette smoking. It has also been well-documented that smoking substantially increases the risk of heart disease, including stroke,



Using advanced neuroimaging technology, scientists can see the dramatic effect of cigarette smoking on the brain and body and are finding a marked decrease in the levels of monoamine oxidase (MAO), an important enzyme that is responsible for the breakdown of dopamine. (Source: Fowler et al., 2003)



Sticky, brown tar coats the lungs of tobacco smokers. Along with thousands of other damaging chemicals, tar can lead to lung cancer and acute respiratory diseases.



heart attack, vascular disease, and aneurysm. Smoking causes coronary heart disease, the leading cause of death in the United States: cigarette smokers are 2–4 times more likely to develop coronary heart disease than nonsmokers.

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.

Although 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

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” (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.

Tobacco Use and Comorbidity

There is clear evidence of high rates of psychiatric comorbidity, including other substance abuse, among adolescents and adults who smoke. For example, it has been estimated that individuals with psychiatric disorders purchase approximately 44 percent of all cigarettes sold in the United States, which undoubtedly contributes to the disproportionate rates of morbidity and mortality in these populations. In addition, studies have shown that as many as 80 percent of alcoholics smoke regularly, and that a majority of them will die of smoking-related, rather than alcohol-related, disease.

In young smokers, the behavior appears to be strongly associated with increased risk for a variety of mental disorders. In some cases—such as with conduct disorders and attention-deficit hyperactivity disorder—these disorders may precede the onset of smoking, while in others—such as with substance abuse—the disorders may emerge later in life. Whether daily smoking among boys and girls is the result or the cause of a manifest psychiatric condition, it is troubling that so very few adolescents have

their nicotine dependence diagnosed or properly treated. Preventing the early onset of smoking and treating its young victims are critical primary-care priorities, the fulfillment of which could have a dramatic impact on our ability to prevent or better address a wide range of mental disorders throughout life.

Among adults, the rate of major depressive episodes is highest in nicotine-dependent individuals, lower in nondependent current smokers, and lowest in those who quit or never started smoking. Furthermore, there is evidence showing that, for those who have had more than one episode, smoking cessation may increase the likelihood of a new major depressive episode. Adult tobacco use also increases risk for the later development of anxiety disorders, which may be associated with an increased severity of withdrawal symptoms during smoking cessation therapy. But the most extensive comorbidity overlap is likely the one that exists between smoking and schizophrenia, since, in clinical samples, the rate of smoking in patients with schizophrenia has ranged as high as 90 percent.

and increased severity of childhood asthma. Additionally, dropped cigarettes are the leading cause of residential fire fatalities, leading to more than 1,000 deaths each year.

Smoking and Pregnancy— What Are the Risks?

In the United States, it is estimated that about 16 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, and concentrations in the fetus can be 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.

The adverse effects of smoking during pregnancy can include fetal growth retardation and decreased birthweight. The decreased birthweights 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 birthweight. 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 and sudden infant death syndrome (SIDS), as well as learning and behavioral problems and an increased risk of obesity in children.



Smoking and Adolescence

In 2010, about 2.6 million American adolescents (aged 12–17) reported using a tobacco product in the month prior to the survey. In that same year, it was found that nearly 60 percent of new smokers were under the age of 18 when they first smoked a cigarette. Of smokers under age 18, more than 6 million will likely 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. There is some evidence that 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 earlier, acetaldehyde increases nicotine's addictive properties in adolescent, but not adult, animals. A recent study also suggests that specific genes may increase risk for addiction among people who begin smoking during adolescence. NIDA continues to actively support research aimed at increasing our understanding of why and how adolescents become addicted, and to develop prevention and treatment strategies to meet their specific needs.

In addition, smoking more than one 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 behaviors. 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



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.



Smoking cessation can have immediate health benefits. For example, within 24 hours of quitting, blood pressure and chances of heart attack decrease.

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 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.

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 with 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 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 primary focus of pharmacological treatments for tobacco addiction has been nicotine replacement, other treatments are also available. 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 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 non-nicotine medications are being investigated for the treatment of tobacco addiction, including

Twin studies indicate that approximately 40–70 percent of a person’s risk of becoming addicted to nicotine depends on his or her genes.



other antidepressants and an antihypertensive medication. 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. A variety of methods can assist smokers with 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 problem-solving skills, and 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.smokefree.gov) offers

online advice and downloadable information to make cessation easier.

Quitting smoking can be difficult. People can be helped during the time an intervention is delivered; however, 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.

New Frontiers in Tobacco Research

If so many smokers want to quit, why are few able to do so successfully? To address this question, scientists are increasingly focusing on the powerful role of genetics in addiction. Twin studies indicate that approximately

40–70 percent of a person’s risk of becoming addicted to nicotine depends on his or her genes.

Although complex diseases like addiction involve large numbers of genes interacting with a wide variety of environmental factors, the contribution of a particular gene can be substantial.

Genetic variants associated with nicotine metabolism, for example, have been shown to influence how people smoke. Slow metabolizers smoke fewer cigarettes per day and have a higher likelihood of quitting, and there is greater abstinence among individuals receiving nicotine patch therapy. A recent NIDA-funded study identified a variant in the gene for a nicotinic receptor subunit that doubled the risk for nicotine addiction among smokers. A subsequent study found that this gene variant also increased susceptibility to the severe health consequences of smoking, including lung cancer and

peripheral arterial disease. NIDA is currently supporting large-scale genome-wide association studies to uncover additional genetic risk factors in order to better understand tobacco addiction and its adverse effects on health.

In addition to predicting an individual’s risk for nicotine addiction, genetic markers can also help predict whether medications (like bupropion) will effectively help a smoker quit. This takes root in the emerging field of pharmacogenomics, which investigates how genes influence a patient’s response to drugs and medications. In the future, genetic screening could help clinicians select treatments, adjust dosages, and avoid or minimize adverse reactions, tailoring smoking cessation therapies to an individual’s unique genetic inheritance.

Glossary

Addiction: A chronic, relapsing disease characterized by compulsive drug-seeking and abuse despite adverse consequences. It is associated with long-lasting changes in the brain.

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

Carcinogen: Any substance that causes cancer.

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.

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 primarily responsible for smoking’s psychoactive and addictive effects.

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

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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Where can I get further information about tobacco/nicotine?

To learn more about tobacco/nicotine and other drugs of abuse, visit the NIDA Web site at www.drugabuse.gov or contact the DrugPubs Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).



What's on the NIDA Web Site

- Information on drugs of abuse and related health consequences
- NIDA publications, news, and events
- Resources for health care professionals
- 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)

NIDA Web Sites

www.drugabuse.gov

www.drugabuse.gov/publications/term/160/DrugFacts

www.easyread.drugabuse.gov

www.drugabuse.gov/blending-initiative

For Physician Information

NIDAMED 

www.drugabuse.gov/nidamed

Other Web Sites

Information on tobacco addiction is also available through these Web sites:

- Centers for Disease Control and Prevention:
www.cdc.gov/tobacco
- National Cancer Institute:
www.cancer.gov
- U.S. Department of Health and Human Services:
www.smokefree.gov
- Substance Abuse and Mental Health Services Administration Health Information Network:
www.samhsa.gov/shin
- Office of the Surgeon General:
www.surgeongeneral.gov/initiatives/tobacco
- Society for Research on Nicotine and Tobacco:
www.srnt.org
- The Robert Wood Johnson Foundation:
www.rwjf.org
- Join Together Online:
www.quitnet.com
- American Legacy Foundation:
www.americanlegacy.org



NIH Publication Number 12-4342
Printed July 1998, Reprinted August 2001, Revised July 2006,
Revised June 2009, Revised July 2012.
Feel free to reprint this publication.