Strategic Plan

National Institute on Drug Abuse

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National Institutes of Health
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Introduction

The mission of the National Institute on Drug Abuse (NIDA) is to lead the Nation in bringing the power of science to bear on drug abuse and addiction. This charge has two critical components: (1) to support and conduct research across a broad range of disciplines and (2) to ensure the rapid and effective dissemination and use of research results to improve practice and inform policy. The ultimate goal of NIDA's drug abuse research program is to reduce the burden of drug abuse and addiction* and their many adverse consequences for individuals and society at large. By advancing the science of addiction, NIDA is helping to change people's perceptions, replacing stigma and shame with a new understanding of addiction as a treatable disease. Much like any other medical disease, addiction demands a public health solution.

Indeed, NIDA-supported scientific advances over the past three decades have revolutionized our understanding of drug abuse and addiction. We have informed the development of more effective prevention and treatment approaches and have identified areas where more work is needed. For example, while our national research surveys show continuing declines in illicit drug use among teens—down 19 percent since 2001, according to NIDA's 2009 Monitoring the Future (MTF) survey of 8th-, 10th-, and 12th-graders—difficult challenges remain. These challenges include the persistence of chronic drug abuse in a considerable number of teens (e.g., 5 percent of 12th-graders are daily marijuana users, a level statistically unchanged since 2001)[1] and the high rates of prescription drug abuse among both adolescents and adults. This trend has prompted a near-doubling of unintentional poisoning deaths nationwide since 1999,[2] mainly from opioid analgesic abuse (see "Emerging Issues and Challenges").

* "Drug abuse," as used throughout this report, refers to the repeated use of licit or illicit psychoactive substances, which may or may not lead to "addiction," which is defined as a complex brain disease characterized by compulsive, at times uncontrollable, drug craving, seeking, and use that persist even in the face of extremely negative consequences. These definitions differ from those in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), which provides diagnostic criteria for drug abuse and dependence, and does not in its present form include the term "addiction." We use the term "addiction" to refer to what the DSM defines as "dependence."

We must continue to aggressively meet these challenges and work to prevent the often devastating consequences of drug abuse and addiction that affect all segments of society. Economic costs alone are estimated to exceed one-half trillion dollars annually in the United States—including health- and crime-related costs, as well as productivity losses, such as those stemming from workplace injuries and accidents. In 2008, 20 million Americans, or 8 percent of the population, aged 12 or older were current (past-month) illicit drug users.[3] Staggering as these numbers are, however, they do not fully describe the breadth of deleterious public health—and safety—implications, which include family disintegration, loss of employment, accidents, failure in school, and domestic violence and other crimes. Substance use and abuse can also exacerbate a variety of health problems, including the spread of infectious diseases such as HIV/AIDS, sexually transmitted diseases (STDs), tuberculosis, and hepatitis C. Frequently comorbid with other mental disorders, drug abuse also contributes significantly to the risk of suicide and suicidal behaviors.[4]

It is plain to see that drug abuse is a ubiquitous, complex, and urgent problem that affects us all. Thus, NIDA continues to engage multiple stakeholders across the community in efforts to integrate substance abuse and addiction diagnosis, referral, and treatment into standard medical practice as well as criminal justice settings, where drug abuse problems are widespread. These settings offer good opportunities for treatment, which can have considerable societal impact.

The pages that follow describe broad strategies that NIDA plans to implement over the coming years. A flexible, dynamic approach allows us to adapt to changing needs and take advantage of scientific opportunities as they arise and are revealed through our ongoing research.

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

Executive Summary

For the past three decades, the National Institute on Drug Abuse (NIDA) has led the way in supporting research to prevent and treat drug abuse and addiction and mitigate the impact of their consequences, which include the spread of HIV/AIDS and other infectious diseases. To confront the most pressing aspects of this complex disease and to tackle its underlying causes, our strategic approach is necessarily a multipronged one. It takes advantage of research programs in basic, clinical, and translational sciences. This includes genetics, functional neuroimaging, social neuroscience, medication and behavioral therapies, prevention, and health services, including effectiveness and cost-effectiveness research. Our burgeoning portfolio has given us a large and growing body of knowledge that informs our strategic directions for the future. These directions are grouped into four major goal areas, reflected in the sections that follow:

I. PREVENTION

II. TREATMENT

III. HIV/AIDS

IV. CROSS-CUTTING PRIORITIES

These four sections and accompanying strategic goals and objectives are summarized below.

I. Prevention

Strategic goal: ***To prevent the initiation of drug use and the escalation to addiction in those who have already initiated use.***

Our prevention research has led to today's improved understanding of addiction and has positioned NIDA to build upon solid epidemiological findings and new insights from genetics and neuroscience. Findings have revealed myriad contributors to addiction and the involvement of multiple brain circuits in addiction processes. A major goal of our efforts is to better understand why some people become addicted while others do not. Our prevention efforts encompass both illicit and licit drugs, such as nicotine and prescription medications. We support research that strives to identify the factors that put people at increased risk of drug abuse or protect them from it. Results will lead to more effective counterstrategies, particularly to prevent young people from ever using drugs in the first place. We are applying modern technologies (e.g., genetics and brain imaging tools) to our prevention studies and are devising creative and targeted communications strategies to encourage their use.

NIDA's Prevention Objectives Include:

1. To identify the characteristics and patterns of drug abuse.

2. To understand how genes, environment, and development influence the various risk and protective factors for drug abuse.

3. To improve and expand our understanding of basic neurobiology as it relates to the brain circuitry underlying drug abuse and addiction.

4. To apply this knowledge toward the development of more effective strategies to prevent people from ever taking drugs and from progressing to addiction if they do.

II. Treatment

Strategic goal: ***To develop successful treatments for drug abuse and addiction and improve treatment accessibility and implementation.***

Given the complex interactions of biological, social, environmental, and developmental factors that underlie drug abuse and addiction, NIDA acknowledges the need to take a "whole systems" approach to treating this disease. We are well-positioned to capitalize on recent discoveries that have uncovered an expanded range of possible brain targets that affect craving, euphoria, motivation, learning, memory, and inhibitory control—key contributors to addiction and relapse. To bring about more customized treatments, our comprehensive therapeutic research portfolio pushes for more effective medication and behavioral therapies. Innovative approaches that consider genetic variation, comorbid conditions (e.g., mental illness, chronic pain), and the addicted person's changing needs over time will usher in promising medications to counteract drug-induced changes in the brain and enhance behavioral therapies. Effectiveness research helps us optimize strategies for disseminating and implementing research-based treatments in health care and criminal justice settings. This objective requires that we continue to strengthen our productive partnerships with treatment practitioners, state substance abuse programs, and other Federal agencies to move proven treatments into clinical practice at the community level.

NIDA's Treatment Objectives Include:

1. To develop effective medications and behavioral interventions to treat drug abuse and addiction and to prevent relapse.

2. To develop treatments for drug abuse and addiction in association with comorbid conditions.

3. To develop the knowledge that leads to personalized or customized treatments.

4. To translate research-based treatments to the community.

III. HIV/AIDS

Strategic goal: ***To diminish the spread of drug abuse-related human immunodeficiency virus (HIV) and minimize the associated health and social consequences, including acquired immunodeficiency syndrome (AIDS).***

Drug abuse continues to be a major vector for the spread of HIV/AIDS through its connection with other risky behaviors, such as needle sharing and unprotected sex. Our research advances the less-acknowledged link between drug abuse in general and the resulting impaired judgment that can lead to risky sexual behavior and HIV transmission. This linkage highlights the value of drug abuse treatment in preventing the spread of HIV. We plan to continue supporting primary prevention research to find the most effective HIV risk-reduction interventions for different populations. Young people are a major focus for these efforts, prompting strategies that start early and can be adapted as the individuals age. NIDA also supports research to develop effective secondary prevention strategies designed to reduce HIV transmission. This includes seeking out the best ways to incorporate HIV education, testing, counseling, and treatment referral, and supporting research to identify and overcome barriers such as

stigma and access to treatment for HIV and drug abuse. NIDA also sponsors research to learn more about the multiple interactions that occur with neurological complications from HIV, substance abuse, and other comorbid psychiatric disorders. This knowledge can inform the development of more responsive counterinterventions. Additionally, we continue to target HIV/AIDS-related health disparities and integrate HIV/AIDS initiatives worldwide.

NIDA's HIV/AIDS Objectives Include:

1. To support research to better understand the etiology, pathogenesis, and spread of HIV/AIDS among drug-abusing populations.
2. To help prevent the acquisition (primary prevention) and transmission (secondary prevention) of HIV among drug abusers and their partners.
3. To decrease the health disparities associated with HIV/AIDS.
4. To support international research on the intertwined epidemics of drug abuse and HIV/AIDS.
5. To improve HIV treatment and outcomes in drug abusers through a better understanding of interactions with drugs of abuse, HIV/AIDS disease processes, and the medications used to treat both.

IV. Cross-Cutting Priorities

Several additional priority areas span NIDA's portfolio and contribute to our overall mission to prevent or reduce drug abuse and addiction. These areas are highlighted below.

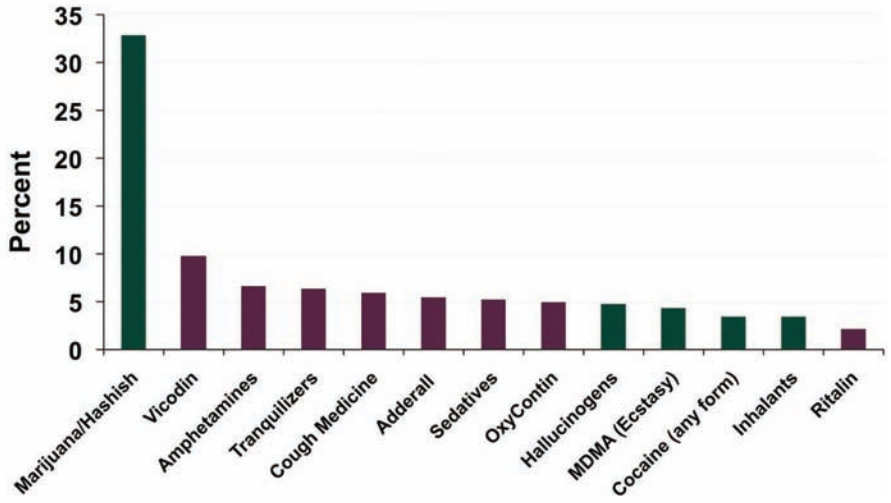
1. To **foster research on other health conditions** that may inform, influence, or interact with drug abuse and addiction (e.g., pain, compulsive behavioral disorders).
2. To **decrease health disparities** related to drug addiction and its consequences.
3. To **educate a variety of audiences** (e.g., criminal justice, medical, and educational systems in the community; media; and legislators) about the science underlying drug abuse.
4. To **train and attract new investigators with diverse experiences**—including those from minority or disadvantaged backgrounds—and to actively recruit chemists, physicists, bioengineers, and mathematicians to conduct translational research on drug abuse.
5. To **promote collaborative international research activities** that address nicotine addiction, HIV/AIDS, and emerging trends, as well as training and dissemination of science-based information on drug abuse.

Focus on Prescription Drugs

Unlike illicit drug use, which shows a continuing downward trend, prescription drug abuse—particularly of stimulants and opioid pain medications—has seen a continual rise through the 1990s, and since 2002 has been at unacceptably high levels among persons age 12 or older.[5]

Figure I-1

8 of the top 13 drugs most commonly abused by high school seniors are prescription or over-the-counter



Past-Year Drug Abuse Among 12th-Graders, 2009

Source: University of Michigan, 2008 Monitoring the Future Survey

Nature and Scope of the Problem

In 2008, approximately 6 million Americans reported current (in the past month) nonmedical use[†] of prescription drugs—more than the number abusing cocaine, heroin, hallucinogens, and inhalants combined.[6] According to the Monitoring the Future (MTF) survey supported by NIDA, 8 of the top 13 drugs most commonly abused by high school seniors are either prescribed or purchased over the counter (see Figure I–1).

While the MTF surveys students in the 8th, 10th, and 12th grades, other survey research shows that young adults ages 18–25 are by far the greatest users overall. This age group also shows the biggest increases, compared to others, in past-month, past-year, and lifetime non-medical use between 2002 and 2008 (National Survey on Drug Use and Health [NSDUH], 2009). Even though not prescribed for them, many are using prescription drugs for their intended purposes, such as to

[†] The terms "prescription drug abuse" and "nonmedical use" are used interchangeably in this document and are based on the definitions used by most national surveys measuring nonmedical use (i.e., the intentional use of an approved medication *without* a prescription, in a manner other than how it was prescribed, for purposes other than prescribed, or for the experience or feeling the medication can produce). Misuse refers to *unintentional* use of an approved medication in a manner other than how it was prescribed.

relieve pain in the case of prescription opioids, or to enhance alertness in the case of attention-deficit hyperactivity disorder (ADHD) medications. A common perception is that because these are legitimate pharmaceuticals that emanate from a controlled system, they are less harmful than illicit drugs. This belief is false, as evidenced by rising numbers of people overdosing on or becoming addicted to prescription drugs. Whether the intent is to relieve pain, stay alert for a test, or get high, any use without a physician's evaluation or monitoring can pose potentially grave health risks.

At the other end of the age spectrum is the swelling population of older people who are frequently prescribed psychotherapeutic drugs and who may be especially vulnerable to the health consequences of their abuse or misuse. This is especially true if other medications or underlying health conditions are involved. Thus, prescription drug abuse and *misuse* affects populations of all ages and is further complicated by differing motivations and consequences for each.

Different Approach Needed From That for Other Licit or Illicit Drugs

Because they can greatly benefit health as well as pose risks, prescription drugs present several challenges on how best to guard against their abuse.

Some patients, such as those with chronic pain, may require prescription painkillers to effectively alleviate their suffering. But for these patients and their physicians, the issues can quickly become complex and difficult to manage. For example, physicians may need to decide whether presenting symptoms indicate a need to increase the dose of an opioid analgesic to adequately manage pain, or signal a potential drug abuse problem. Moreover, predicting who is at greatest risk for addiction is a difficult and increasingly relevant problem, one that is particularly urgent for war veterans returning from Iraq and Afghanistan who sustain serious injuries. Thus, NIDA continues to diligently support research in this area, including pursuing pain medications that have little or no addiction liability.

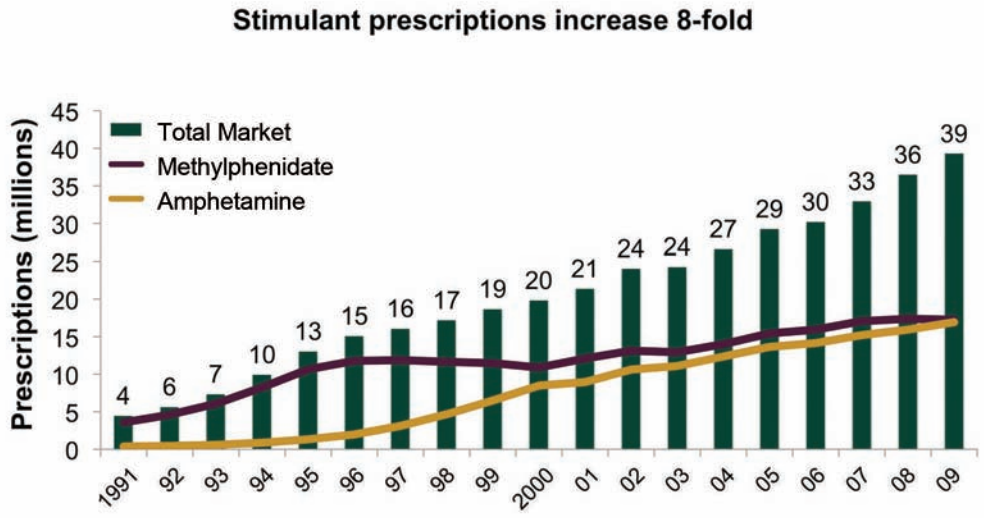
Another challenge involves crafting prevention messages to effectively combat the abuse of prescription drugs without alarming patients who need them. Because physicians are usually the prescribers of these medications, involving them in our efforts to curb prescription drug abuse is critical. Dramatic increases in the number of prescriptions written, greater social acceptance of using medications, and aggressive marketing by pharmaceutical companies have likely contributed to the current broad "environmental availability" of prescription drugs (see Figure I–2). This notion is consistent with 2008 NSDUH survey data wherein most people report obtaining prescription drugs from friends and family members for whom they were prescribed. Thus, physicians need to be cognizant of the various risks and serve as the front-line responders when a problem is suspected, particularly if a patient may be developing abuse or addiction problems. NIDA continues to engage physicians and physicians-in-training to raise their awareness.

We are bolstering efforts to test and evaluate treatments for addiction to prescription drugs, tailoring interventions according to type of medication and reason for its abuse. These variables are often biased by age and gender. To stay on top of who is using and why, NIDA-supported researchers continue to gather information about the latest trends through large-scale epidemiological studies investigating the patterns and sources of nonmedical use, particularly in high school and college students. These years are often when young people initiate or increase their abuse of prescription medications and other drugs.

Again, our approach must address the question of balance, which is difficult to achieve, so that people suffering from chronic pain, ADHD, or anxiety can get the relief they need while minimizing abuse potential.

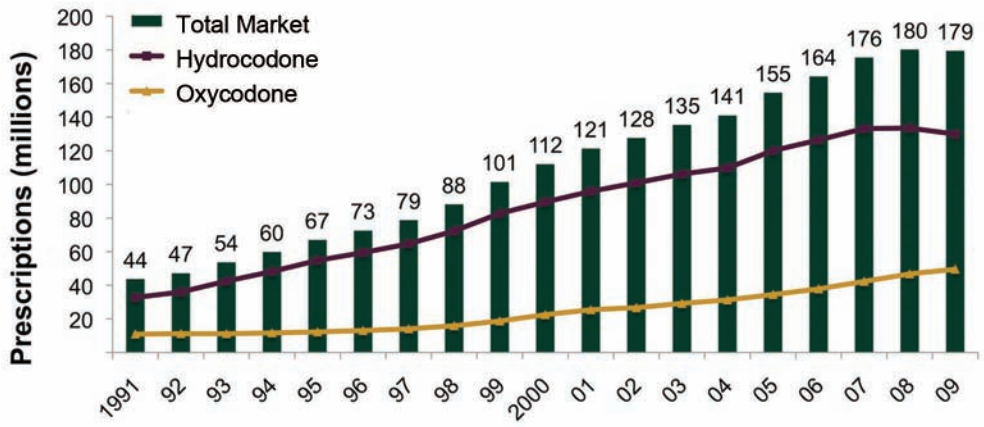
Figure I-2

Dramatic increases in stimulant and opioid prescriptions



Projected Number of Prescriptions for Stimulants* Dispensed by U.S. Retail Pharmacies, 1991-2009

**excludes modafinil and atomoxetine products*



Total Number of Prescriptions for Hydrocodone and Oxycodone Products Dispensed by U.S. Retail Pharmacies, 1991-2009

Source: SDI's Vector One®: National

I. Prevention

Strategic Goal

To prevent the initiation of drug use and the escalation to addiction in those who have already initiated use.

Objectives

1. To identify the characteristics and patterns of drug abuse.
2. To understand how genes, environment, and development influence the various risk and protective factors for drug abuse.
3. To improve and expand our understanding of basic neurobiology as it relates to the brain circuitry underlying drug abuse and addiction.
4. To apply this knowledge toward the development of more effective strategies to prevent people from ever taking drugs and from progressing to addiction if they do.

Introduction: The Value of Research-Based Prevention Approaches

The basic and clinical research sponsored by NIDA for more than 30 years has led to a vast and growing body of knowledge that informs our strategic directions for the future. And while multiple challenges remain, NIDA continues to capitalize on opportunities to meet our short- and long-term goals. These are, respectively, to prevent those who are abusing drugs from intensifying their abuse and becoming addicted, and to develop and deploy the best strategies to prevent drug use.

This expanding body of knowledge is leading to evidence-based prevention strategies that build upon solid epidemiological, genetic, and neuroscience research. Our prevention portfolio continues to examine the impact of both micro- (e.g., family, peers) and macro- (e.g., poverty, stigma) environments, using a data-driven approach to prevent drug abuse and addiction in all populations.

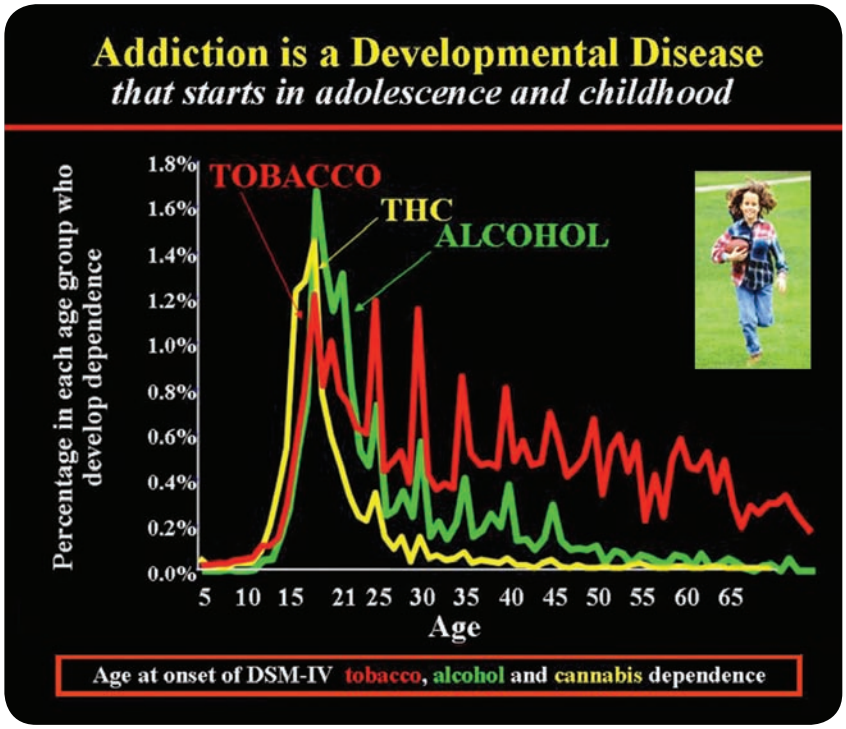
Although NIDA recognizes that addiction only affects a subset of those exposed, any illicit or inappropriate drug exposure can place an individual at risk for serious health consequences. Even a one-time drug experience

could lead to accidents (e.g., drugged driving) or disease (e.g., HIV/AIDS) stemming from drug intoxication. Because experimentation is a common motivation for adolescents to use drugs, our prevention messages must be aimed at keeping young people from trying drugs in the first place.

Indeed, the adolescent population is of particular interest for NIDA because drug abuse typically begins during this period of heightened risk-taking (see Figure 1). By supporting **epidemiological studies**, such as the MTF survey, we are able to identify emerging trends among adolescents and guide responsive national prevention efforts. For example, MTF revealed that in 2008, prescription medications along with over-the-counter drugs (cough medicine), accounted for 8 of the top 13 drug abuse categories reported by 12th-graders[7] (see "Focus on Prescription Drugs").

NIDA is vigorously pursuing research on the effects of abusable substances and how multiple factors—genes, the environment, developmental variables, and their interactions—influence **vulnerability to and protection against addiction**. The impact of drug abuse varies throughout the lifespan. NIDA therefore supports research that spans from prenatal exposure to older adulthood to uncover how life transitions influence the likelihood and trajectory of drug abuse and addiction. Future studies will examine how developmental shifts interact with genes and the environment to influence disease vulnerability and progression.

Figure 1



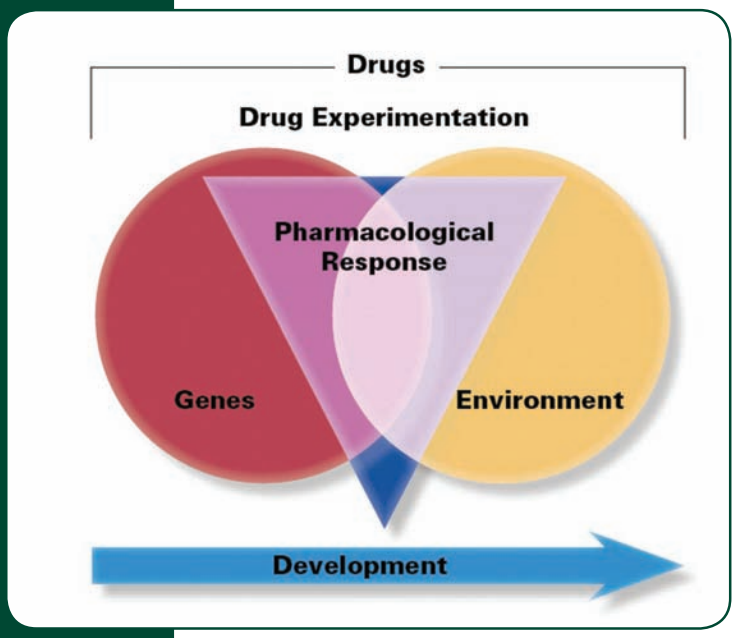
Individuals who initiate drug use early are more likely to develop subsequent dependence.

Source: National Epidemiologic Survey on Alcohol and Related Conditions, 2003

Adding to this understanding is our growing knowledge of the **multiple brain circuits** associated with drug abuse and addiction, such as those implicated in reward, inhibitory control, emotional states, learning and memory, and interoception (sensitivity to stimuli originating inside the body). In addition, basic research on brain development is illuminating how age affects the response to drugs, as well as addiction propensity and progression. With the powerful tools of modern neuroimaging, we can "see" how various brain mechanisms interact with drugs of abuse to influence decisionmaking (e.g., willingness to take risks). We can do this in real time, throughout development, and as people engage socially.

Finally, NIDA is moving aggressively to tap into the power of imaging research in order to **develop more effective prevention interventions**. We know that specific target audiences—adolescents, young adults, pregnant women, and older adults—require tailored prevention approaches to more effectively reduce their risks and enhance the value of protective factors.

Sidebar 1



Whether or not the exposure to drugs of abuse will lead to addiction is a function of the interaction between multiple domains, including genetic background, a person's response to a drug, and his or her environment and developmental stage.

Strategic Approaches to Prevention Research

The following section is organized according to four guiding questions to describe NIDA's approach of using basic, clinical, and health services research to improve our prevention efforts.

1. How can NIDA research inform the focus of prevention?

NIDA continues to identify areas of particular concern and to spot trends early through our epidemiological work in the field. We monitor national and regional substance abuse trends through our nationwide Community Epidemiology Work Group (CEWG), the MTF survey, and other sources. These mechanisms help us identify the who, what, where, and when of drug abuse trends as well as associated attitudes and consequences.

We also encourage research that capitalizes on other databases available through our sister Institutes and Federal agency partners, such as the National Epidemiologic Survey on Alcohol and Related Conditions, sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Survey of Parents and Youth, sponsored by the White House Office of National Drug Control Policy. In addition, we support a number of longitudinal studies that gather information on children's cognitive and emotional development, as well as their vulnerability to addiction later in life if they have been exposed to drugs.

To continue to make the most of these rich data sources and to improve upon them, NIDA is encouraging researchers to include genetics in epidemiological studies, whenever relevant, to try to zero in on gene-environment interactions at different developmental stages. This potential treasure trove of genetic information, combined with brain imaging data, is likely to reveal even more about the trajectory of addiction and the contribution of social–environmental factors. This, in turn, will lead to increasingly customized interventions for those at risk.

2. Why do some people become addicted while others do not?

Our research has already identified many factors that can either enhance or mitigate an underlying propensity to initiate or continue drug use. Exposure to drugs is, of course, an environmental risk factor—along with socioeconomic status, quality of parenting, and peer group influence, to name a few. Advances in genetics are allowing us to identify biological factors, such as genetic

polymorphisms (normal genetic variations) that confer increased vulnerability or protection. Epigenetics research—the study of long-term changes in gene function that result from environmental impacts—will lead to discoveries about the dynamic interactions of genes with environment, along with developmental factors (see Sidebar 1). We know that addiction is a multifactorial, complex, and chronic disease of the brain so a better understanding of the many contributors to drug abuse and addiction, and the different ways they operate at the individual, group, and community levels, is critical to designing more effective prevention messages.

The influence of biological factors on a person's addiction risk

Numerous biological factors confer risk of or protection against drug abuse and addiction. These include genetics, developmental stage, gender, comorbid diseases, and pharmacological response or sensitivity to a drug's effects. As particular biological factors emerge from epidemiological and clinical studies, they can be put to the test in animal models (and possibly even *in vitro*) to help validate, trace, and explore their mechanisms for conveying addiction risk.

The use of animal models allows the manipulation of genetic, environmental, and developmental conditions to investigate related changes in the brain and behavior. NIDA researchers have developed relevant models in different species that help reveal various behavioral components of addiction. For example, these models can help tease apart susceptibility to drug taking, the role of stress and social factors in triggering drug-taking behaviors, and the transition from controlled intake to compulsive drug self-administration.

Why genes matter

A person's genetic makeup plays an important role in his or her addiction vulnerability and, possibly, in the decision to take drugs in the first place. Research shows that approximately 50 percent of the predisposition to addiction can be attributed to genetics. However, this influence is not a simple one. Like many complex diseases, addiction is likely to display a multifactorial pattern of inheritance—which means that many genes contribute, each having a relatively small effect—influenced by environmental factors. A better understanding of these genetic influences is critical to our prevention efforts. Indeed, ongoing developments in the field of high-throughput genomic screens herald a much faster means of identifying specific gene variants that can contribute to (or guard against) addiction. The resulting knowledge could then be leveraged preventively to identify people at risk, well before a substance use disorder emerges.

In addition to the genetic vulnerabilities one is born with, gene function or gene expression is also influenced by environmental events. These in turn can alter brain function and behavior, and ultimately addiction risk or resilience. Epigenetic changes can be triggered, not just by drug exposure, but also by factors such as maternal behavior, aggression, and stress. Understanding the causes and effects of epigenetic changes will engender interventions to counter, prevent, or capitalize on them.

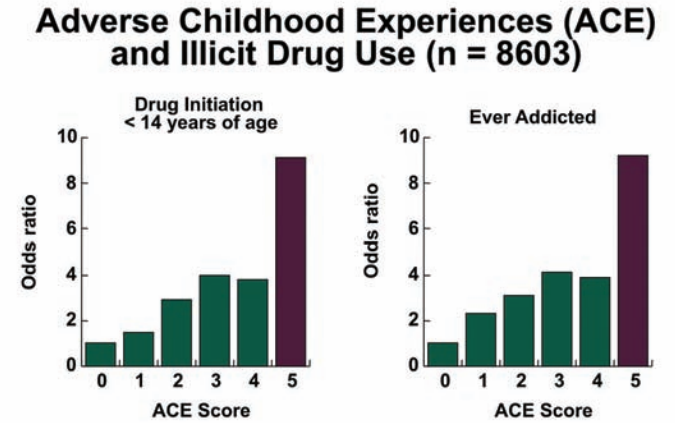
How a person's environment affects his or her risk of drug abuse or addiction

Working in concert with biological risk and protective factors are those that stem from our environment as we progress from fetal development to adulthood. For example, an individual's genetic predisposition to drug abuse will never manifest itself without drug exposure. A variety of factors need to be taken into account and better characterized to fully understand what contributes to drug abuse and addiction and what is amenable to modification.

Sidebar 2

Environmental Factors Can Increase Drug Abuse Risk

Research demonstrates a relationship between illicit drug use and adverse childhood experiences (ACEs). A retrospective study cohort of 8,603 adults who attended a primary care clinic in California completed a survey about childhood abuse, neglect, and household dysfunction; illicit drug use; and other health-



ACE account for one-half to two-third of serious problems with drug use.

related issues. Each ACE reported increased the likelihood for early drug use (by age 14) two- to fourfold and raised the risk of later addiction; people with 5 or more ACEs were 7–10 times more likely to report illicit drug use problems than those with none.

Why it's important: Research is needed to understand and evaluate the impact of environment and experience on the initiation of drug use and subsequent problems at any age. Progress in reducing drug use will demand attention to various types of stressful experiences, such as those identified in this study.

Source: Dube et al., 2003 – *J Pediatr* 111:564–572

Social neuroscience. The initial decision to use drugs is often made in group situations, yet little is known about how social dynamics influence the basic cognitive and motivational processes that go into that decision and others involving risky behaviors. Social neuroscience seeks to explain social behavior in terms of its underlying neurobiological mechanisms (genetic, epigenetic, hormonal, biochemical, physiological). This discipline is being increasingly applied to understand a range of behaviors and experiences, including aggression, affiliation, attitudes, social decisionmaking, moral judgment, sexuality, communication, and others. NIDA is encouraging basic and clinical research that applies a social neuroscience perspective to drug abuse and decisionmaking over the course of a person's lifespan.

Stress and trauma. Particularly if experienced early in life, stress and trauma can alter the brain and the response to stress throughout life. In humans, subsequent social stressors such as economic adversity, isolation, and parental abuse and neglect are known to influence age of first drug use, level and duration of use, and psychiatric comorbidities. The reasons are complex, but many people who have experienced trauma may turn to alcohol or other drugs to help themselves feel better. Often, a vicious cycle ensues in which abusing drugs to self-medicate engenders additional stress and leads to repeated substance abuse.

NIDA is seeking to better understand how these variables influence drug abuse vulnerability (see Sidebar 2) and how they work in concert with a person's larger environment. Studies continue to reveal that the interplay of biological and social influences affects individual choices and decisions about drugs. To learn more about this interplay, NIDA supports research to develop a comprehensive classification of

social and built environments (including family, peers, school, neighborhood, community, and culture).

Neurobiological underpinnings. Research is needed to unravel how environmental factors like social stress induce brain changes that interact with drugs of abuse and alter behavior. We also need research to learn how to identify ways to counter or minimize stress effects. Animal research has begun to reveal mechanisms by which environmental variables can positively and negatively affect drug abuse risk. Further, brain imaging technologies are increasingly being used as part of drug abuse and addiction research in both animals and humans to illuminate how the brain is affected by stress and social influences (e.g., peer pressure) within the context of drug abuse or decisionmaking (see Sidebar 3). A better understanding of how social and other environmental factors influence behavior and how they might be reversed is important for prevention, particularly in adolescents.

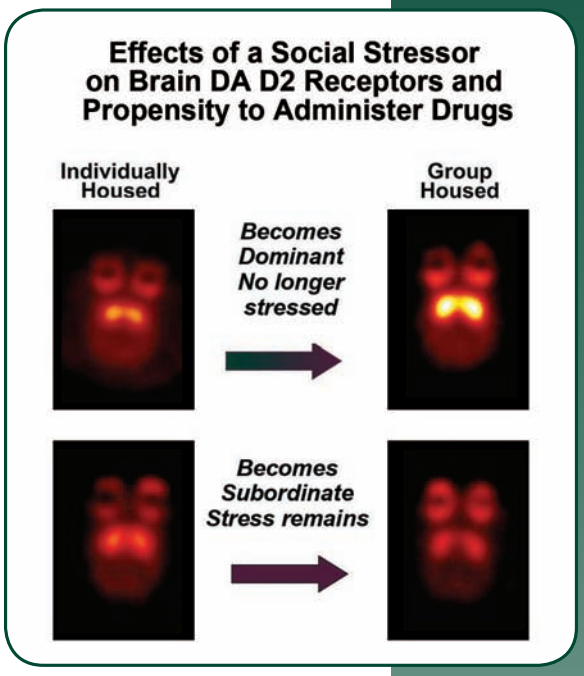
Why young people are at special risk

The trajectory of drug use, abuse, and addiction typically begins in adolescence but sometimes even earlier. The greater risk of young people becoming addicted involves two major components. First, children and adolescents are naturally inclined, and much more likely than adults, to engage in risky behaviors, which may include experimenting with drugs of abuse. Current evidence—derived mainly from human brain imaging studies—suggests that this phenomenon stems from still-developing brain regions involved in judgment, decisionmaking, and emotional control, which do not fully mature until early adulthood (see Sidebar 4). Second, because the young developing brain is constantly changing—physically and functionally—the effects of psychoactive drugs may be more pronounced and enduring if drug use starts

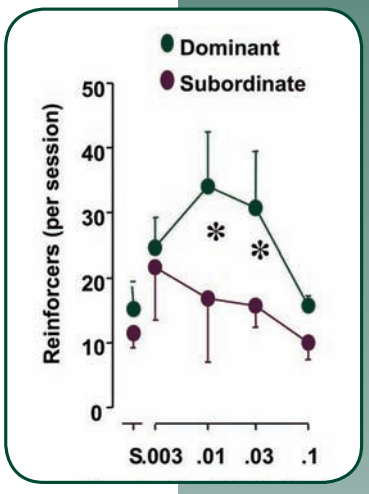
Sidebar 3

Study Sheds Light on the Underlying Connections Between Social Stress and Drug Abuse Behaviors

In this study, monkeys that were transferred from isolation to group living and became dominant in the new social structure underwent biological changes that gave them stronger dopamine signaling and less interest in cocaine compared to animals that became submissive. These findings demonstrate that alterations in an organism's social environment can produce profound biological changes that have important behavioral consequences, including vulnerability to cocaine's rewarding effects.



Why it's important: The emerging field of social neuroscience will examine how neurobiology and the social environment interact in abuse and addiction processes to influence initiation, maintenance, treatment, and relapse.

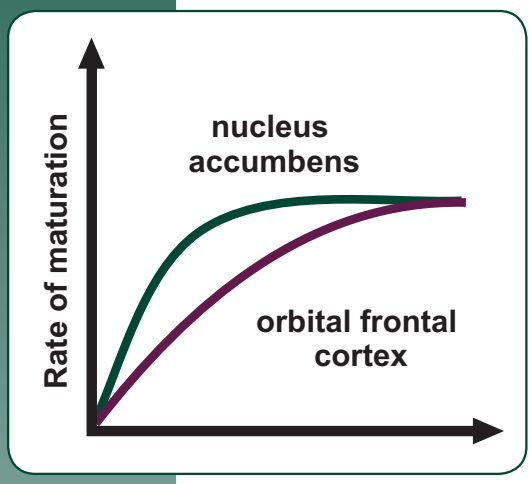


Source: Morgan et al., 2002 – *Nat Neurosci* 5:169

Sidebar 4

Differential Rates of Brain Maturation May Account for Teenagers' Risk-Taking Proclivity

This study reported that the nucleus accumbens, a part of the brain's reward circuitry, matured faster than the orbital frontal cortex, which is involved in behavioral inhibition and control. This pattern of brain development was associated with a different valuing of rewards by adolescents as compared with adults and children, suggesting that the relative immaturity of the orbital frontal cortex in adolescents might underlie their propensity toward risk-taking behavior.



Why it's important: These findings suggest that maturing subcortical systems become disproportionately activated (relative to later maturing top-down control systems), biasing the adolescent's action toward immediate gratification over long-term gains.

Source: Galvan et al., 2006 – *J Neurosci* 26:6885

early. Although this question is difficult to investigate in humans, animal studies have provided considerable evidence supporting this hypothesis. NIDA continues to encourage both basic and clinical research in this area.

Even the very earliest exposure (i.e., in utero) can affect a variety of cognitive and mental health outcomes later in life. Abilities related to problemsolving, memory, learning, language, and reasoning are all vulnerable, as is a person's risk for addiction. For example, prenatal exposure to nicotine was recently shown to influence the risk for nicotine addiction 30 years later.[8] This outcome could reflect nicotine's ability to influence the expression of genes affecting fundamental processes in the developing brain. NIDA-supported longitudinal studies of prenatal exposure to several drugs of abuse help us understand the drug-specific impacts on developmental outcomes. These include outcomes affecting health, cognition, executive function, emotion, and attention regulation.

How drug abuse risk varies across the life span

Significant developmental shifts occur throughout life and can shape drug abuse trajectories. Such transitions include post-high school, a time of greater independence (associated with increased substance use and progression from abuse to addiction); adult role transitions, such as marriage, parenting, and full-time work (associated with decreased substance abuse); and older-age transitions, such as retirement and age-related medical issues (associated with increased potential for substance abuse-related medical consequences). Because the risk factors associated with a person's biology and environment vary as a function of age, NIDA supports studies across all age groups, with a particular focus on life transitions.

It is clear that the course of drug addiction is related to both biological and cultural transitions. However, we need to further investigate how these developmental shifts interact with individual genetic and environmental backgrounds to influence the course of the disease. Doing so will lead to developmentally appropriate interventions.

The role of gender in drug abuse and addiction

Research has repeatedly shown that a broad spectrum of differences related to gender (e.g., social environment, physiological response to drugs, sexual dimorphisms in brain circuitry and hormones) can greatly influence not only drug abuse trajectories but also the characteristics of prevention (and treatment) programs that work best for either females or males.

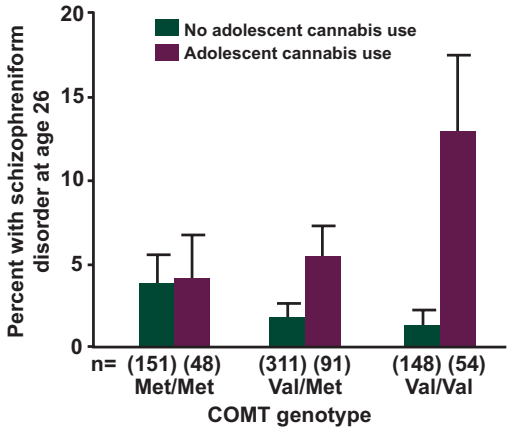
For example, research has identified the menstrual cycle (i.e., the estrous cycle in animals) as a determinant of drug action—pharmacokinetic and behavioral—in both animals and humans. In animals, many behavioral effects of drugs are influenced by the estrous cycle and are eliminated by ovariectomy and subsequently restored by administering estradiol.[9] Suggestive evidence from both animal and human studies indicates that progesterone may also play a role in the subjective effects of drugs and contribute to gender differences in sensitivity to the drugs. These differences, observed in preclinical and clinical studies, highlight the complexities of just one influence on behavior—hormonal cycles in females—and emphasize the continuing need for studies targeting the ways in which gender influences drug abuse and addiction risk.

Sidebar 5

People With Particular Gene Variants May Suffer More Harmful Effects From Drugs of Abuse

A longitudinal study of people followed from birth to adulthood highlights the complex interactions between genetics, drug exposure, and age of use in the risk of developing a mental disorder. The catechol-O-methyltransferase (COMT) gene, which comes in two forms, "Met" and "Val," produces an enzyme that regulates dopamine, a brain chemical involved in schizophrenia. Individuals with one or two copies of the "Val" variant have a higher risk of developing symptoms of psychosis (e.g., hallucinations, delusions) or schizophrenic-type disorders if they used cannabis in adolescence; no effect was seen in those who did not carry this allele.

Genetic variation in COMT influences the harmful effects of abused drugs



Why it's important: This study reveals a new approach for understanding how genetics, environment, and development interact to increase vulnerability to drug-related consequences.

Source: Caspi et al., 2005 – *Biol Psychiatry* 57:1117–1127

Sidebar 6

Individuals vary in their response to drugs of abuse, in part, because of genetic influences on brain circuits that control emotional reactivity. The emerging field of neurogenomics is beginning to reveal the crucial pathways that connect genes to behaviors.

Genetic research has shown that functional variants in the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO); and in the serotonin transporter (SERT) can affect the processing of emotional stimuli, which may also be influenced by other developmental and environmental factors.

COMT. This enzyme degrades the catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine. A less active variant of the gene for COMT has been associated with improved working memory, executive functioning, and attentional control, but also with a higher risk of anxiety-related behaviors.

MAO. This enzyme degrades the monoamines serotonin and dopamine. Several genetic variations have been described that affect the levels of the MAO enzyme, particularly during brain development, that contribute to individual differences in aggressiveness.

SERT. This protein on the surface of some neurons plays a role in turning off the response to serotonin. Variations in a gene that regulates SERT expression affect the processing of aversive stimuli in the amygdala, the emotion center of the brain. Carriers of a short variant show stronger amygdala reactivity to stimuli and to particular contexts that are relatively uncertain and perhaps more stressful. This may put them at increased risk for developing anxiety disorders.

Why it's important: Vulnerability to addiction and other mental disorders likely resides in brain circuits regulating such functions as executive control and emotional reactivity. Identification of the genetic factors that influence these functions will enhance our ability to identify those most at risk, allowing us to more effectively target our prevention efforts.

Sources: Heinz et al., 2006 – *Rev Neurosci* 17(3):359–367; Volavka et al., 2004 – *Ann NY Acad Sci* 1036:393–398; Heinz et al., 2007 – *Biol Psychiatry* 61(8):1011–1014

The relationship between drug abuse and other mental illnesses

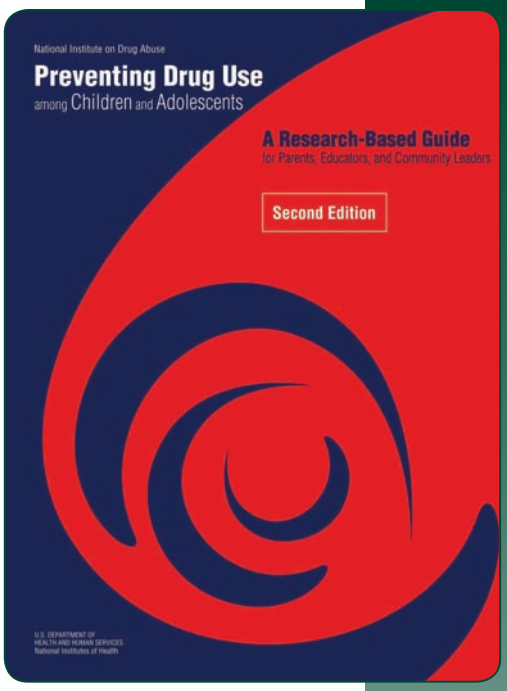
Many people who have a substance abuse disorder also have some other psychiatric disorder, and vice versa. For example, close to 90 percent of people with schizophrenia smoke,[10,11] for reasons that are not fully understood. Other studies show that exposure to certain drugs may increase risk for mental illness in vulnerable individuals (see Sidebar 5 on page 17). Thus, a continuing NIDA priority is to unravel the intimate connections between drug abuse and addiction and other mental disorders. Good prevention hinges on a better understanding of whether these disorders have a shared origin, and of when early drug use increases the risk for mental illness—or vice versa.

Because comorbidity intersects with the missions of other National Institutes of Health (NIH) constituents (e.g., National Institute of Mental Health), NIDA continues to work with our colleagues to encourage research on the epidemiology, genetics, and neurobiological bases of comorbidities.

3. Which parts of the brain are involved in drug abuse?

Research shows that the brain circuits affected by drugs of abuse are mainly those involved in reward, decisionmaking, emotional reactivity (Sidebar 6), motivation, and cognitive inhibition. Drugs of abuse tend to activate reward and motivational circuits more effectively than natural rewards, leaving behind robust memories of their effects. The interactions among the densely interconnected circuits mentioned above determine the final course of action for an individual. For example, if the reward, motivation, and memory circuits overcome the inhibitory control circuit, a person may compulsively seek the rewarding stimulus, which could be drugs of abuse. Again, some of these circuits are not fully mature until early adulthood, making them potentially more vulnerable to disruption by exposure to drugs.

Sidebar 7



Research has revealed a number of basic principles that underlie effective drug prevention programs for youth. These are highlighted in NIDA's Preventing Drug Use among Children and Adolescents, a research-based guide for multiple audiences, including parents, educators, and community leaders.

Our vision is broad and applies the full power of basic and clinical research, neuropsychological testing, and functional neuroimaging to help us understand not just one molecule or one pathway at a time, but the addiction circuitry as an integral part of a wider network. In this network, pathways influence one another in highly complex ways.

4. How are research results used to improve practice?

A general set of science-based prevention principles has emerged from biological, psychological, and social science discoveries. This knowledge has been used to develop prevention programs with proven efficacy and effectiveness (see Sidebar 7). Similarly, to capitalize on new research findings, NIDA sponsors a Prevention

Sidebar 8

Schools Adopt Smarter Strategies To Get the Message Across

Similar to ATLAS (Athletes Training and Learning to Avoid Steroids) for male athletes, ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternatives) for female athletes has the goal of increasing healthy behavioral choices and preventing drug abuse. Program activities, delivered by coaches during a sports team's usual practice schedule, focus on the benefits of healthy sports nutrition and effective exercise training, as well as the dangers associated with drug abuse and other unhealthy behaviors. This intervention correlated with reduced use of drugs—including abuse of diet pills, stimulants, and steroids—as well as with other positive changes, such as healthier eating behaviors.

Why it's important: Innovative prevention programs incorporated into the school setting present an effective way to reach young people, particularly when delivered by role models whom young people naturally admire and respect.

Source: Elliot et al., 2004 – *Arch Pediatr Adolesc Med* 158:1043

Network of research centers nationwide. This network integrates research from various disciplines to stimulate its translation and to inform basic science hypotheses that may help develop new approaches or refine existing programs.

NIDA is also exploring new areas in prevention science, such as the effects of physical activity on substance abuse. Assessing aggregated neighborhood risk factors can inform strategies for more effective programs that yield lasting results. These would synthesize family, school, and community efforts. Indeed, emerging research demonstrates that prevention interventions can have long-term and even cross-over effects (e.g., on driving behaviors and psychological functioning),[12,13] and can alter life trajectories.

Although NIDA-supported research has identified effective prevention programs, they are not being widely implemented. Therefore, we are looking to expand research efforts on the factors that influence the adoption and long-term sustainability of evidence-based prevention initiatives in schools and other settings.

How science can help refine prevention messages

NIDA recognizes that, along with addressing risk and protective factors, effective messages also depend on incorporating imaginative communication strategies aimed at different target audiences. Such a tailored approach is reflected in NIDA's successful school-based prevention programs for male and female athletes (see Sidebar 8).

Changing times require innovative research-based communication tools to help us decode and incorporate the preferences of young people, so that our prevention messages are salient. Closer attention to prevention science is increasingly critical in a media environment where the landscape is constantly changing. For example, research on health-related e-tools, social networking sites, virtual worlds, and other new media is crucial. Trends suggest that the Internet may be an inexpensive and effective means of delivering interventions with a wide reach.

Our ultimate goal is to improve message effectiveness with the intended audience. The addition of new tools and methods of

analysis help refine our interventions and provide a means of testing how the brain reacts to prevention messages. Neuroimaging technology could be applied to reveal how people process media messages in anti-drug advertising. Though we are not yet ready to design a prevention strategy on the basis of how adolescents might view a message in comparison to adults, the fundamental research that will form the basis for scientifically rational design is now under way. Indeed, these studies may spark a new generation of effective, tailored, anti-drug messaging that integrates cultural and social influences.

Our Vision for the Future of Prevention of Drug Abuse and Addiction

We envision a future where new knowledge and leading-edge technologies produce selective, cost-efficient, and effective prevention products and initiatives. Our prevention toolkit someday will allow us to develop messages that flow from a dramatically better understanding of the many complex and interdependent phenomena that characterize drug abuse and addiction. Improved prevention efforts will incorporate what we have learned about genetic contributions to addiction vulnerability, about the function of the human brain and developmental processes under normal conditions or after drug exposure, and about specific brain and behavioral responses associated with an individual's age and social context. We are working toward a future in which early recognition of significant addiction risk is no different from early recognition of any other chronic disease, such as hypertension, diabetes, or asthma.

II. Treatment

Strategic Goal

To develop successful treatments for drug abuse and addiction and improve treatment accessibility and implementation.

Objectives

1. To develop effective medications and behavioral interventions to treat drug abuse and addiction and to prevent relapse.
2. To develop treatments for drug abuse and addiction in association with comorbid conditions.
3. To develop the knowledge that leads to personalized or customized treatments.
4. To translate research-based treatments to the community.

Introduction: The Value of a Multipronged and Integrated Approach to Addiction Treatment

Decades of research have led to today's improved understanding of addiction as a chronic, relapsing brain disease caused by the complex interaction of genetic, social, environmental, and developmental factors. NIDA therefore recognizes the need for a whole systems approach to treating drug abuse and addiction.

Drugs of abuse alter normal brain functioning in profound and long-lasting ways so that the brain can become "reengineered" to seek the drug above all else. This behavior occurs because the addicted person is conditioned to need the drug and finds it difficult, if not impossible, to resist. This dysfunctional state makes the addicted individual vulnerable to relapse triggers, even absent of conscious awareness of them.

NIDA supports multidisciplinary research addressing the multiple factors that can influence drug abuse and addiction trajectories. Research results inform treatment strategies to facilitate abstinence and prevent relapse. New findings continue to inspire **development**

of medications and behavioral interventions to counteract drug-induced alterations in the circuits responsible for motivational, cognitive, and emotional functions. Advances come from the continued application of approaches that tap into potential benefits of the following:

- Expanding the range of drugs or populations that can be targeted with addiction medications that have already been approved.
- Developing medications for molecules and circuits affected by specific drugs, as well as for targets more generally affected by many drugs.
- Developing research-based treatments that **match an addicted person's changing needs**, attitudes, and motivations over time.
- Developing medications to restore cognitive functions disrupted by addiction, which may have impeded the success of behavioral therapies.
- Weakening the power of relapse triggers.

For more information visit our Web site at: www.drugabuse.gov

- Taking into account the influence of **comorbid conditions** (e.g., mental illness, chronic pain, HIV/HCV) and genetic makeup to achieve truly **customized treatments**.

NIDA recognizes that despite major strides in treatment research, only limited improvements have occurred in nonresearch settings. A scientific approach must be brought to bear on understanding how to most effectively **test and disseminate research-based treatments** and how health services systems and settings influence treatment implementation. Ultimately, it is our goal to make research-based treatments user-friendly, cost-effective, and available to a broad range of practitioners and their patients.

Strategic Approaches to Treatment

NIDA supports research to develop treatments that address the multiple and specific needs of a person trying to recover from drug abuse and addiction. The addition of tools such as neuroimaging technologies and those designed to generate detailed genetic information may help us to individualize treatments and predict treatment response. This knowledge will lead to more targeted and cost-effective approaches for greater specificity.

1. How can NIDA research help develop and enhance medications and behavioral therapies to reduce drug abuse and prevent relapse?

NIDA's approach to medications development

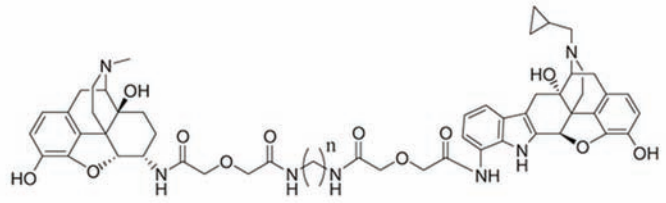
NIDA supports a dual strategy: one that takes advantage of already-approved medications with putative addiction applications, and the other that develops new compounds to interact with novel targets for treating drug abuse and addiction and their health consequences. In both cases, NIDA encourages researchers to work with commercial companies. The advantages of testing already-approved medications include the availability of safety profile information, lower development costs, and shorter times for obtaining FDA approval.

On the other hand, the development of new compounds may be more responsive to breakthrough scientific discoveries. For instance, NIDA research has uncovered several components of the cannabinoid system, along with heterodimeric receptors (i.e., receptors that combine, or "dimerize," to create targets with novel biological properties that could be harnessed to provide a broader array of medication options). This approach is already being exploited to develop medications for chronic pain that could circumvent the problematic side effects (e.g., tolerance and dependence) of many current medications (see Sidebar 9).

Sidebar 9

Pain Management: Alternative Approaches Promise Pain Relief Without Abuse Liability

Glia. Research reveals that glial cells (historically regarded as supporting players) play key roles in regulating pain signals. Through the secretion of a host of molecules, glial cells influence pain and inflammatory processes. Targeting glia and their soluble products may provide a novel and effective therapy for controlling clinical pain syndromes.



3 - 8, MDAN Series

CB2. Activation of cannabinoid type 2 (CB2) receptors inhibits acute, inflammatory, and neuropathic pain responses in animal models. Since these receptors are located largely outside the brain, selective CB2 agonists are promising candidates for the treatment of acute and chronic pain without the psychoactive effects.

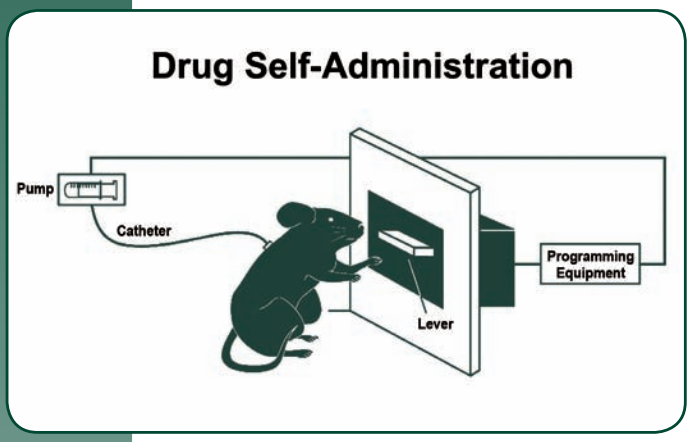
Opioid receptor heterodimers. Opioid receptors exist as dimers—protein molecules composed of two linked subunits—whose variable makeup affects resulting pharmacology. Strategies are being developed to identify compounds that will specifically bind and activate different opioid receptor combinations. Such compounds could represent the next generation of pain relievers with decreased side effects, including reduced drug abuse liability.

Sources: Watkins LR et al., 2007 – *Brain Behav Immun* 21:131–146; Whiteside GT et al., 2007 – *Curr Med Chem* 14:917–936; Daniels et al., 2005 – *PNAS* 102(52):19208–19213

Sidebar 10

Animal Models Are Crucial to Research on Drug Abuse and Addiction

Animal models have greatly contributed to our understanding of addiction's underlying substrates, the abuse liability of novel compounds, the role of candidate vulnerability genes and stress in relapse, and the persistence of drug taking. They allow scientists to rigorously control and analyze biological and environmental factors related to drug abuse and test novel approaches to prevention and treatment. The noteworthy development of buprenorphine as a treatment for opiate addiction began with studies using animal models, as is the case for most medications being tested in human clinical trials.



Self-administration, or the voluntary intake of abusable substances by animals, is now among the most widely used paradigms by pharmaceutical companies around the world to evaluate the abuse liabilities of new medications. Because animals will self-administer nearly all drugs of abuse and continue to take them when available, they allow us to study the chronic effects of drugs on their brains and behavior.

Source: Caine, et al. (ed), 1993 – Behavioural Neuroscience: A Practical Approach, Vol. 2 117–143

Regardless of the approach used, NIDA takes advantage of the combination of validated animal models and translational human laboratory studies to develop and test medications (see Sidebar 10).

How behavioral treatments help drug abusers

Behavioral therapies have already been successfully developed to help individuals with addictions engage in the treatment process, modify their attitudes and behaviors, and nurture those skills that are conducive to a healthy lifestyle. These treatments can also enhance the effectiveness of medications (and vice versa) and help people stay in treatment longer.

Addiction to drugs such as cocaine and methamphetamine can disrupt cognitive functioning and interfere with treatment retention and efficacy. Therefore, NIDA is supporting research on medications such as Modafinil (which is currently FDA-approved for treating narcolepsy) as an adjunct to behavioral therapy because of their proven cognitive-enhancing properties. Early results are promising for cocaine treatment, and research in methamphetamine abusers is under way.[14]

NIDA also plans to explore cutting-edge cybertechnologies for both developing new treatments and expanding treatment delivery. New technologies are opening the door to shared virtual worlds (environments, social networks, communities), digitally controlled environments, augmented realities, robotics, and brain computer interfaces, among many others. All these could have applications in drug abuse treatment. NIDA is already exploring the potential of computer-delivered interventions as a comparatively low-cost means of widely disseminating evidence-based approaches while ensuring treatment fidelity. Early

studies of cognitive-behavioral therapy and community reinforcement approaches support the feasibility and acceptability of this strategy.[15,16]

What effective treatments are designed to do

Drug abuse disrupts the brain circuits involved in reward, memory/learning, and control over behavior. Memories linked to the drug experience, for example, can trigger powerful drug cravings that can "mute" other parts of a person's life so that drug seeking and use become an all-consuming focus. Craving is therefore a major contributor to relapse, posing what seems an insurmountable challenge to an addicted person (see Sidebar 11). NIDA's strategic approaches to treatment are thus being employed to (1) counter relapse triggers, (2) strengthen self-control, and (3) reinstate the reward value of natural reinforcers while decreasing that of drug stimuli.

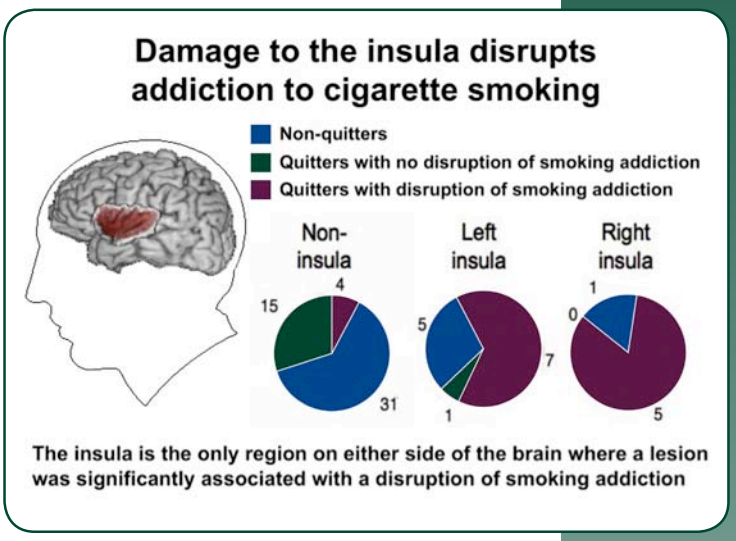
Prevent Relapse. The most frequent triggers of relapse include stress, exposure to conditioned cues, and priming (re-exposure to drugs of abuse). Medications that block reinstatement of drug-taking behaviors in animals by these three triggers are now being tested in humans.

Both clinical reports and preclinical studies have documented the important role that stress plays in relapse. Medications or behavioral treatments that can interfere with or mitigate the response to stress may thus offer promise for relapse prevention. Corticotropin-releasing factor (CRF) is known to be a key brain chemical involved in organizing the brain and body response to stress. Thus, medications that target CRF are of interest. Animal studies have shown that compounds that block CRF signals attenuate the reinstatement of drug taking following exposure to stressors. Since drug withdrawal syndromes and the often chaotic lifestyles of drug abusers are manifestly stressful states, strategies that improve coping mechanisms or reduce the stress response could help prevent stress-induced relapse.

Sidebar 11

Brain Region Linked to Reduced Drug Craving

Despite being aware of negative consequences, many smokers have serious difficulty quitting, and those who quit experience urges to smoke and often relapse. A recent study of patients who had suffered various brain injuries revealed a new role for the insula (shown in red) in regulating conscious urges, including drug craving. Researchers at the University of Iowa monitored the quit histories of approximately 70 smokers and found that those **with specific damage to the insula were much more likely to quit easily and immediately** and to remain abstinent than those with damage to other brain areas.

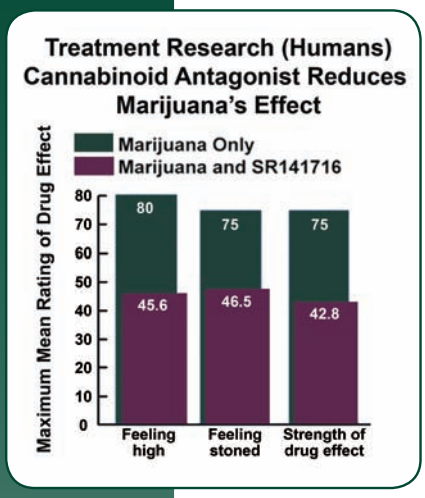


Why it's important: This discovery could identify a new target to inhibit craving.

Source: Naqvi, N. et al., 2007 – *Science* 315:531

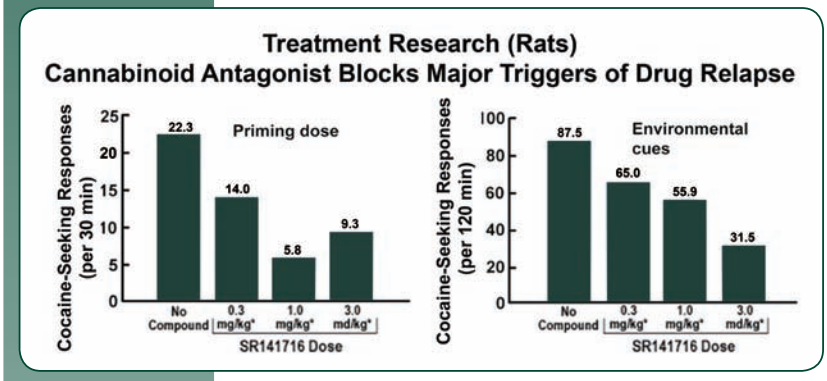
Sidebar 12

Compound Reduces Marijuana's Intoxicating Effects and May Help Prevent Relapse From Drug Exposure (Priming) and Environmental Cues



(A)

Marijuana smokers given an experimental compound (SR141716, rimonabant) reported reduced highs (and smaller heart rate increases) compared with untreated smokers (see A). Because SR141716 partially blocks the intoxicating effects of marijuana's active ingredient (THC), it may prove valuable in treating marijuana addiction and perhaps other addictions as well. Indeed, in a rat model of relapse to drug seeking, SR141716 dramatically reduced resumption of cocaine-seeking triggered by two of the three most common relapse triggers: a priming dose of cocaine and conditioned cues associated with cocaine reward (see B). The compound did not reduce cocaine-seeking triggered by stress.



(B)

Why it's important: The cannabinoid system is a new player in our understanding of the rewarding effects of drugs, and compounds that target this system may have application for not only marijuana treatment, but also for other drugs since they can block relapse triggers.

Sources: Huestis et al., 2001 – *Arch Gen Psychiatry* 58(4):322–328; De Vries et al., 2002 – *Pharmacol Rev* 54:1–42

Conditional cues are stimuli (e.g., people, places, moods, things) that become associated with the drug experience and can serve as triggers to relapse. Conditioned cues can pose formidable obstacles to successful therapy for many individuals because they can elicit craving without conscious recognition of their influence. Medications designed to blunt conditioned responses or promote their extinction (an active process whereby previously learned associations are weakened) could enhance the efficacy of psychotherapeutic interventions. A proof-of- concept for this approach has already been shown with D-cycloserine (DCS), a partial agonist of the NMDA (glutamate) receptor. DCS may facilitate extinction and promote new learning, and has been successfully used in conjunction with psychotherapy for treating acrophobia (the fear of heights).[17] Medications available for other indications are also being tested for their ability to reduce cue-induced drug cravings.

Priming, or drug exposure, is the response to a drug in a formerly addicted person that propels him or her to further drug use and, often, to relapse. Data show that people in treatment who "slip" are at higher risk of relapse or of returning to former levels of drug abuse.

Research in this area has already produced positive results. Cannabinoid and opioid antagonists, for example, have been shown to block the priming response in animals and suppress their self-administration of drugs in a relapse model of drug seeking (see Sidebar 12).

Another strategy being explored is to block priming attempts by harnessing the immune response. The rationale is to develop "vaccines" that induce the body to produce drug-specific antibodies. At

high enough concentration, these antibodies would sequester drug molecules while they are still in the bloodstream, preventing them from reaching the brain and exerting their psychoactive effects. Nicotine and cocaine vaccines have already been developed and are undergoing further testing in animals and humans. A methamphetamine vaccine is in development. NIDA has also requested proposals for a heroin vaccine, which could be particularly valuable in areas of the world where opioid agonist medications are not accepted. NIDA plans to continue supporting research on strategies designed to block the priming response.

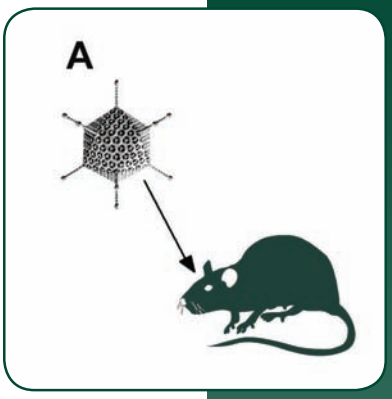
Strengthening Self-Control. The decision-making circuits of the human brain, which are not even fully developed until a person's mid-20s, govern our ability to control impulses. Drug abuse and addiction can severely disrupt these processes, contributing to the compulsive features of addiction. A complementary strategy supported by NIDA is to strengthen the function of brain regions involved with decisionmaking and inhibitory control (distributed throughout the frontal cortex).

Noninvasive brain stimulation and "neurofeedback" may prove to be useful therapeutic tools in this context. Researchers are exploring the use of technologies such as repetitive transcranial magnetic stimulation (rTMS) and feedback training using real-time functional magnetic resonance imaging (fMRI) (see Sidebar 19 on page 33) to noninvasively influence brain activity in specific regions. Though not yet demonstrated for addiction, these techniques show promising results in managing depression and in influencing pain perception, respectively.[18] Further validating research could render these technologies powerful psychotherapeutic interventions for rescuing the circuits and behaviors impaired by addiction.

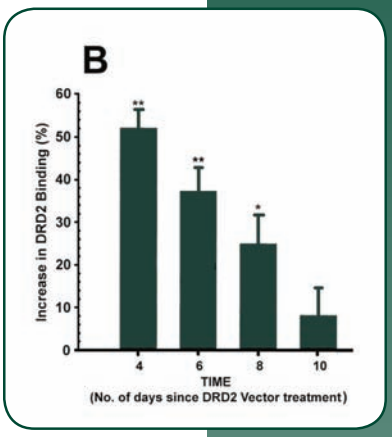
Sidebar 13

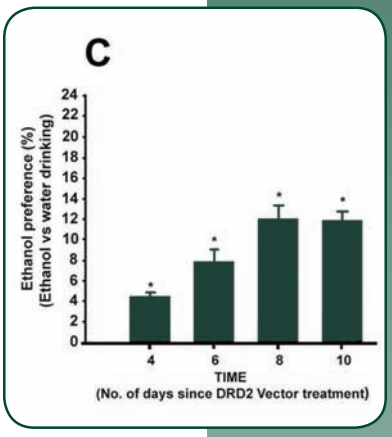
Overexpression of Dopamine D2 Receptors Reduces Alcohol Self-Administration in Rats

Addiction is characterized by decreased sensitivity to natural rewards, likely related to diminished function in dopamine brain circuits. Human brain imaging studies have provided substantial evidence showing that individuals addicted to a variety of substances have low levels of dopamine type 2 receptors (DRD2) in the striatum (a part of the reward circuit).



In this experiment, researchers sought to determine whether increasing levels of DRD2 in the brain could reduce alcohol consumption in animals trained to self-administer the drug. Brain levels of DRD2 in rats were increased by injecting a virus that expresses high levels of DRD2 protein in a key area of the brain's reward pathway (see A). This manipulation led to an overexpression of DRD2 receptors that dissipated over time (see B) and a corresponding decrease in alcohol consumption that resumed when the receptors returned to baseline (low) levels (see C).





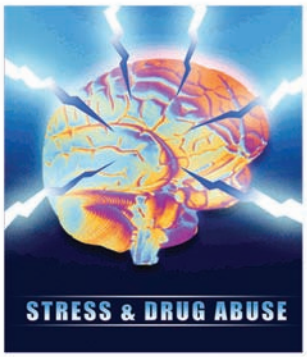
Why it's important:
Although the use of viral vector–delivered genes is not practical for clinical use, these results provide a proof-of-concept that enhancement of dopamine D2 receptors may be a useful approach for treating drug abuse. Medications and behavioral strategies to reinstate dopamine receptor function in the reward circuitry may be beneficial in treating addiction.

Source: Thanos et al., 2001 – *J Neurochem* 78(5):1094–1103

Sidebar 14

Many Common Factors Are Involved in Addiction and Mental Illness

Addiction:
- Genetics
- Epigenetic marks
- Social stressors
- Early physical or sexual abuse
- Mental illness
- Peers who use drugs



Mental Illness:
- Genetics
- Epigenetic marks
- Social stressors
- Early physical or sexual abuse
- Drug and alcohol abuse

Co-occurrence of addiction and other mental disorders is common. Substance abuse sometimes begins as a way to alleviate symptoms of a mental illness. Further, substance abuse may increase the vulnerability to other mental illnesses. Also, some of the factors that contribute to substance abuse and other mental illnesses are the same. Stress is one example, and patients suffering from post-traumatic stress disorder (PTSD) have high rates of drug and alcohol abuse. Because of the projected increases in PTSD due to members of the military returning from service, NIDA will increase its research investment in this area and collaborate with the Department of Veterans Affairs, the Substance Abuse and Mental Health Services Administration (SAMHSA), and multiple NIH Institutes—NIMH, National Cancer Institute, NIAAA, and the National Heart, Lung and Blood Institute—in developing its research agenda.

Reinstating the Value of Natural Rewards. Drug abuse and addiction impair the reward system, diminishing the value of formerly rewarding stimuli in a person's life. NIDA therefore seeks approaches to counter drugs' effects on brain systems affecting reward and motivation—and help restore the value of natural rewards.

Animal research has demonstrated the feasibility of modulating the dopamine reward system in ways that affect sensitivity to drug taking. For example, alcohol-preferring rats induced to overexpress dopamine receptors in the nucleus accumbens (a part of the reward circuitry) decreased their alcohol consumption (see Sidebar 13 on page 27). Further, in studies of nonhuman primates, social factors have been shown to influence the function of the dopamine system and vulnerability to drug taking (see Sidebar 4 on page 16). These studies suggest a malleable reward system that may be capable of recovering from drug addiction. The goal would be to heighten dopamine system sensitivity in drug-addicted individuals so as to enhance the value of natural reinforcers (i.e., social interactions, eating good food, etc.).

How patients sustain recovery

There are many pathways to recovery. Some patients may require lengthy treatment protocols in residential therapeutic settings, while others may benefit from less intensive outpatient treatment. The goal is the same: to help patients develop the internal motivation and skills to abstain from drugs and regain their lives.

However, because of the chronic nature of addiction, continuing care (e.g., "booster" treatment sessions, recovery groups, and other social support systems) can be crucial to a person's ability to sustain a drug-free lifestyle. A patient may require varying combinations of services and treatment components during the course of recovery. Along with counseling, psychotherapy, and medical services, patients may also benefit from family therapy, parenting instruction, vocational rehabilitation, and social and legal services. NIDA continues to support

research to better understand how such therapies work and how to implement them in community settings to engage and keep patients in treatment and prevent relapse.

2. What if people have another mental disorder—how does that affect treatment for addiction?

Mental illness is highly comorbid with substance use disorders. In fact, as many as 6 in 10 people who have an illicit drug use disorder also suffer from other mental illnesses.[19] Having both can greatly increase the challenge of diagnosing and treating the disorders; and ignorance of or failure to treat one disorder can jeopardize the chances of a successful intervention for the other. Patients with co-occurring disorders often exhibit symptoms that are more persistent, severe, and refractory to treatment, compared with those with just one disorder. Health care providers and caregivers should therefore be aware that drug abuse and other mental illnesses often occur together, necessitating a comprehensive treatment approach (see Sidebar 14). Thus, NIDA supports research aimed at adapting and integrating treatments that tackle these overlapping conditions, which affect some of the same circuits in the brain.

For some mental disorders, pharmacotherapies are already available to alleviate symptoms. Medications such as stimulants, antidepressants, mood stabilizers, and neuroleptics may be critical to treatment success for ADHD, depression, anxiety disorders, bipolar disorder, and schizophrenia. How these medications are affected by, or alter the effects of, abused substances is not well understood. Some medications may even prove efficacious for treating both drug addiction and other mental illnesses. Effective

Sidebar 15

Groundbreaking Genetics Tools Will Lead to More Personalized Prevention and Treatment Approaches for Drug Abuse and Addiction

New knowledge derived from large, comprehensive genetic databases, combined with new genetics technology, will allow researchers to study thousands of addiction-relevant gene variants at once. Potential applications of this knowledge include studies to understand how genetic differences contribute to brain development and to differential brain responses to drugs of abuse. This knowledge could also be applied to prospective epidemiological studies to understand how genes and environment interact throughout the lifespan to modulate addiction risk. Clinical trials could use genetic information to tailor treatments based on a patient's genetic makeup (i.e., to enhance treatment effectiveness and minimize, or even prevent, adverse effects). Finally, genetics could inform studies aimed at advancing the understanding of disease vulnerability in relation to psychiatric comorbidity (i.e., depression, ADHD, schizophrenia).

Sidebar 16

Gene Cluster Linked to Nicotine Dependence and Associated Diseases

A recent study provides an example of how genome-wide analyses are being used to identify novel candidate mechanisms of disease vulnerability and therapeutic targets. Here, investigators interrogated the genomes of close to 11,000 Icelandic smokers with a platform displaying over 306,000 single nucleotide polymorphisms (SNPs)—or

single-base changes in a person's DNA (millions of which have been catalogued by the Human Genome Project). The study identified a cluster of three nicotinic receptor subunit genes (α3, α5, and β4) linked to smoking quantity, nicotine dependence, and the risk of two smoking-related diseases: lung cancer and peripheral arterial disease.

Why it's important: Identification of this genetic cluster converges with growing evidence from prior studies of its linkage to nicotine dependence and to serious health consequences. This new information reveals a novel target for the development of medications to treat tobacco addiction and related diseases.

Source: Thorgeirsson et al., 2008 – *Nature* 452:638–642

medications also exist for opioid, alcohol, and nicotine addictions. However, their use has not been well studied in comorbid populations or among those taking other psychoactive medications. Various forms of behavioral treatment, alone or in combination with medications, can be the cornerstone to achieving successful outcomes for both substance abuse and other mental disorders. Their use in comorbid populations should also be evaluated.

3. How will treatments be tailored for optimal effectiveness?

NIDA's research program is poised to play an important role in developing treatments that can take individual and group vulnerabilities into account. Doing so will help us derive more personalized and, thus, more effective treatments for people with drug use disorders. To this end, NIDA is capitalizing on advances in genetics, epigenetics, and brain imaging technology, and on research revealing the influence of environmental and developmental factors.

Genetic expression profiles are affected by substance abuse and can change throughout development. To investigate, NIDA researchers are constructing a comprehensive database of single nucleotide polymorphisms (SNPs) relevant to addiction (http://zork.wustl.edu/nida/neurosnp.html) (see Sidebar 15 on page 29). SNPs are variations in DNA sequence that occur when a single nucleotide in the genome sequence is altered. By assembling all genes identified as biologically relevant to addiction, NIDA is helping to identify potential novel targets for the development of medications (see Sidebar 16). We are also expanding the knowledge base so that next-generation pharmaceuticals can use information about a person's genetic makeup to predict how

he or she will respond to a therapeutic medication. Promising findings have already emerged relative to the treatment of nicotine and alcohol addictions.

NIDA is encouraging research that develops and evaluates new platforms for potential use in screening for the telltale signatures of chronic drug abuse in blood cells, serum, or saliva. Looking at messenger RNA (mRNA), epigenetic marks, and protein expression profiles (proteomics) could dramatically enhance our ability to diagnose chronic drug exposure in primary care and other settings.

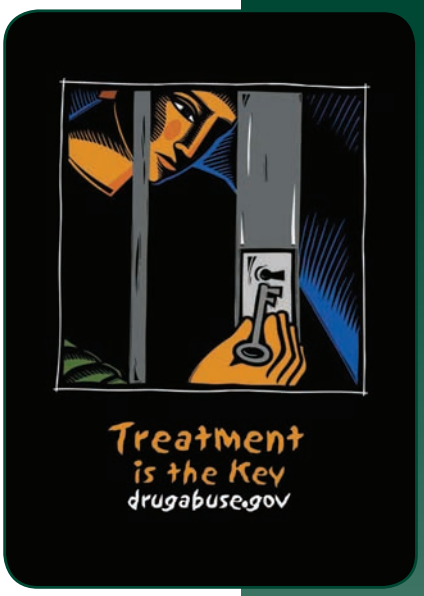
4. How will drug abuse treatment reach the people who need it?

NIDA's clinical trials are the foundation for testing and evaluating promising drug abuse and addiction treatments. We support research trials for all phases of medications and behavioral treatment development. We also encourage collaboration with industry to optimize costs and resource allocation and to more efficiently develop or adapt treatments.

As effective treatments emerge, NIDA tests them in real-world settings. These efforts are exemplified by our National Drug Abuse Treatment Clinical Trials Network (CTN) and our collaborative Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) (see Sidebar 18 on page 32). The CTN studies, for example, continue to reveal information for optimizing the treatment of comorbid conditions and the translation of new medications to community settings. They also assess novel interventions to reduce HIV risk among drug-abusing populations. CJ-DATS broadens the testing of proven drug abuse treatments

Sidebar 17

Methadone Maintenance Works for Prisoners

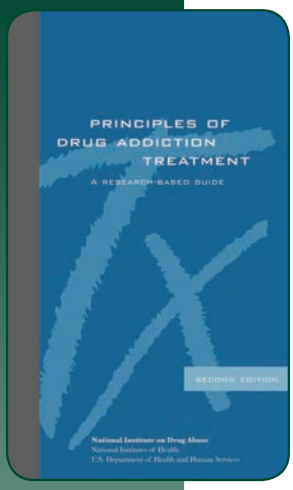


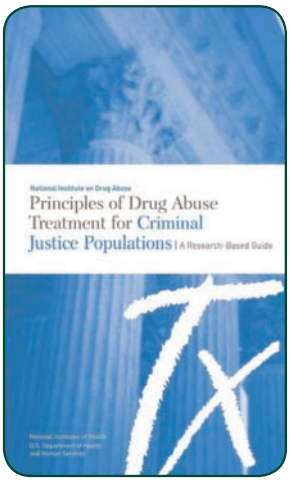
More than 200 heroin-dependent inmates in Baltimore were randomly assigned to one of three groups: (1) educational counseling only; (2) counseling in prison with the opportunity to enroll in methadone maintenance treatment upon release; and (3) counseling and methadone maintenance during incarceration, with transfer to community-based methadone maintenance after release. Six months after release, those who began methadone maintenance in prison were significantly more likely to enter and remain in community-based treatment, were less likely to test positive for illicit opioids, and had significantly fewer days of heroin use and criminal activity than participants who received counseling only.

Why it's important: Despite its demonstrated effectiveness in treating opioid abuse, methadone maintenance is rarely provided in correctional facilities. However, this study shows that methadone maintenance treatment begun prior to or upon release from prison is an inexpensive and effective intervention that may prevent the devastating cycle that can happen to formerly incarcerated drug abusers who go untreated—that is, a return to drug abuse upon re-entry to the community, further criminal activity, exposure to infectious diseases, and re-arrest and imprisonment.

Sources: Kinlock et al., 2007 – *Drug Alcohol Depend* 91(2–3): 220-227; Kinlock et al., 2008 – *Crim Justice Behave* 35(1): 34-47; Gordon et al., 2008 – *Addiction* 103: 1333–1342

Sidebar 18





Science Reveals Treatments that Work for Drug Abuse and Addiction

Research has revealed a number of basic principles that underlie effective drug addiction treatment, as highlighted in NIDA's treatment guides for the general population and for criminal justice offenders.

in criminal justice settings, including CJ settings with adolescents. It continues to solicit the greater involvement of public health and public safety institutions across all system levels. NIDA plans to support ongoing research on drug courts to learn how they work and how to advance their use, looking at the judge's role in changing drug court participant behavior and outcomes, for example.

All of these initiatives allow NIDA to exploit an open-channel communication approach with relevant stakeholders to collect information on how to generalize and further enhance treatments so they are more community/justice system-friendly.

Overcoming barriers to more rapidly translate research findings

NIDA's overall mission is not just to develop knowledge about drug abuse but also to disseminate that knowledge into practical use. We engage in multiple activities aimed at closing the unacceptably long lag between the discovery of effective treatment interventions and their integration into community clinical practice.[20] Despite major strides in drug abuse treatment research, the adoption of science-based programs has been rather limited. This may relate to several unique characteristics that distinguish treatment for drug abuse from that for most other diseases, including:

- service delivery outside of mainstream health care settings;
- overburdened treatment systems, often with low pay and high staff turnover rates;
- external (i.e., court-mandated) pressure on individuals seeking care;
- nonreimbursement for costs of care;
- reliance on public sources for program funding; and
- stigma attached to the disease and to those seeking treatment for it.

NIDA continues to support research that addresses the organizational, workforce, funding, and policy issues known to influence the success of addiction treatment. This includes cost-effectiveness and implementation research to determine how best to overcome systemic obstacles and foster the adoption of proven treatments by communities nationwide (see Sidebar 18). Moreover, we continue to build our productive partnerships with state agencies and encourage them to team with research organizations to enhance their research capacity and their delivery of publicly supported drug abuse treatments.

NIDA is also working to engage the medical community in drug abuse screening and referral to treatment. Primary care physicians are ideally positioned to serve as the first line of defense for detecting drug use early and for referring symptomatic drug-abusing patients to specialized treatment. Therefore, NIDA continues to make research on screening and brief intervention (SBI) a strategic priority, focusing first on primary care and emergency room physicians. SBI has already been shown to be effective in reducing alcohol and tobacco use, though more research is needed for effects on illicit and prescription drug abuse. Also, drug abuse can influence the course and progression of

other medical diseases (including adherence to treatment regimens), underscoring the need for screening.

Our Vision for the Future of Treatment for Drug Abuse and Addiction

NIDA's research program is entering an exciting new era in which treatments will be increasingly tailored to the individual—a more personalized approach that will translate into better and more cost-effective treatments for substance abuse disorders. This approach will be more effective than past approaches thanks to our new understanding of the plastic adaptations that characterize addiction. These adaptations erode the very same neural substrates that enable functions such as self-control, decisionmaking, accurate reward prediction, motivation, and memory. We are committed to harnessing knowledge on how drugs affect circuits and behaviors and parlaying it into effective treatments to restore the addicted brain and allow people to regain their cognitive abilities and capacity to enjoy life.

Glimpses of this future can already be seen in various research areas. Indeed, next-generation screening and monitoring devices, therapeutic compounds, behavioral interventions, and neurofeedback training (see Sidebar 19) suggest a panoply of treatment options to efficiently counteract the drug-induced breakdown in brain neurochemistry. Addiction treatments will become increasingly adept at reducing the rewarding properties of drugs while enhancing those of healthier alternatives. Inhibiting conditioned memories and strengthening cognitive control are other treatment objectives.

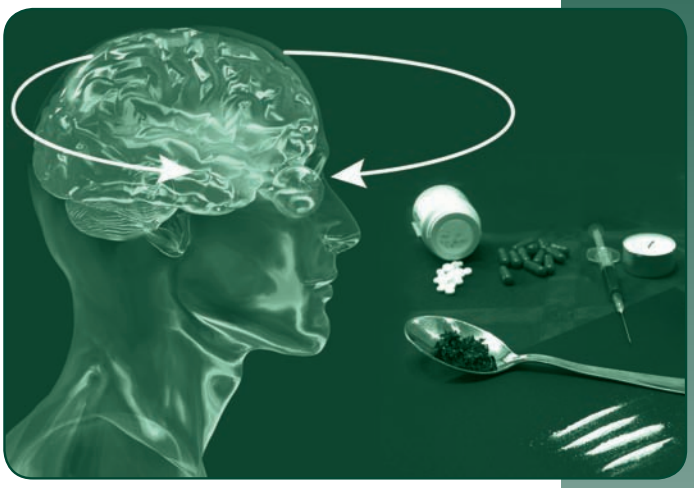
In the future, we will seize upon new therapeutic opportunities stemming from deciphering an individual's genetic code to better prevent and cure disease. At the same time, however, we must recognize the responsibility that comes with such technological advances to ensure confidentiality and privacy.

NIDA is constantly striving to transform scientific insight into effective and responsible public health interventions. This endeavor continues to be shaped by promising discoveries and by the accompanying need to consider ethical concerns when treating illnesses like drug addiction.

Sidebar 19

Neurofeedback Offers Exciting Potential for Future Use with Addicted Patients

Researchers are exploring the use of neurofeedback, where subjects are trained to modulate neural activity in specific regions of their brains by having pictorial representations of the activity in those areas fed back to them in real time. Though not yet demonstrated for addiction, this technique has shown promising results for altering the perception of pain in some healthy adults and chronic pain patients.



Why it's important: This line of research could evolve into a powerful psychotherapeutic intervention capable of restoring function to the circuits and behaviors impaired by addiction.

Source: DeCharms et al., 2006 – *Proc Natl Acad Sci* 102(51):18626–18631

III. HIV/AIDS

Strategic Goal

To diminish the spread of drug abuse-related human immunodeficiency virus (HIV) and minimize the associated health and social consequences, including acquired immunodeficiency syndrome (AIDS).

Objectives

1. To support research to better understand the etiology, pathogenesis, and spread of HIV/AIDS among drug-abusing populations.
2. To help prevent the acquisition (primary prevention) and transmission (secondary prevention) of HIV among drug abusers and their partners.
3. To decrease the health disparities associated with HIV/AIDS.
4. To support international research on the intertwined epidemics of drug abuse and HIV/AIDS.
5. To improve HIV treatment and outcomes in drug abusers through a better understanding of interactions with drugs of abuse, HIV/AIDS disease processes, and the medications used to treat both.

Introduction: The Need for Responsive Prevention and Treatment Strategies

HIV/AIDS remains one of the most serious medical consequences of drug abuse. Thus, NIDA continues to support research to improve HIV prevention among drug abusers and enhance treatment access and use for HIV/AIDS and other co-occurring conditions, particularly hepatitis C (HCV) infection (85–90 percent of HIV-positive injection drug users [IDUs] are also HCV-positive). For example, NIDA continues to study HCV treatment patterns in patients with and without HIV co-infection to examine clinical outcomes following treatment.

Our strategic plan relies on research across diverse areas, including basic science, epidemiology, prevention, health disparities, medical interactions, and disease consequences. To effectively diminish the spread and consequences of HIV/AIDS, we must better understand how HIV is transmitted among different groups and communities. Genetics research will elucidate individual factors that determine vulnerability or resistance to infection and to disease progression. Epigenetic studies may offer clues as to how the virus becomes incorporated into

cells, but remains latent. In addition, studies that advance our knowledge of the changing behavioral and social **epidemiology** of drug abuse, HIV/AIDS, and comorbid conditions will help guide our approach to preventing HIV transmission. We have already learned important lessons by focusing on (1) the link between drug abuse and risky sexual behaviors and (2) the distinct characteristics of the epidemic among special populations (women, youth, minorities, prisoners).

A key step in curtailing the spread of HIV is improving our **understanding of why certain populations are exceptionally vulnerable**, along with developing **primary prevention** strategies that target infection among high-risk groups. The Centers for Disease Control and Prevention (CDC) estimates that 21 percent of people living with HIV in the United States do not know they are infected,[21] which heightens their risk of unknowingly transmitting the virus. Therefore, NIDA also supports research to develop effective **secondary prevention** strategies that promote testing and education among the undiagnosed to further reduce HIV transmission. NIDA is building on earlier research that helped prompt the CDC's decision to broaden its guidelines for providing HIV screening to populations at risk. An important aspect of encouraging testing and counseling is the need to make followup treatment more accessible to people with HIV and substance abuse problems.

A disproportionate number of affected people are ethnic minorities, whose access to and utilization of treatment options is often limited. Such **health disparities** particularly affect African-Americans, who also tend to be late testers, putting them at greater risk for disease transmission and accelerated disease progression. Gathering meaningful data on the various factors contributing to

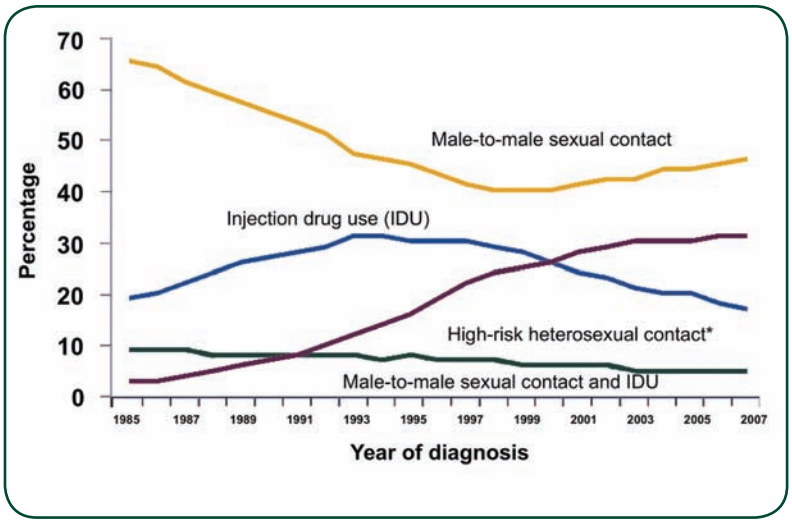
these disparities is integral to efforts to resolve them through earlier diagnosis and treatment. Moreover, HIV/AIDS associated with drug use continues to expand globally. **International research** that systematically monitors changes and patterns in the transmission and manifestation of HIV disease will more effectively prevent and treat the AIDS epidemic.

Treatment with highly active antiretroviral therapy (HAART) can dramatically reduce HIV-related morbidity and mortality. HAART is enabling more people to live longer with HIV, helping to redefine it as a chronic illness. This circumstance brings about accompanying chronic **medical disease consequences**—particularly, adverse consequences for the brain. Moreover, interactions between neurological complications, substance abuse, and other comorbid psychiatric disorders may contribute to poor adherence and worse outcomes, requiring responsive counterinterventions. To optimize HAART for drug abusers, we must investigate interactions between HAART, drugs of abuse, and medications used to treat addiction. More research is needed to better understand and address the long-term clinical complications in drug-abusing populations.

Finally, because HIV/AIDS extends across many public health domains, NIDA is collaborating on projects with other NIH Institutes and Centers, focusing on complementary work in the areas of drug abuse, HIV/AIDS, and other sexually transmitted diseases (STDs).

Figure 2

AIDS from injection drug use has declined steadily while risk from heterosexual contact has increased



Percentages of AIDS Cases Among Adults and Adolescents by Transmission Category and Year of Diagnosis In United States and Dependent Areas

Note: Data have been adjusted for reporting delays and missing risk-factor information.

Source: CDC, U.S. Department of Health and Human Services, 2008

Strategic Approaches to HIV/AIDS Research

NIDA continues to encourage basic, clinical, services, and natural history research that explores the underlying mechanisms of HIV-associated health outcomes in the context of drug abuse.

1. How has the HIV/AIDS epidemic changed over the past few decades in the United States?

The patterns of HIV/AIDS relative to drug abuse are changing in this country. Formerly, injection drug use was a main vector through which HIV was spread. However, over the past three decades, a substantial reduction has occurred in the proportion of new HIV/AIDS cases attributable to injection drug use. NIDA research that has resulted in improved treatment for injection drug users (e.g., methadone and buprenorphine for heroin addiction) has contributed to this decline. At the same time, the proportion of cases attributable to high-risk heterosexual contact has increased steadily (see Figure 2).

Recent findings illustrate the trend in HIV infection moving from injection drug use to noninjection drug use (see Sidebar 20). Drug use impairs people's judgment and lowers their inhibitions, which can lead to impulsive and unsafe behaviors; therefore, effective drug abuse treatment is also HIV prevention. Indeed, the integration of HIV risk-reduction interventions into drug abuse treatment is imperative.

Epidemiological and natural history studies help us to monitor epidemic trends, follow more closely the changing clinical manifestations of HIV disease and comorbid conditions, and measure the effects of HIV prevention efforts among drug abusers. New studies will also inform the development of effective primary and secondary prevention interventions. Looking at diverse settings can help us characterize individual risk factors as well as the influence of social and sexual networks, environmental contexts, and their interactions. Such research will help elucidate HIV transmission dynamics, the disparate health effects of drug use and HIV/AIDS among different populations, and the best ways to reach them.

NIDA is focusing more intently on criminal justice populations to learn how best to address the special risks of a group with high drug abuse and background infection rates compared with the general population. This pertains to populations both in prison or jail and upon return to the community.

For more information visit our Web site at: www.drugabuse.gov

2. How does NIDA plan to focus research efforts to better understand and prevent HIV infection in drug abusers and limit its progression?

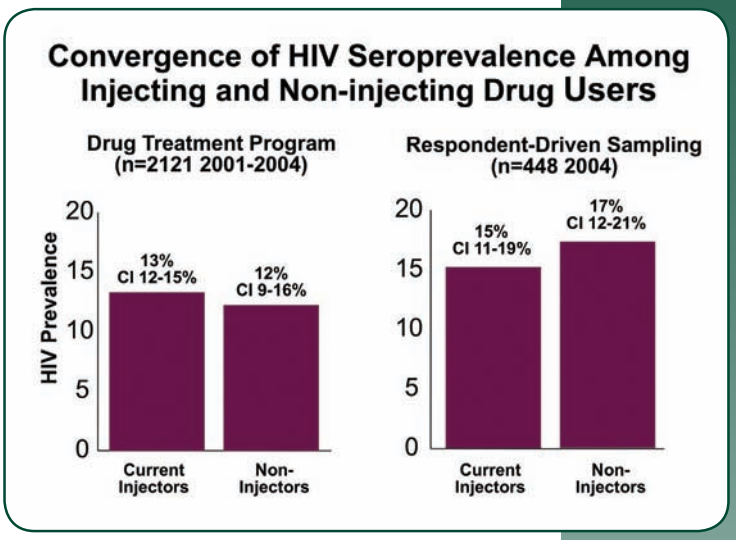
NIDA's basic research portfolio will focus on host and viral factors related to HIV susceptibility and progression in drug abusers. Genetics, epigenetics, proteomics, and other related high-throughput technologies will be employed. These can help identify changes in gene and protein expression, as well as molecular signatures of disease vulnerability and progression in both humans and model organisms.

Another promising new area of study with respect to AIDS progression involves the depletion of T cells in gut-associated lymphoid tissue (GALT) in the very early stages of HIV infection. This depletion—and how well it is restored with antiretroviral treatment—seems to determine the outcome of infection, or how quickly AIDS progresses. NIDA is interested in research on the link between substance abuse and the GALT immune responses. We also want to learn more about the impact of HAART on the restoration of the gastrointestinal mucosal immune system—within the context of substance abuse. A new research initiative will encourage basic and clinical research in these areas.

Sidebar 20

Non-Injection Drug Abuse is Also Risky for Spreading HIV

Rates of HIV infection are converging in drug abusers who inject drugs and those who do not inject. This indicates that HIV is being spread among drug abusers by means other than needle sharing (i.e., risky sexual behaviors).



Why it's important: We need to shift focus toward reducing risky sexual behaviors among drug abusers, regardless of the route of drug administration.

Source: Des Jarlais et al., 2007 *AIDS*, 21:231–235

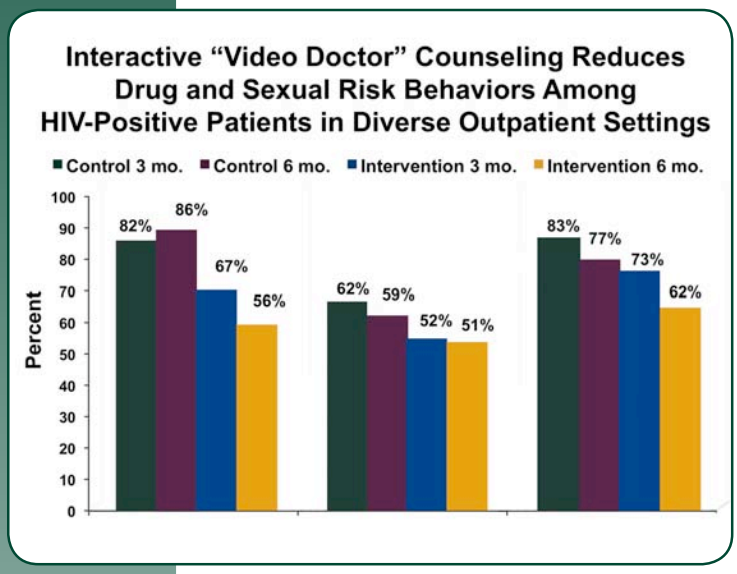
Primary prevention efforts to reduce drug abuse–HIV risk behaviors

HIV prevention must be a component of early drug abuse prevention efforts. Therefore, NIDA-supported research aims to develop and test new age-appropriate behavioral HIV risk-reduction interventions that start with the youngest age groups and "grow" along with them. NIDA is supporting initiatives aimed at developing youth- and community-based HIV prevention programs designed specifically for urban youth, a population that is considered particularly

Sidebar 21

Interactive "Video Doctor" Approach Shows Promise for Reducing Drug Use and HIV Risk Behaviors

A novel "video doctor" intervention in primary care settings reduced risky behaviors among HIV-positive patients. Using computer simulation, an actor-portrayed physician engaged patients in a confidential "face-to-face" discussion about their behaviors. The intervention group reported significantly reduced drug use, risky drinking, and unprotected sex, an effect that persisted at the 6-month followup.



Why it's important: Such interventions could provide a comparatively low-cost means of reaching and teaching patients and may be an important addition to risk reduction efforts in routine clinical practice.

Source: Gilbert P. et al., April 2008 – *PLoS ONE* 3(4): e1988.

vulnerable to drug abuse and HIV exposure. We continue to support research to develop innovative means of delivering prevention programs to various high-risk populations.

Secondary prevention efforts to reduce HIV risk behaviors

More attention needs to be given to strategies for how best to incorporate HIV education, testing, counseling, and referral into drug abuse treatment and outreach efforts. This direction requires that we identify and address barriers, including stigma and treatment access—both for HIV and drug abuse—that restrict the benefits associated with early HIV detection and linkage to care. It also requires finding creative new ways to reach and motivate patients (see Sidebar 21).

To assist in these efforts, NIDA is pursuing research on the best ways to integrate testing and counseling into drug abuse treatment settings in communities, among criminal justice populations, and in international regions hit especially hard by the epidemic. This includes efforts to advance the adoption of rapid-screen technologies. Screening for HIV in health care settings is as cost-effective as screening for other common diseases;[22] thus, it makes sense to incorporate screening among populations where HIV risk is higher than average. Individuals who learn they are HIV-positive can significantly reduce their risk behaviors and, when linked to HAART, become less efficient transmitters from the resulting reduction in viral load. Therefore, such screening would not only provide important health and survival benefits for those with HIV, but would also help mitigate the likelihood of HIV transmission to noninfected people.

In community treatment programs affiliated with NIDA's CTN and in the criminal justice system through our collaborative CJ-DATS initiative, NIDA plans to test HIV

rapid-screen technologies plus counseling to reduce risky sexual behaviors. To improve HIV outcomes for criminal justice populations before and after release, NIDA will test a new approach termed "Seek, Test, and Treat," which involves reaching out to high-risk, hard-to-reach groups who have not recently been tested *(seek)*, providing HIV testing *(test)*, and initiating, monitoring, and maintaining HAART therapy for those who test positive *(treat)*. It also involves providing drug abuse treatment, without which individuals may not comply with their antiviral medications. NIDA hopes this initiative will not only expand access to HIV testing for those in the criminal justice system, but will improve the provision and maintenance of HAART following community reentry, when treatment lapse and viral load rebound can heighten risk of HIV transmission.

3. What can be done to mitigate the health disparities associated with HIV/AIDS?

While all groups are affected by HIV/AIDS, not all are affected equally. Associated health disparities fall disproportionately on ethnic minorities, particularly African-Americans, who are at especially high risk for developing AIDS. Even though they comprise only 13 percent of the U.S. population, African-Americans accounted for approximately half of the total AIDS cases diagnosed in 2007.[23] Consequences have been particularly harsh on African-American women, who accounted for 68 percent of the female HIV/AIDS diagnoses from 2001 to 2004.[24] Focused research is needed to understand the factors leading to such disparities and to develop targeted interventions to reduce HIV/AIDS and its consequences.

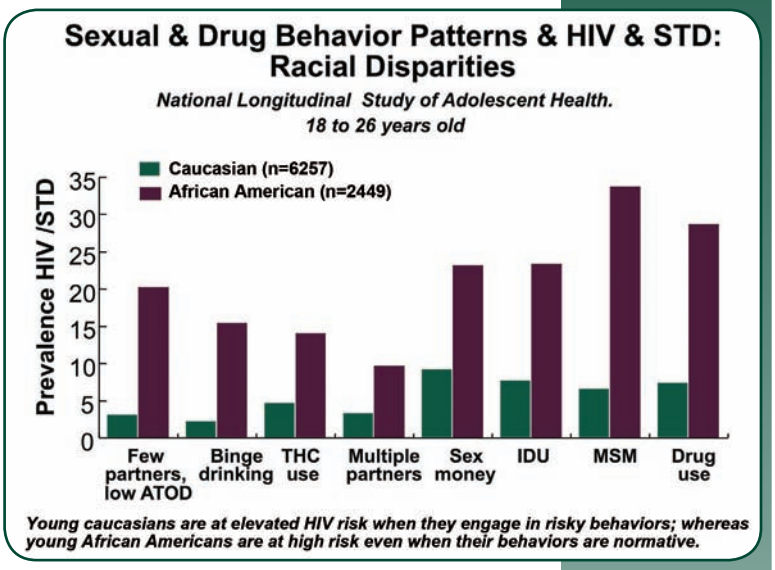
Studies are also needed to characterize the risk-mitigating roles of culture, family, and environmental factors. Indeed, recent research suggests that a strategy of targeting risk behaviors at the individual level may work for Caucasians but not for African-Americans, a population that appears to be at very high risk for STDs even if their behavior is normative[25] (see Sidebar 22).

In addition, although the rates of testing are approximately equal across ethnic groups, minority members tend to be tested late in the course of infection and frequently experience delays in being linked to treatment. This delay contributes to meaningful health disparities in terms of disease consequences. We hope to improve this situation by increasing knowledge of HIV treatment, which is currently less among African-Americans and Hispanics than among

Sidebar 22

Racial Health Disparities Go Beyond Individual Risk Factors

A study examining the relationship between race and sexually transmitted disease (STD)/HIV prevalence showed Caucasian young adults in the United States to be at elevated STD/HIV risk only when their behavior is high-risk; whereas African-American young adults are at high risk even when their behavior is normative.



Why it's important: This study suggests that factors other than individual risk behaviors appear to account for racial health disparities, which argues for population-level interventions.

Source: Hallfors et al., 2007 – *Am J Public Health* 97(1):125–132

Sidebar 23

NIDA Public Health Campaign Encourages Teens to 'Learn the Link' Between Drug and Alcohol Use and HIV

NIDA's multimedia "Learn the Link" campaign uses TV, print, and Web public service announcements to send the message to America's youth that using drugs and alcohol can have serious consequences, including HIV infection (http://hiv.drugabuse.gov/index.html). NIDA's new Spanish-language public service announcement is designed to reach Hispanic youth with culturally sensitive messages about HIV prevention.

Caucasians. NIDA is encouraging studies investigating the relationship of disease progression to treatment and service availability, awareness, and use by African-Americans and other minority groups.

Finally, aggressive outreach must be part of our strategy. Media campaigns must strive to inform high-risk subgroups of the prevalence of HIV infection (see Sidebar 23); reduce stigma associated with testing; and provide testing, counseling, and treatment services through nontraditional avenues.

For more information visit our Web site at: www.drugabuse.gov

4. How is NIDA's HIV research program contributing to global HIV prevention and treatment?

It is estimated that about 30 percent of new HIV infections worldwide (outside sub-Saharan Africa) stem from injection drug use.[26] Drug intoxication contributes an additional burden of new infections by facilitating risky sexual behaviors that can transmit HIV. In Eastern Europe and Central Asia, for example, intravenous drug use is driving 62 percent of new infections[27] and fueling a multidrug-resistant tuberculosis epidemic as well as higher rates of sexually transmitted diseases and HCV. Thus, our disease prevention strategies seek both to increase rates of HIV screening and to advance culturally relevant educational interventions that include information about drug abuse as a major vector for the spread of disease.

NIDA's multifaceted response works to better integrate international initiatives by region and to take advantage of the international research infrastructure funded by the National Institute of Allergy and Infectious Diseases. The latter aims to develop research that targets drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings (see Sidebar 24). These involve behavioral as well as medication interventions, such as the development of a heroin vaccine to help decrease injection transmission of HIV.

5. What are we doing to improve HIV/AIDS treatment and outcomes in drug abusers?

The development of HAART has enabled many HIV-infected individuals to experience remarkable improvements in their general health and quality of life. However, since drug abuse can interfere with the efficacy of HAART, an urgent need exists to better understand drug interactions, both between drugs of abuse and HAART and between prescribed anti-addiction medications and HAART. This interaction can decrease the efficacy of a given treatment.

Recent studies show that injection drug users can benefit from HAART therapy just as people do who do not inject drugs.[28] Nonetheless, nonadherence to antiretroviral therapy could impact treatment response or the development of resistance to HAART. Adherence can be particularly problematic for drug abusers with chaotic lifestyles, which can interfere with their ability to follow prescribed regimens. In addition, because HAART reduces viral load, some patients mistakenly believe that they do not need to adhere to the treatment regimen or that reduced viral load means elimination of the risk of transmitting HIV. This belief can, in turn, lead to complacency about risk behaviors and resumption of unsafe sex and injection practices. NIDA supports research to better assess the extent to which HIV-positive drug abusers adhere to their HAART medications, along with research to improve medication adherence among substance abusers.

Sidebar 24

Effective Drug Abuse Medications Being Adopted by HIV-Plagued Countries

Malaysia has lagged behind in the treatment of drug addiction and related disorders, even as it is coping with the second highest HIV prevalence rate among adult populations and the highest proportion of HIV cases from injection drug use. Historically, drug abusers were “rehabilitated” involuntarily in correctional facilities. This primarily criminal treatment approach had limited effectiveness, which led to widespread public dissatisfaction and the recent introduction of medications for addiction. These include naltrexone (1999), buprenorphine (2001), and methadone (2003).

Why it’s important: These drug treatment programs, rapidly embraced by the country’s medical community, have resulted in tens of thousands of opiate-dependent patients receiving medical treatment. A similar success story is starting to unfold in China as well. Such treatment success stories encourage other countries to establish their own drug treatment programs. Russia, for example, continues to prohibit the use of opioid agonist maintenance treatments.

Source: Mazlan et al., 2006 – *Drug Alcohol Rev* 25(5):473–478

Sidebar 25

Pharmacogenomics is Transforming our Ability to Predict Medication Effectiveness

The harnessing of increasingly powerful genomic tools and databases is already having an impact on our ability to predict response to medications and to deliver treatments. Continuous advances in the nascent field of pharmacogenomics are bound to greatly increase the efficacy of pharmacotherapeutics by matching a medication with the patients who, based on their genetic background, are most likely to benefit from it and suffer the least adverse effects.

Case in point: Abacavir (Ziagen) is an antiretroviral medication that works by slowing the spread of HIV infection in the body. Abacavir is not a cure and does not prevent the spread of HIV, but it is used in combination with other medications to treat HIV infection in patients with or without AIDS. Unfortunately, excitement over abacavir's therapeutic promise has been dampened by severe allergic reactions that can lead to death. However, recent studies have established that the serious and sometimes fatal hypersensitivity reactions are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*5701.

Why it's important: The research suggests that a pretreatment genetic screen for HLA-B*5701 can reduce the risk of hypersensitivity reaction to abacavir by close to 100 percent, enhancing the therapeutic potential of this promising medication.

Source: Mallal et al., 2008 – *NEJM* 358:568–579

Integrating treatment of HIV and HCV with drug abuse treatment services is one of NIDA's pivotal goals. This requires us to identify the organizational factors that limit the provision of coordinated drug abuse, HIV, HCV, and other treatment services; evaluate innovative approaches to achieve better treatment coordination; and determine the behavioral and social supports needed by drug abusers to engage in and adhere to HIV treatment regimens.

Supporting studies to examine conditions that result from HIV/AIDS infection and drug abuse

Because of HIV's ability to invade the brain, it is often complicated by central nervous system dysfunction. Before the advent of HAART, approximately 20 percent of those living with HIV eventually developed HIV-associated dementia (HAD),[29] characterized by a loss of mental functioning with notable

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motor deficits. HAART has reduced the prevalence of HAD; however, the prevalence of milder forms of neurological complications may be increasing because more people are living longer with the disease.[30]

Emerging evidence suggests a relationship between drug abuse (particularly stimulants) and accelerated or more severe nervous system complications of HIV (or neuroAIDS). Because HIV-positive drug abusers can suffer greater neurological complications, it is critical to better understand how drug abuse affects disease progression and pathology. NIDA is encouraging both animal and human studies examining the interactions between drugs of abuse and HIV with respect to neuropathological and neurobehavioral effects.

We are also interested in research tools that may provide information on latent viral infection in the brain. Animal models are valuable for examining the basic mechanisms of HIV-associated disease progression and resulting brain dysfunction in the context of substance abuse. A broad range of anticipated studies will increase collaboration among researchers in multiple areas, including drug abuse, virology, neurobiology, and immunology.

What Is NIDA's Vision of the Future?

Our ultimate vision is the eradication of HIV/AIDS throughout the world. This would require the development and worldwide distribution of effective prevention strategies (behavioral interventions and, perhaps, a vaccine) and therapeutic interventions. We will also ensure that drug abusers are represented in trials for all types of interventions as we strengthen our national collaborative network to conduct clinical trials. Expected areas of research concentration include promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected patients and those at risk of infection. Further, through pharmacogenomic studies, we expect to be able to tailor therapies to minimize adverse reactions and drug interactions (see Sidebar 25). And, given that drug abuse may play a unique role in exacerbating neurologic and psychiatric consequences, the future should see significant efforts applied to understanding their pathogenesis and to developing better therapies for addressing associated impairments. Finally, we envision adapting and translating interventions proven effective in this country to other areas of the world.

IV. CROSS-CUTTING PRIORITIES

Several additional priority areas span NIDA's portfolio and contribute to our overall mission to prevent or reduce drug abuse and addiction. These areas are highlighted below.

Major Goals

1. To **foster research on other health conditions** that may inform, influence, or interact with drug abuse and addiction (e.g., pain, compulsive behavioral disorders).
2. To **decrease health disparities** related to drug addiction and its consequences.
3. To **educate a variety of audiences** (e.g., criminal justice, medical, and educational systems in the community; media; and legislators) about the science underlying drug abuse.
4. To **train and attract new investigators with diverse experiences**—including those from minority or disadvantaged backgrounds—and to actively recruit chemists, physicists, bioengineers, and mathematicians to conduct translational research on drug abuse.
5. To **promote collaborative international research activities** that address nicotine addiction, HIV/AIDS, and emerging trends, as well as training and dissemination of science-based information on drug abuse.

NIDA has built a solid foundation designed to achieve these goals by nurturing interactions with different NIH Institutes, agencies, and other stakeholders, and by supporting research and outreach that respond to the following five questions:

1. What are other health conditions that interact with drug abuse and addiction?

Multiple health conditions share important features with drug abuse and addiction. Thus, research in these areas may inform and impact drug abuse research and vice versa. For example, the brain circuitry involved in natural rewards that motivate us to engage in everyday survival behaviors, such as eating, overlaps with the neural circuitry engaged by addictive drugs to reinforce drug taking. These brain circuits are part of normal adaptive processes; and when challenged with powerful reinforcers such as drugs of abuse or fattening foods, these circuits can bring about a loss of control and subsequent addiction or obesity, respectively.

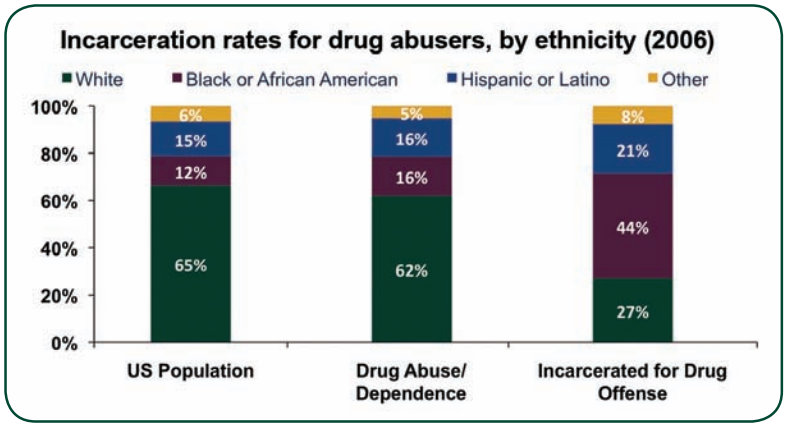
Understanding the biological underpinnings of how addiction and other independent or co-occurring disorders (e.g., compulsive behavioral disorders, pain, etc.) interrelate may give us insight into more effective treatment and prevention approaches for these disorders. NIDA continues to encourage research to explore these linkages from several perspectives—basic biology, epidemiology, prevention, and treatment—with the hope of leveraging the science from one disorder to inform another.

Compulsive Behavior Disorders. A number of mental disorders have hallmark symptoms (e.g., compulsive behaviors and obsessive thinking) similar to those of addiction, with obsessive-compulsive disorders (OCDs) and eating disorders among the most common. Their shared symptomatology may reflect similarities in the brain regions affected by the disorder. For example, the orbitofrontal cortex, which has been associated with the subjective experience of drug craving in addicted subjects, has also been implicated in OCD behaviors. Similarly, reduced brain activity of dopamine, a naturally occurring substance that regulates feelings of pleasure, has been implicated both in drug addiction and in obesity, which may reflect a common motivational deficit, but with food instead of drugs. Thus, NIDA seeks to understand the common etiologies of these disorders at the genetic, molecular, cellular, and circuit levels.

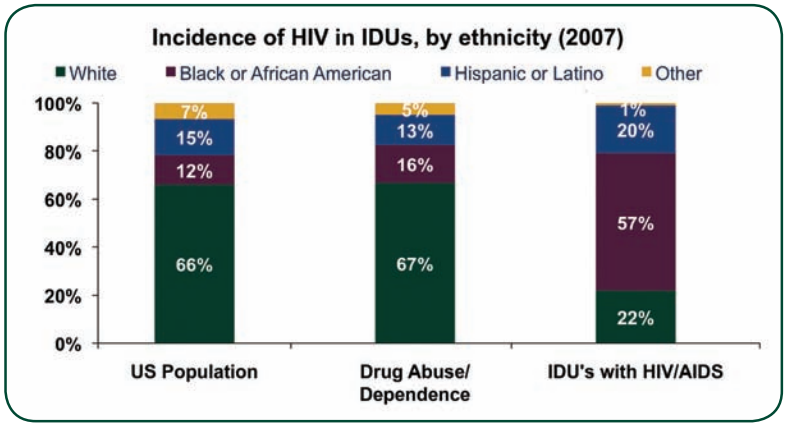
Pain. For the more than 50 million Americans with chronic pain, prescription opioid pain medications are a necessary and useful treatment. However, opioid treatment can produce negative health consequences, such as physical dependence and addiction. The prevalence of chronic pain and how to prevent, reduce, and treat its negative health consequences are not well understood. NIDA continues to examine the factors (including pain itself) that predispose or protect pain patients from opioid abuse and addiction. We also are pursuing ways to prevent opioid abuse when treating pain, including supporting development of novel pain medications with reduced or no abuse and addiction liability.

Figure 3

Incarceration rates and HIV incidence in IDUs are disproportionately higher in ethnic minorities



(A)



(B)

Ethnic Breakdown of (A) Incarceration Rates for Drug Abusers, 2006, and (B) Incidence of HIV in IDUs, 2007

Sources: (a) U.S. Census Bureau, Population Estimates Program, 2006; NSDUH, 2007; U.S. DOJ, BJS, Prisoners in 2006, Bulletin (b) U.S. Census Bureau, Population Estimates Program, 2007; NSDUH, 2008; CDC, HIV/AIDS Surveillance in Injection Drug Users (through 2007)

2. How is NIDA addressing health disparities related to drug abuse and its consequences?

The pattern of addictions and the burden of disease are not shared equally among members of our population. For example, the disproportionate abuse of methamphetamine among American Indians and Alaskan Natives—higher than any other subgroup—prompts a need for targeted interventions that can effectively reach these groups. However, contrary to a common stereotype, overall rates of drug abuse among racial and ethnic minorities, particularly African-Americans and Hispanics, are similar to rates in the general population. Nonetheless, these groups incur *greater medical and social consequences* of their drug use than Whites (see Figure 3), including involvement with the criminal justice system and greater disease vulnerability (see section III, "HIV/AIDS").

Sidebar 26

NIDA-Developed Materials on Drug Abuse Widely Used in School Curricula

Brain Power! The NIDA Junior Scientist Program is designed to take students through a step-by-step exploration of the scientific process and how to apply it to learn about the brain and the effects of drugs on the nervous system and body. Such materials have already been developed for elementary and middle school grades K-9.

NIDA has developed a separate Strategic Plan on Reducing Health Disparities that includes research, infrastructure and capacity building, and community outreach components (for more details, see http://www.drugabuse.gov/StrategicPlan/HealthStratPlan.html). Brief highlights of our ongoing and planned activities follow:

- Epidemiologic data clearly show that minority groups differ in drug use patterns, preferences, accessibility, and risks. Thus, research is needed to look at factors that convey protection or risk across different ethnic and age categories. Studies must examine the role of culture, religion, ethnic identity, family, peer, and environmental/community-level factors in drug initiation and drug abuse trajectories.
- We must also better understand the racial/ethnic implications of genetic variation that modifies the neurotoxicity of different drugs, as well as the neurobiological processes underlying tolerance, dependence, and relapse. Pharmacokinetic studies have revealed distinct differences in some ethnic populations' ability to metabolize different drugs— this affects sensitivity to the drugs' or medications' pharmacological effects.

3. How does NIDA "get the word out" about the many facets of drug abuse and addiction to better prevent it?

As the supporter of most of the world's research on the health aspects of drug abuse and addiction, NIDA is uniquely positioned to educate the public and displace long-held mistaken beliefs about drug abuse with scientific evidence about drugs and addiction.

Because most drug use begins during adolescence, it is vitally important that youth are informed of drugs' effects on their developing brains and bodies to help them choose not to use drugs.

- NIDA continues to develop and update science-based educational materials for grades K–12 (and beyond) and disseminate them for free to schools (see Sidebar 26). By exposing children of all ages to neurobiology and drug education in fun, age-appropriate, and relevant ways, we hope to prevent them from using drugs and also spark their interest in scientific careers.
- NIDA is updating the design of our "NIDA for Teens" Web site (http://teens.drugabuse.gov), aimed primarily at educating middle school adolescents ages 11–15 (as well as their parents and teachers) on the science behind drug abuse. We have enlisted the help of teens in develop-

ing this site to ensure that the content addresses appropriate questions and timely concerns. Interactive games are among the recent additions.

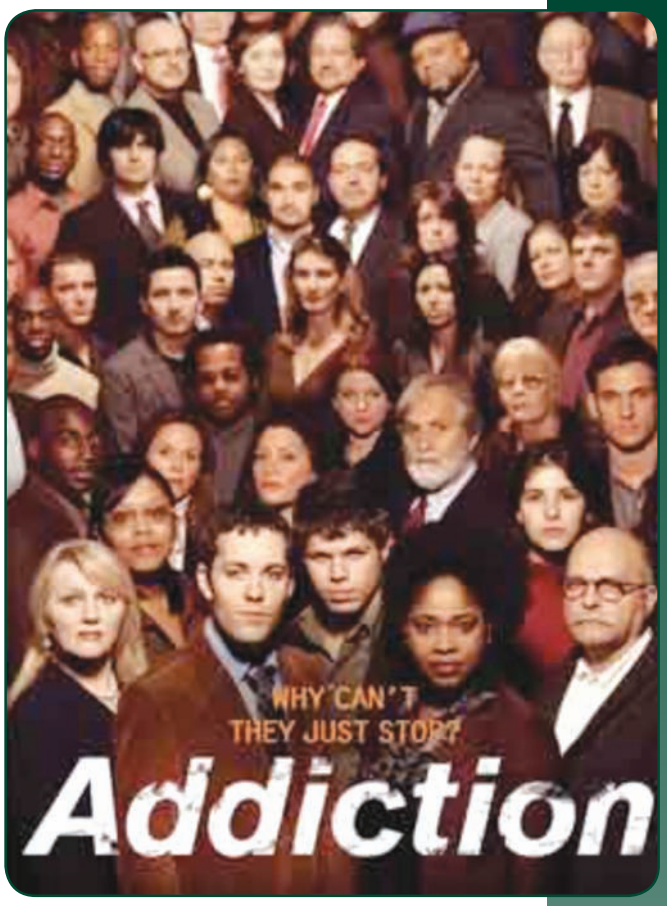
- NIDA intends to expand our foray into new media. We have begun a blog aimed at teens and use it as a two-way communications tool, responding to the many comments it elicits. NIDA has also started "tweeting" and continues to place short, topical videos on YouTube, as well as host a MySpace page on the link between drugs and HIV. As an expansion of our annual "Chat Day," where students from across the country learn the facts about drug abuse from NIDA scientists, NIDA plans in 2010 to launch "National Drug Facts Week," with Chat Day at its center. Other events will take place nationwide to arm teens with information that can help them make healthy decisions.

- NIDA continues to design and develop public information and education campaigns, as well as materials on drug abuse and addiction for a variety of audiences. For example, we are building on the success of our award-winning public service announcement on the link between drug abuse and HIV/AIDS risk, and continue to take advantage of mainstream and emerging media vehicles such as HBO broadcasts (see Sidebar 27) and Internet chats.

4. How does NIDA help ensure a continuing supply of well-trained scientists equipped to conduct high-impact drug abuse research?

An important part of NIDA's mission is to promote an ongoing source of trained clinicians and clinical research scientists from diverse backgrounds who can conduct research on various aspects of addiction, including HIV/AIDS, health disparities,

Sidebar 27



NIDA Works with HBO and Other Partners to Present 'Addiction' Documentary

NIDA partnered with HBO, NIAAA, and the Robert Wood Johnson Foundation on a groundbreaking and Emmy Award–winning documentary called *Addiction*. The feature-length film is part of a multimedia public health campaign that also included a Web site, book, and community outreach activities. The goal of this project, launched in 2007, was to help Americans understand addiction as a chronic yet treatable brain disease through spotlighting promising scientific advancements and personal testimonials. Circulation of these materials has reached tens of millions.

Sidebar 28

Research Training Programs Ensure Continuing Supply of Investigators Studying Drug Abuse and Addiction

NIDA offers a strategic set of funding mechanisms to support the development of research scientists through various stages of their careers. These awards are designed to ensure that scientists of the very highest caliber are available in adequate numbers and in the appropriate research areas and fields to meet the Nation's need for drug abuse and addiction research.

and other issues critical to drug abuse research. We also need to reach across domains to engage scientists from fields such as mathematics, bioengineering, and physics to apply their knowledge to the study of drug abuse and addiction.

To sustain our research infrastructure, NIDA continues to support training initiatives that support a broad range of scientists, from diverse backgrounds, both within and across scientific boundaries (see Sidebar 28). The following briefly summarize several initiatives:

- **National Research Service Awards (NRSA)** to institutions and individuals, including the predoctoral diversity awards. NIDA currently funds more than 50 institutional training sites for both predoctoral and postdoctoral fellows nationwide.
- **Career Development (Mentored K) Awards** for emerging scientists or those changing career trajectories to study drug abuse and its related consequences (e.g., HIV/AIDS). These include the **Mentored Clinical Scientist Development Award (K08)** and **Mentored Patient-Oriented Research Career Development Award (K23)**, designed to provide "protected time" for clinically trained individuals to participate in an intensive, supervised training program in biomedical or patient-oriented drug abuse research. The **K25 Award** is for quantitative scientists interested in applying their expertise to research related to drug abuse or HIV/AIDS.
- **Pathway to Independence (PI) Award Program (K99/R00)**, designed to augment existing programs that provide mentored research and career development experiences for new investigators. This program provides a unique opportunity for highly promising postdoctoral scientists to obtain support for both the initial 1–2-year mentored phase and the later independent phase, before applying for an NIH R01 grant.
- **Dissertation Awards (R36)** for specific drug abuse topic areas; **Research Education Awards (R25)** for curriculum and program development; and **Small Grant Programs (R03)** to allow researchers new to a field to obtain data for developing research programs in needed areas, such as imaging, AIDS, behavioral research, and chemistry.

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Diversity Supplements and other training experiences are available for minority students, beginning in high school and continuing through their postdoctoral phase and beyond.

- **NIH Loan Repayment Programs**, a vital component of our Nation's efforts to attract health professionals to research careers, are reflective of NIDA's commitment to developing clinical and pediatric researchers.
- **Diversity-Promoting Institutions' Drug Abuse Research Programs (DIDARP)** include grants and cooperative agreements, aimed at building research capacity at institutions serving minority populations.

5. What are NIDA's strategic international priorities?

Since the early 1990s, the NIDA International Program has worked to create local, regional, national, and international networks that advance scientific knowledge through research. The International Program extends our mission through building up other countries' research capacities to address the public health impact of drug abuse and addiction by creating opportunities for collaboration, training, and scientific exchange, and disseminating that knowledge to scientists, treatment providers, and policymakers around the world. These efforts help to translate our domestic successes in curtailing drug abuse and related consequences, such as with HIV/AIDS, to other countries, and allow us to learn from their strides in disease prevention and eradication.

Stemming the global spread of drug abuse-related HIV is a top NIDA priority for our international efforts (see section III, question 5), and one for which international collaboration is vital. Through our International Program, NIDA is facilitating collaborations with partners in about 20 countries, developing research networks and tailoring studies to meet local needs and conditions. In addition, NIDA is to become a Collaborating Center of the World Health Organization, formalizing the long-standing cooperation between the two agencies.

Among the top priorities are reducing nicotine addiction and gaining knowledge about new drug abuse trends internationally. While smoking prevention and cessation programs have contributed to a significant decline in the United States, the rest of the world continues to experience high rates of smoking and associated illnesses. NIDA continues to work cooperatively with other countries to reduce smoking worldwide and to share the latest research findings by facilitating collaboration with U.S.-based resources.

As new drug abuse threats emerge around the world, we identify and address them. NIDA has identified five research priorities for which we are advancing international collaborative efforts to set standards, design comparative research protocols, and improve data collection on core variables—all to ensure a scientific approach to the study of these priorities. These five priorities are (1) linkages between HIV/AIDS and drug abuse; (2) adolescent and prenatal tobacco exposure; (3) inhalant abuse; (4) methamphetamine; and (5) drugged driving.

As part of efforts to increase the capacity and capability of affected countries, NIDA's International Program works closely with the Fogarty International Center, whose mission is to facilitate international cooperation throughout NIH. In collaboration with the Fogarty International Center's AIDS International Training and Research Program, we support joint research training and infrastructure-building programs through partnerships with U.S.-based academic centers.

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