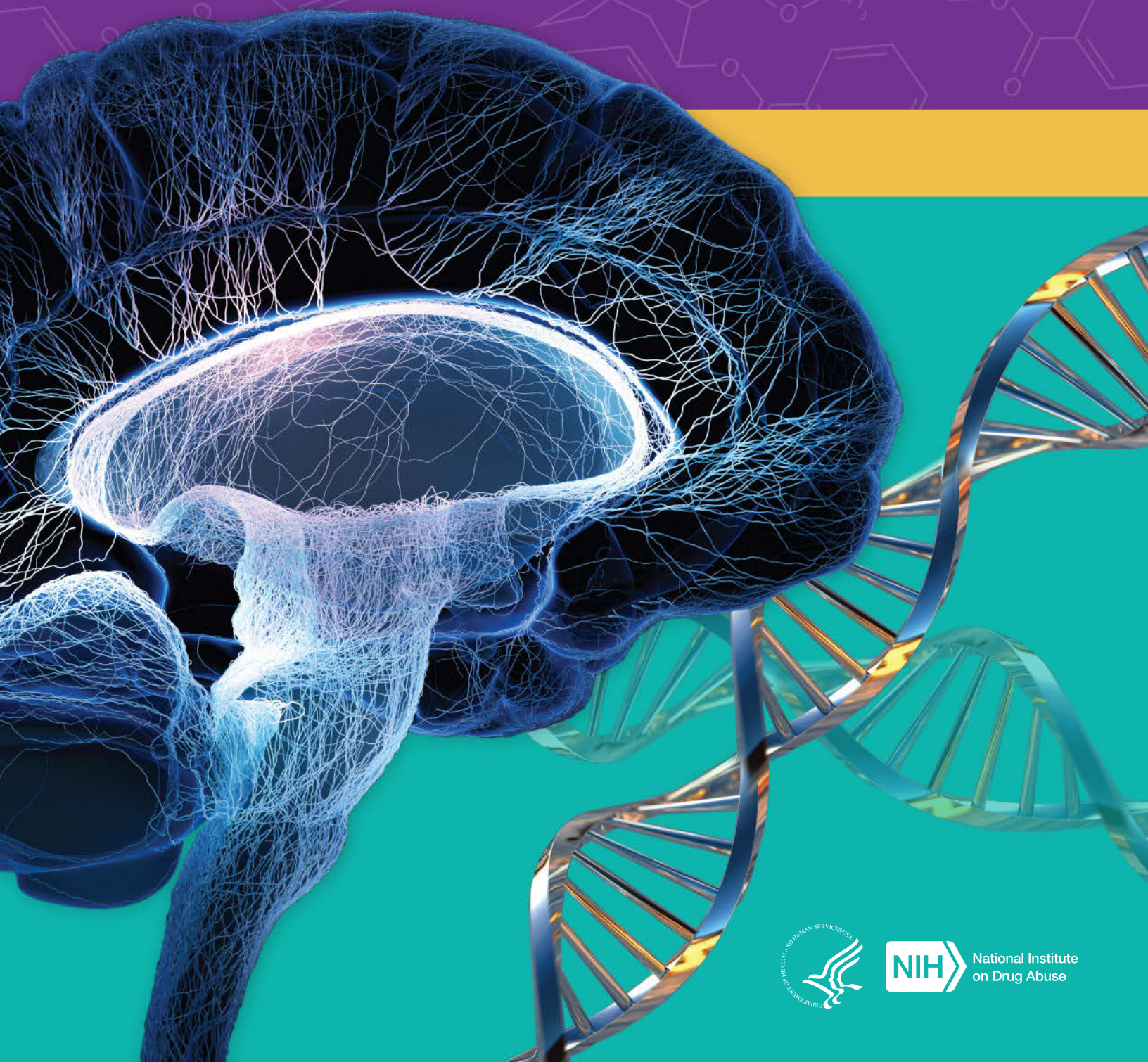
2016–2020
NIDA STRATEGIC PLAN
Advancing Addiction Science



National Institute on Drug Abuse

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Director's Message

As the lead federal agency supporting scientific research on drug use and its consequences, the mission of the National Institute on Drug Abuse (NIDA) is to advance science on the causes and consequences of drug use (including nicotine) and addiction and to apply that knowledge to improve individual and public health. Over the last four decades, NIDA-supported research has revolutionized our understanding of drug use and addiction, driving a new understanding of the neurobiological, genetic, epigenetic, social, and environmental factors that contribute to substance use disorders. These advances have helped to transform how drug use and addiction are conceptualized. Society's responses to drug use have often been shaped by the misconception that people with addictions are morally flawed and lacking in willpower, resulting in an emphasis on punishment rather than prevention and treatment. Today, thanks to groundbreaking scientific discoveries about the brain and its role in addiction, society's views are changing in ways that will enable us to respond more effectively to the problem.

Drug use and addiction represent major public health challenges in our nation. In 2014 alone, more than 47,000 Americans died as a result of an unintentional drug overdose,* and the past few years have seen rapid increases in babies born with neonatal abstinence syndrome, an unprecedented outbreak of HIV, an increasing prevalence of hepatitis C, and new synthetic drugs flooding the market. The combined consequences of drug use and addiction take an enormous toll, creating individual suffering, lost productivity, and stress and heartache for family and friends. And while research has identified many evidence-based prevention and treatment strategies, there remains a frustrating "bench-to-bedside gap" that persists in our field—a failure of dissemination and adoption of effective interventions so they can actually improve the lives of individuals, families, and communities.

Despite these challenges, this is a time of great opportunities. The last few years have seen tremendous advances in technologies with applications in research, including gene sequencing and manipulation, increasingly sensitive imaging technologies, mobile health tools, and electronic health records. A shift in culture is promoting open access and data sharing to allow diverse data sets to be broadly accessible to researchers. Advances in information technologies and analytics capabilities are producing unprecedented capacity to integrate and analyze these data and enabling novel research into the complexity of a disorder that is driven by the dynamic interactions of diverse biological, social, environmental, and behavioral mediators. In addition, national investments in basic research, including President Obama's BRAIN and Precision Medicine Initiatives, have us poised to accelerate neuroscience, genetics, and health services research. In parallel, ongoing health care and criminal justice reform efforts, as well as changing state drug policies (e.g., legalization of marijuana for medicinal or recreational use) are creating new opportunities for policy research on how to maximize public health benefits and increase access to prevention and treatment services. Finally, increased public concern related to the ongoing opioid overdose epidemic is fostering widespread collaborative efforts to address this public health crisis. This plan reflects our commitment to leverage these opportunities to drive scientific advances that will help address current public health needs related to substance use and addiction while providing transformative solutions for the future.

Updating our strategic plan provided an opportunity to step back and reflect on the scientific and technological advances of the last few years and to re-envision what science can accomplish over the next 5 years. Our main goals throughout this process were to undertake an inclusive and thoughtful approach to developing our strategic priorities that emphasized innovative approaches to addressing scientific challenges. Developing this plan was a collaborative effort incorporating guidance from the National Advisory Council on Drug Abuse, scientific and clinical experts, stakeholder organizations, and the public.

This plan outlines our broad goals across basic science, prevention, treatment, and public health; identifies four priority focus areas that we believe present unique opportunities to be leveraged over the next 5 years; and reflects a flexible, dynamic approach that will allow us to adapt to new scientific and technological advances and changing public health needs, and to take advantage of scientific opportunities as they arise.

While exploring all of the exciting new opportunities in our field, we considered many real-world practicalities. How do we balance the needs of people suffering with substance use disorders right now with longer-term investments in basic research at a time when NIH has lost 22 percent of its purchasing power? How can we ensure that treatment interventions developed through NIDA-supported research can be sustainably implemented in today's health care landscape? How do we encourage more research that reflects the complexities of substance use disorders in the real world, including polydrug use, physical and mental health comorbidities, changing risks across the lifespan, and the impacts of poverty and social inequality, among others? This plan aims not only to expand our knowledge of the effects of drug use and addiction on the individual, the community, and society, but to increase the traction of what is learned by effectively translating new findings into real-world interventions, reaching a greater number of people and getting the most out of limited prevention and treatment resources.

The NIDA Strategic Plan for 2016 to 2020 reflects the optimism we feel at this juncture about our prospects for advancing addiction science as we enter the second half of the decade. I want to thank everyone who contributed their thoughts and expertise along the way. I hope that you will continue to work with us to achieve these ambitious goals.

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

*This number represents all overdose deaths that were attributed to drugs based on ICD-10 codes for prescription drugs (T36-T39, T40.2-T40.4, T41-T43.5, and T43.8-T50.8), prescription opioid pain relievers (T40.2-T40.4), benzodiazepines (T42.4), antidepressants (T43.0-T43.2), heroin (T40.1), and cocaine (T40.5).

Executive Summary

Drug use and substance use disorders (SUDs) affect millions of Americans and impose enormous costs on our society. In 2014, nearly 27 million people in the United States were current users of illicit drugs or misused prescription drugs, and almost 67 million people smoked or used other harmful tobacco products.[1] NIDA's mission as the lead federal agency devoted to research on the health effects of drug use is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health through:

- Strategically supporting and conducting basic and clinical research on drug use (including nicotine), its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved
- Ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disorder

The NIDA Strategic Plan for 2016 to 2020 outlines our plan for fulfilling this mission through the end of this decade. The strategic priorities outlined in this plan are intended to leverage the vast array of new tools and technologies at our disposal for studying the biological, environmental, behavioral, and social causes and consequences of SUDs and to help researchers integrate and analyze the unprecedented amounts of information being generated in the era of Big Data and precision medicine.

SUDs are complex disorders involving disruption of brain circuits involved in reward, decision-making, learning, and self-control. They are mediated by complex biological, social, environmental, and developmental factors that dynamically interact to influence risk, trajectory, and outcomes. Understanding this complexity will require drawing upon multiple disciplines across biomedicine, including neuroscience, genetics/epigenetics, behavioral and social sciences, development research, and information sciences. Technological advances over the past several years in neuroimaging, optogenetics, gene editing technology, epigenomics, and other innovations are giving us the ability to probe this complexity in entirely new ways, enabling researchers to deepen our understanding of the brain and its responses to drug use in ways that would have been unimaginable even a decade ago.

Over the next 5 years, NIDA will harness the new opportunities presented by scientific and technological advances, changes to the health care landscape, ongoing criminal justice reform, and a growing public attention on drug-use-related issues to increase the impact of our research and improve the translation of new findings into real-world interventions that can maximize limited resources and reach more people.

While advancing basic and clinical research, NIDA will continue to prioritize science that is relevant to the most pressing health challenges in our nation, such as the prescription opioid and heroin overdose epidemic, the slow adoption of evidence-based prevention and treatment interventions, new synthetic drugs flooding the market, and the spread HIV resulting from drug use.

The strategic priorities outlined in this plan are intended to address the full breadth of addiction science (from basic to translational, clinical, and health services research) and to encompass drug use ranging from occasional use to SUDs of all severity levels (from problematic use to addiction). NIDA's strategic priorities for the next 5 years are designed to increase our understanding of the basic science of the brain as it relates to behavior and translate what is learned into more effective prevention and treatment interventions that can ultimately reduce the negative impacts of drug use and SUDs on society.

To achieve this mission, NIDA will focus on advancing the following high-level strategic goals centered on *basic science, prevention, treatment,* and *public health,* respectively:

GOAL 1 **Identify the biological, environmental, behavioral, and social causes and consequences of drug use and addiction across the lifespan.** Recent technological advances now enable scientists to study the multiple causal factors for substance use and addiction and how they interact to influence vulnerability for initiation of drug use, escalation, and transition between the stages of SUDs. They also enable us to study how drug use and SUDs impact an individual's health, environment, behavior, and social interactions. The objectives of this goal include:

- **Objective 1.1:** Characterize the genetic, neurobiological, environmental, social, and developmental factors that mediate risk and resilience for drug use and addiction
- **Objective 1.2:** Identify the factors that influence drug use trajectories
- **Objective 1.3:** Establish the effects of drug use, addiction, and recovery on genes, molecules, cells, brain circuits, behavior, and health across the lifespan
- **Objective 1.4:** Identify the bidirectional effects of drug use and common comorbidities

GOAL 2 **Develop new and improved strategies to prevent drug use and its consequences.** We now have considerable evidence that SUDs can be prevented through interventions targeting both individual and community risk and protective factors. To design targeted prevention approaches and deliver them to the individuals and communities that could most benefit, NIDA will support research that leverages the accumulating basic science on mechanisms underlying risk for drug use and addiction and that builds on our growing experience evaluating implementation of prevention interventions. Thus for this goal, NIDA will support research on the following objectives:

- **Objective 2.1:** Determine the mechanisms that underlie individual risk and resilience for addiction and common comorbidities
- **Objective 2.2:** Develop and test innovative prevention interventions that target mechanisms underlying risk factors
- **Objective 2.3:** Develop and test strategies for effectively and sustainably implementing evidence-based prevention interventions
- **Objective 2.4:** Develop and test novel strategies for preventing prescription opioid misuse and addiction

GOAL 3 **Develop new and improved treatments to help people with substance use disorders achieve and maintain a meaningful and sustained recovery.** Despite our rapidly increasing understanding of the biology of addiction, the range of available treatment options for most SUDs is limited. However, there are many promising approaches that may be added to our treatment toolkit in future years. These include new medications, behavioral therapies, vaccines/immunotherapies, biofeedback, and manipulation of brain activity using transcranial magnetic stimulation or electrical deep brain stimulation. To facilitate the development of innovative intervention strategies, NIDA will support research to:

- **Objective 3.1:** Develop and test novel treatments based on the science of addiction
- **Objective 3.2:** Develop and test metrics for measuring the quality and efficacy of treatment
- **Objective 3.3:** Identify biomarkers that predict response to treatment and risk for relapse
- **Objective 3.4:** Develop and test strategies for effectively and sustainably implementing evidence-based treatments

GOAL 4 **Increase the public health impact of NIDA research and programs.** Many people in the United States need help for SUDs right now and cannot wait for new treatments. Approximately 7.1 million Americans are dependent on or abuse illicit drugs, yet only about 15 percent receive treatment for their disorder.[1] The good news is that this is an ideal time to address the "bench-to-bedside gap" and advance SUD treatment across the Nation. The Affordable Care Act, the Excellence in Mental Health Act, and laws requiring parity of insurance coverage for SUD and other behavioral health treatments will significantly expand access to needed services and create new incentives for integrating SUD care into the general health care system. These changes create an unprecedented opportunity to advance SUD treatment in this country. To promote science-informed decision-making to improve Americans' health, NIDA will:

- **Objective 4.1:** Determine the impact of drug use and addiction on individuals, families, peers, and society
- **Objective 4.2:** Assess the impact of federal-, state-, and systems-level policies related to drug use and substance use disorders on public health and well-being
- **Objective 4.3:** Increase strategic partnerships with the community to improve dissemination and implementation of evidence-based research findings into policy and practice

PRIORITY FOCUS AREAS

In addition to these four goals, NIDA has identified four ***priority focus areas*** presenting unique opportunities to leverage during the next 5 years. These areas include:

1. **Understanding the complex interactions of factors influencing drug use trajectories.** NIDA will capitalize on emerging technologies and discoveries to facilitate integration and analysis of diverse data sources, including genomic, epigenomic, behavioral, neurobiological, environmental, and other phenotypic data associated with the stages of drug use and addiction.
2. **Accelerating development of treatments.** NIDA will translate basic knowledge of the molecular pathways and brain circuits involved in SUDs to develop new approaches that modulate specific targets and networks, accelerating development of new therapeutics for SUDs. NIDA will also leverage existing safety profiles and pharmacology data to lower development costs and shorten the timeline for obtaining approval from the U.S. Food and Drug Administration.
3. **Addressing real-world complexities.** NIDA will conduct research to better understand the barriers to successful and sustainable implementation of evidence-based practices and develop implementation strategies that effectively overcome these barriers to ensure that all populations benefit from the Nation's investments in scientific discoveries.
4. **Advancing bidirectional translation.** NIDA is fostering stronger collaborations across basic and clinical researchers, in part through a recent reorganization of the Institute's organizational structure[2], to integrate and coordinate human and animal research on the substrates of addiction across scales—from molecular to societal—and across the trajectory—from initiation to recovery.

The strategic plan also highlights a number of exciting initiatives that will transform the science of drug abuse and impact a wide range of other health fields over the coming years, including:

- ***The Adolescent Brain Cognitive Development (ABCD) study***, a collaborative 10-year longitudinal imaging study to understand the role of environmental, social, and genetic factors in health, behavior, and life outcomes, including substance use and addiction
- ***The Addictome project***, to harness Big Data for addiction science
- ***JJ-Trials***, an implementation science initiative to prevent and treat SUDs in the criminal justice system
- ***Avenir Awards***, to support innovative, high-risk, high-reward research
- ***The NIDAMED Initiative***, to train health care providers to prevent, identify, and treat SUDs
- ***The PATH Study***, a collaborative, longitudinal cohort study on tobacco use behaviors, attitudes, beliefs, exposures, and related health outcomes

Drug use and addiction remain major health problems in our country, but it is a time of optimism in the field: New technologies, meaningful changes to the health care system, and increased awareness of SUDs as brain disorders are just now providing new opportunities for addressing the problem. As NIDA enters 2016, we look forward to capitalizing on these trends and exerting a profound and lasting impact on drug-use- and addiction-related health outcomes across the country.

NIDA's Mission

NIDA is the lead federal agency supporting scientific research on drug use and its consequences. Our mission is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health through:

- Strategically supporting and conducting basic and clinical research on drug use (including nicotine), its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved
- Ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disorder

The strategic priorities outlined in this plan are intended to address the full breadth of complexity related to drug use and its health and social consequences across the spectrum, from occasional use to problematic use and substance use disorders (SUDs). SUDs include both behavioral and neurobiological components that are strongly influenced by diverse environmental and social factors. Advances in research technologies and informatics are helping us to understand the complex mediators of SUDs in unprecedented ways. NIDA's strategic priorities for the next 5 years are designed to leverage these advances to translate our increasing understanding of the basic science of the brain and behavior into more effective prevention and treatment interventions that can ultimately reduce the negative impacts of drug use on society. To achieve this mission, NIDA will focus on advancing the following high-level strategic goals:

GOAL 1: Identify the biological, environmental, behavioral, and social causes and consequences of drug use and addiction across the lifespan

GOAL 2: Develop new and improved strategies to prevent drug use and its consequences

GOAL 3: Develop new and improved treatments to help people with substance use disorders achieve and maintain a meaningful and sustained recovery

GOAL 4: Increase the public health impact of NIDA research and programs

Introduction

As of 2014, nearly 27 million Americans were current users of illicit drugs, and almost 67 million Americans were current users of tobacco products.[1] Drug use and substance use disorders (SUDs) represent major public health problems that affect millions and place enormous burdens on society. The accumulated costs to the individual, the family, and the community are staggering and arise as a consequence of many direct and indirect effects, including compromised physical and mental health, loss of productivity, reduced quality of life, increased crime and violence, abuse and neglect of children, and health care costs. The combined yearly economic impact of these factors is estimated at $193 billion for illicit drug use and $295 billion for tobacco use.[3,4]

The profound complexity of human behavior and of behavioral disorders like SUDs requires a deeper understanding of the fundamental processes that give rise to them. How do biological and environmental mechanisms influence behavior, and how does the disruption of these mechanisms lead to addiction? A more detailed understanding of the links between genes, brain structure and function, and behavior—in both health and disease—will lead to more personalized and precise interventions to prevent and treat addiction. For example, we now have an unprecedented capacity to screen for thousands of genetic variations and catalog how they affect addiction risk by influencing brain maturation and architecture, brain circuit function, and behavioral patterns.[5] NIDA-supported researchers are using whole-genome sequence analysis to identify genes that modulate addiction risk and exploring how environmental factors—such as early-life stress and peer influences—can affect the expression of those genes (via epigenetic modifications) to either increase or decrease risk across the lifespan and across different stages of the addiction trajectory.

Stunning technological advances, particularly in the field of neuroscience, are allowing scientists to ask questions that were unimaginable only a few years ago. Ever more powerful tools in neuroimaging, transgenics, opto- and chemogenetics, molecular modeling, and bioinformatics are supporting the systematic identification of genetic, environmental, and neural circuit variables that influence an individual's risk for drug use and addiction. For example, clustered regularly interspaced short palindromic repeats (CRISPR), a powerful new gene editing technology, is poised to revolutionize biomedical research.[6] This technology is inexpensive, fast, and easy to use and has rapidly been adopted by researchers across the country to understand the role of specific genetic variations in complex processes including addiction. This research will improve our overall understanding of the various phases of addiction and identify targets for new therapies that could ultimately revolutionize our prevention, diagnosis, and treatment capabilities. It will also inform our understanding of the role of genetics in the susceptibility to adverse medical consequences associated with drug use.

Recent advances in clinical technologies are also presenting new opportunities for research. Technologies that can target and modulate brain activity, including transcranial magnetic and electrical stimulation and electric deep brain stimulation, as well as neurofeedback techniques are being explored to translate new knowledge about the underlying neurobiology of addiction into novel diagnostic techniques and personalized therapeutic approaches.

NIDA is also committed to harnessing recent advances in health care technologies. Recent federal efforts[7] have led to a rapid increase in the adoption of electronic health records by health care providers and spurred advances in other health information technologies, including telehealth and mobile health applications. These technologies have the potential to revolutionize behavioral health care and related research. The synergistic implementation and deployment of these technologies with Big Data mining will allow researchers to draw on unprecedented amounts of health information, transforming our understanding of how individual-level factors contribute to health and disease and ushering in a new era of personalized medicine. It will also provide a better understanding of how substance use and SUDs influence outcomes for diverse health conditions.

To understand the causes and trajectories of SUDs, it is critical to investigate the biological, medical, social, and economic factors that contribute to them. NIDA strives to translate the returns of its investments in genetics, epigenetics, neuroscience, pharmacotherapy, behavioral science, and health services research into the most effective strategies for preventing and treating substance use and addiction. In addition to advancing basic and clinical sciences related to drug use and its consequences, NIDA prioritizes research efforts relevant to current public health challenges, such as:

- the opioid overdose epidemic
- changes in state marijuana laws
- implementation of evidence-based SUD interventions
- emerging drugs and new delivery systems
- spread of infectious disease

The Opioid Overdose Epidemic

In recent years, the interrelated problems of prescription opioid misuse and heroin use have awakened high levels of public health awareness and concern, demanding a robust, evidence-based, and multifaceted response. An estimated 1.9 million people in the United States suffered from SUDs related to prescription opioid pain medications in 2014, and 586,000 suffered from a heroin use disorder.[1] These high rates of opioid use disorders are accompanied by devastating medical and social consequences, including deaths from overdose, a rising incidence of neonatal abstinence syndrome in newborns due to maternal opioid use during pregnancy, and increased spread of infectious diseases such as HIV and hepatitis C (HCV) due to sharing of needles for injection drug use and increased risky sexual behaviors.[8–11]

Research has demonstrated the efficacy of multiple types of interventions, including behavioral prevention interventions;[12] monitoring and risk reduction through prescription drug monitoring programs;[13–16] programs to provide overdose education and distribute the overdose-reversal drug naloxone to opioid users and potential bystanders;[9,17,18] drug courts in lieu of incarceration to increase access to treatment;[19] pharmacological treatments including methadone, buprenorphine, and extended-release naltrexone, combined with behavioral interventions;[20–23] and abuse-deterrent formulations for opioid pain relievers.[24,25] NIDA will continue its close collaborations with other NIH institutes and private industry partners to develop analgesics with reduced abuse potential and to identify biomarkers of pain severity that can be used to evaluate new treatments and further personalized interventions. Similarly, NIDA will continue its partnership with other federal agencies and communities in addressing the challenges posed by abuse of prescription opioids and heroin in this country.

Saving Lives: Intranasal Naloxone

Deaths from opioid overdoses (prescription pain relievers and heroin) have skyrocketed since 1999, leading the U.S. Department of Health and Human Services to deem the trend an epidemic and prompting widespread federal, state, and local actions. We can attack the epidemic on several fronts, including reducing the diversion of prescription drugs, making effective medical treatments more available to people who are addicted, and creating new ways to treat pain that do not involve addictive opioid compounds. But another crucial way we can combat the epidemic of deaths from opioids is with naloxone, a medication that reverses an opioid overdose. Naloxone can quickly restore normal breathing to a person in danger of dying from an opioid overdose.

Naloxone is already carried by emergency medical personnel and other first responders. But by the time an overdosing person is reached and treated, it is often too late to save him or her. To solve this problem, several experimental Overdose Education and Naloxone Distribution (OEND) programs have given naloxone directly to opioid users, their friends or loved ones, and other potential bystanders, along with brief training on how to use this medication. These programs have been shown to be a very effective, as well as cost-effective, way of saving lives.[18,26,27]

Until recently, only injected forms of naloxone were approved by the U.S. Food and Drug Administration (FDA), but many OEND programs use syringes fitted with an atomizer so the drug can be sprayed into the nose. Because the drug is not designed to be given this way, the dose and other properties of the medicine may not be optimal. However, in November 2015, the FDA approved a user-friendly intranasal formulation of naloxone, Narcan® nasal spray, that matches the injectable version in terms of how much of the drug gets into the body and how rapidly. The development of Narcan® nasal spray was supported by NIDA through a public-private partnership with Lightlake Therapeutics, Inc. and Adapt Pharma.

According to the Centers for Disease Control and Prevention, more than 74 Americans die each day from an overdose involving prescription pain relievers or heroin.[28] If we are to reverse these trends, we need to do all we can to ensure that emergency personnel, as well as at-risk opioid users and their loved ones, have access to life-saving tools like intranasal naloxone.

Changes in State Marijuana Laws

Marijuana is the most commonly used illicit drug in the United States, with more than 22 million people (8.4 percent) over the age of 11 reporting use in the past month.[1] In light of rapidly shifting state policies regarding marijuana use for medical and recreational purposes, it is more important than ever to produce and disseminate accurate information about marijuana's health effects and potential therapeutic uses and to conduct the research needed to fill the gaps in our knowledge.

Regular use of marijuana among adolescents is correlated with detrimental changes in the developing brain and negative social and behavioral outcomes;[29] however, it is currently unclear how changes in local, state, and national policies will impact—and will be impacted by—adolescent use and related outcomes, particularly during the most formative years of learning and development. There are many open questions related to marijuana legalization that research can help to address, including how policy changes will affect:

- use of marijuana and related health outcomes, including mental illness
- health outcomes—positive and negative—related to medical marijuana use
- usage patterns of other drugs, alcohol, and tobacco
- public safety outcomes related to drugged driving, crime, etc.
- potency and cannabinoid content of commonly consumed strains
- new routes of administration (*e.g., vaping, dabbing, edibles*)
- societal norms and perceptions

In addition, more research is needed to develop prevention interventions that target marijuana use among youth in the context of changing norms, to understand the health consequences related to the increasing potency of marijuana, to characterize the consequences of marijuana use on the developing brain, and to develop new treatment strategies for cannabis use disorders. NIDA-supported science aims to address these gaps and to help inform decision-making related to state and federal marijuana policies. In addition, in line with NIDA's mission of reducing the burden of drug use and SUDs, ongoing research will continue to explore the therapeutic potential of marijuana-derived compounds for pain and addiction.

Implementation of Evidence-Based SUD Interventions

Addiction is a complex but treatable disorder that affects brain function and behavior. Unfortunately, we have a significant and ongoing treatment gap in our nation. Among those who need treatment for an SUD, few receive it. In 2014, 22.5 million Americans needed treatment for an SUD, but less than 12 percent received treatment at a specialty substance abuse facility.[1] Further, many specialty treatment programs do not provide current evidence-based treatments—less than 50 percent provide access to medication-assisted treatment for opioid use disorders.[30] In addition, it is clear that preventing drug use before it begins—particularly among young people—is the most cost-effective way to reduce drug use and its consequences.[31] However, evidence-based prevention interventions also remain highly underutilized.

NIDA is committed to reducing these gaps using a multipronged approach including health services and implementation research to develop and test strategies to:

- Facilitate the dissemination and sustainable adoption of evidence-based treatments for SUDs in diverse health care settings including primary care and the criminal justice system
- Increase access to evidence-based treatments including pharmacotherapies and behavioral interventions for SUDs
- Identify individuals with problematic drug use and connect them to appropriate care
- Address stigma and discrimination to encourage people to seek treatment
- Facilitate the dissemination and sustainable adoption of evidence-based prevention interventions, including both targeted and community-based interventions, in diverse settings including communities, schools, health care, and criminal justice

NIDA works with diverse stakeholders to raise awareness about the value of addiction prevention and treatment interventions and to encourage people with problematic drug use to seek care. Our NIDAMED initiative and Blending Initiative develop medical education courses and materials to train clinicians on evidence-based practices related to prescribing for pain, on identifying individuals with risky substance use, and on treating adolescents with SUDs. In addition, NIDA, through the NIH Pain Consortium, helps to fund 11 Centers of Excellence in Pain Education that act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, and pharmacy schools.

Emerging Drugs and New Delivery Systems

NIDA monitors and investigates emerging threats to public health stemming from new patterns of drug use. One current trend of concern is the increasing use of synthetic drugs, including synthetic cannabinoids (e.g., K2, herbal incense), synthetic cathinones (e.g., bath salts, Flakka), and synthetic hallucinogens (e.g., 2-C, NBOME). Recent surges in calls to poison control centers, hospitalizations, and deaths linked to consumption of synthetic drugs have prompted concern across the country.[32] Basic research is needed to better understand the pharmacology and health effects of these synthetic drugs, sociocultural factors that influence their use, and effective strategies for prevention and treatment.

Another trend that NIDA researchers are watching closely is the rising popularity of e-cigarettes and vaporizer (vape) pens. E-cigarettes are often promoted as safer alternatives to traditional cigarettes, which deliver nicotine by burning tobacco, but little is actually known about the neurobiological consequences and health risks of using these devices. While they do not produce tobacco smoke, e-cigarettes often contain nicotine—a highly addictive drug—along with other potentially harmful chemicals and additives, such as formaldehyde, acetaldehyde, and toxic metals.[33] E-cigarettes are increasingly popular among adolescents, a population that is particularly vulnerable to the addictive power of nicotine and other drugs. A recent study found that adolescent e-cigarette users are significantly more likely to begin smoking conventional cigarettes compared to those who have not used e-cigarettes.[34] NIDA is also concerned about the use of these devices for administration of other drugs, including high-potency cannabis extracts (hash oil) and synthetic cannabinoids. It is not yet clear how use of these devices will affect risk for addiction or other adverse health effects.

Spread of Infectious Disease

Between January and August 2015, a rural community of 4,200 residents in southern Indiana saw the emergence of 184 people newly infected with HIV[35], 95 percent of whom were co-infected with HCV. This outbreak was driven primarily by injection of the opioid medication oxymorphone.[8] This highlights that injection drug users cannot be ignored in the efforts to achieve an AIDS-free generation and eliminate HCV. Even in the United States, where significant progress had been made in reducing the number of new HIV infections attributable to injection drug use (IDU)[36], the latest report coming out of Indiana highlights the challenges that IDU presents in tackling the intertwined HIV and HCV crises. Effective, evidence-based strategies exist for preventing the spread of HIV and other infectious diseases among drug-using populations. This includes the use of antiretroviral therapy as prevention for HIV transmission—a strategy known as Seek, Test, Treat, and Retain[37]—combined with treatment for opioid use disorders with medication-assisted treatment to improve compliance with antiretroviral treatment.[38] However, implementation of these treatment strategies among substance users has been slow, highlighting the need for new research to scale up efforts in this area. In addition, basic research is still needed to develop approaches to identify and eliminate HIV reservoirs and latent virus and to understand how drugs of abuse affect them. Unlike HIV, HCV can be cured;[39] however, new research is needed to identify effective models for linking comorbid HIV- and HCV-positive drug users to appropriate care and improving their treatment retention and outcomes.

Goals and Objectives

A central element of NIDA's mission is strategically supporting and conducting basic and clinical research on drug use (including nicotine), its consequences, and the underlying neurobiological, behavioral, and social mechanisms involved. The central focus of NIDA's mission is to support and conduct biomedical research to understand, prevent, and treat drug use and its consequences. The goals and objectives laid out in this strategic plan provide an overview of the broad research priorities in this area spanning basic science, translational, clinical, applied, and population-based research. In addition, this plan outlines four priority focus areas that present unique opportunities to leverage over the next 5 years.

The four strategic goals are:

GOAL 1: Identify the biological, environmental, behavioral, and social causes and consequences of drug use and addiction across the lifespan

GOAL 2: Develop new and improved strategies to prevent drug use and its consequences

GOAL 3: Develop new and improved treatments to help people with substance use disorders achieve and maintain a meaningful and sustained recovery

GOAL 4: Increase the public health impact of NIDA research and programs

The four priority focus areas are:

1. **Understanding the complex interactions of factors influencing drug use trajectories**
2. **Accelerating development of treatments**
3. **Addressing real-world complexities**
4. **Advancing bidirectional translation**

GOAL 1 Identify the biological, environmental, behavioral, and social causes and consequences of drug use and addiction across the lifespan

The human brain is incredibly complex, with hundreds of billions of neurons and glial cells interacting to enable us to think, feel, perceive, learn, and act in extraordinarily nuanced ways. Recent advances in neuroimaging, opto- and chemogenetics, genetics, epigenetics, and other research technologies are revolutionizing our understanding of the brain and brain disorders, spanning molecules, cells, circuits, systems, and individual and social behaviors.

This goal includes a focus on basic science, which involves investigating fundamental brain functions relevant to drug use (including nicotine) and addiction, such as reward, motivation, decision-making, impulse control, emotional regulation, and stress reactivity, among others. Fully understanding a circuit requires identifying and characterizing the component cells, defining their synaptic connections, observing the dynamic patterns of activity as the circuit functions in the living brain, and perturbing these patterns to test their significance. It also requires an understanding of the algorithms that govern information processing within a circuit and between interacting circuits. Basic studies of neuronal, glial, and neural circuit functions and how they are perturbed by drugs is also fundamental for identifying new therapeutic targets, feeding the translational pipeline toward development of new prevention and treatment strategies.

Miniature Microscope "Sees" Inside a Rodent's Brain

The holy grail of neuroscience is the ability to trace complex behaviors to the activity of specific neurons within discrete neuronal ensembles. Now, a technological advance that allows researchers to "see" individual neurons and record their activity while rodents perform a specific behavior is bringing us significantly closer to achieving this goal.

To image neuronal activity deep inside the brain of freely moving animals, NIDA researchers developed a miniaturized microscope that can be mounted on the skull of mice and rats. The prototype consists of a 3D-printed microscope body equipped with miniature optics and a cell-phone-camera-like photographic image detector, called a CMOS chip. The CMOS chip, image-acquisition electronics, and software were developed in collaboration with Dr. Eugenio Culurciello's lab at Weldon School of Biomedical Engineering, Purdue University.

This amazing optical device is just 20 mm tall and weighs 2.7 grams—about the weight and diameter of a penny. With it, researchers will now be able to focus on a 900 µm (9/10ths of a millimeter) field of view and record the activity of hundreds of thousands of neurons simultaneously. This microscope can be used to visualize brain activity in genetically modified mice that express a protein called GCaMP6, which fluoresces as a function of intracellular calcium levels, making neuronal activity visible to the sensor. In early studies, this miniature microscope was capable of detecting GCaMP6 fluorescence changes deep in the brain, in an area called the dorsal striatum, which plays a role in reward and addiction.

This technology heralds a new era in our ability to study the exquisitely choreographed neuronal activity that underlies both simple and complex behaviors.

This goal will also focus on understanding the role of behavioral, social, and environmental factors in substance use and addiction. Research is needed to better understand how these factors interact to influence vulnerability for initiation of drug use, escalation to substance use disorders (SUDs), and transitions between the stages of SUDs. It is also important to understand how drug use and SUDs impact an individual's environment, behavior, and social interactions. In addition, understanding how these factors interact with one another and with genetic and neurobiological mediators of drug use and SUDs is important for developing novel prevention and treatment intervention strategies. NIDA will continue to support behavioral and cognitive research and develop new animal models that better capture the complexities of behavioral, cognitive, environmental, and social aspects of addiction.

President Obama's BRAIN Initiative is accelerating technology development in neuroimaging and brain circuit manipulation, driving a qualitative shift in the questions we can answer through research. Much of the research conducted under this initiative in the past few years has focused on a few isolated brain regions, but these new tools and maps are beginning to provide us with the opportunity to study the complex interactions that exist among neurons and functional brain circuits; how these are influenced by genetics, environment, drugs, and addiction; and how they respond to treatments. This fundamental knowledge will allow researchers to start to address critical public health questions such as:

- how, when, and for how long to intervene (for both prevention and treatment)
- how to maximize prevention of SUDs
- how to enhance treatment response and recovery
- how to mitigate harms

Advances in genetic and epigenetic approaches are contributing to our understanding of the causes of drug use and SUDs. SUDs are complex developmental disorders with high heritability that are also strongly influenced by environment—particularly during childhood and early adolescence.[40] New scientific and computational methodologies are needed to elucidate the complex interplay of genetic and environmental factors across developmental trajectories of SUDs and comorbid conditions.

Gene discovery efforts provide the foundation for identification of drug targets, tailoring treatments by genotype (pharmacogenetics) and ultimately defining how environmental factors interact with genetic factors to contribute to SUD risk. By comparing SUD gene discovery data sets with other genome-wide association studies (GWAS), it is possible to identify gene variants that are comorbid with other disorders. Human genetic data will be used to inform preclinical genetic studies and vice versa, so that animal genetic studies can advance our understanding of human addiction.

Recent advances in genome editing using techniques such as CRISPR/Cas9[6], as well as sequencing technology, single-cell sampling, and computational tools,[41–43] provide the necessary tools to study reward phenotypes through precise manipulation of gene expression within specific neuronal populations. Studies using cell culture models of human neurons from people suffering from SUDs are allowing researchers to understand the effects of drugs on human neurons in vitro, which can be used to validate animal models or more efficiently screen the potential safety and efficacy of new medications. In addition, the arsenal of tools to directly modify the activation of brain cells (e.g., optogenetics, Designer Receptors Exclusively Activated by Designer Drugs [DREADDs]) is allowing causal investigation of circuits and behaviors in animals and the effects of drug use.[44, 45]

To improve our understanding of the range of factors that mediate drug use behaviors and risk for addiction and build the foundation for future interventions, NIDA will support the following objectives:

- **Objective 1.1:** Characterize the genetic, neurobiological, environmental, social, and developmental factors that mediate risk and resilience for drug use and addiction
- **Objective 1.2:** Identify the factors that influence drug use trajectories
- **Objective 1.3:** Establish the effects of drug use, addiction, and recovery on genes, molecules, cells, brain circuits, behavior, and health across the lifespan
- **Objective 1.4:** Identify the bidirectional effects of drug use and common comorbidities

Objective 1.1

Characterize the genetic, neurobiological, environmental, social, and developmental factors that mediate risk and resilience for drug use and addiction

Like most behavioral health disorders, SUDs are polygenic disorders with a complex pattern of inheritance that results from the combined effects of multiple genes and their interaction with the environment.[40] There are likely to be many regions of the genome that contribute to SUD risk, and their individual effects may vary across developmental stages. Understanding the confluence of biological, behavioral, environmental, social, and developmental factors that mediate risk and resilience will provide a foundation of knowledge necessary for designing new prevention and treatment strategies that are tailored towards an individual's unique risk profile.

Understanding the gene x environment x development interactions that contribute to the risk for SUD phenotypes using GWAS will require methods to overcome statistical challenges due to multiple comparisons. One of the primary challenges to understanding how these factors contribute to the various stages of SUDs (e.g., escalation, relapse, etc.) is to determine how to detect relatively small genetic effects that contribute to the overall heritability of SUDs and then examine how these genetic effects operate within changing environments and across human development. Though GWAS has been one of the most productive methods for identifying genetic variants associated with disease, the reduced costs and high throughput of genome sequencing will make it increasingly feasible to apply this technique to SUD research. The development of advanced analytical and computational tools will be essential to take advantage of this rich information.

In addition, mice with defined genetic backgrounds (e.g., inbred strains, recombinant inbred strains, strains carrying defined naturally occurring and induced genetic variations, etc.) provide a way to test gene x environment and gene x development interactions under controlled experimental conditions.

Approaches

- Conduct human molecular genetics studies, including large-sample GWAS and genome sequencing, to identify genetic variants that contribute or provide resilience to SUDs
- Integrate GWAS and sequencing efforts with behavioral phenotype identification, environmental effects (including social contexts), postmortem molecular changes, and epigenomic characterization across human development
- Expand efforts to characterize epigenetic modifications associated with SUDs
- Functionally validate and characterize SUD-related gene variants in animal models and identify opportunities for clinical translation

The Neuroscience of Addiction

We have learned an enormous amount in the last decade about the effects of drugs on the brain and the biological processes involved in developing SUDs. The process involves major changes to multiple interconnecting circuits in the brain.

First, drugs of abuse affect, or in some cases directly mimic, the actions of signaling chemicals in the brain (neurotransmitters), including raising the level of the neurotransmitter *dopamine* in reward circuits (the nucleus accumbens and dorsal striatum). This produces feelings of euphoria. However, with repeated drug use, these circuits adapt to the dopamine surges by reducing their sensitivity. A person then needs more of the drug to get the initial effect (tolerance) and to avoid withdrawal symptoms (dependence).[5]

When someone develops an addiction, not only these reward circuits but also circuitry involved in stress, learning, and self-control become altered. "Anti-reward" circuits involving the amygdala and other brain areas that control our emotional responses cause an addicted person to feel severe stress when not using the drug; the person then needs the drug to feel physically well. In addition, the brain learns to associate the drug with many other aspects of the person's daily life and routine. Frequent reminders of the drug (triggers) reinforce constant preoccupation and craving. And, crucially, parts of the prefrontal cortex needed for decision-making and exerting self-control also become desensitized to dopamine.[46] This makes it very difficult for the person to stop or limit drug use even if he or she is aware of negative consequences and has a strong, sincere desire to quit.

As a result of these changes, people with an addiction do not feel motivated by ordinary rewarding behaviors, need the drug just to feel temporarily normal, and experience powerful urges to seek and use the drug despite knowing that it is harming them and causing disastrous effects in their lives. This compromised self-control is one of the most painful aspects of addiction. It is also the hardest for nonaddicted people to understand, leading to persistent stigma against people with SUDs.

The good news is that it is possible for brain circuit function to be repaired and for the brain to readapt to the absence of drugs. However, like all healing processes in the body, it takes time. SUDs are chronic, relapsing disorders; successful recovery often involves months to years of treatment. In many cases, such as opioid addiction, medications can be an important part of treatment to reduce withdrawal symptoms and reduce the chance of relapse.[47] Future research will capitalize on our growing understanding of the neurobiology of addiction by creating new and better methods for prevention and treatment, including new medications and other nondrug therapeutics.

Objective 1.2

Identify the factors that influence drug use trajectories

SUDs are complex conditions that develop over time and are characterized by stages of initiation, escalation, problematic use, and addiction, the latter often being associated with cycles of withdrawal and relapse. However, not all individuals who initiate drug use progress to addiction; some discontinue use quickly, and others maintain a low level of use without escalating to problematic use or addiction. Also, some individuals who develop problem use or addiction are able to stop without formal treatment, whereas others are treatment-resistant.[48, 49]

Genetic epidemiology suggests that individual trajectories are influenced by the environment, the age of initiation, and genetic vulnerabilities. Initiation and dependence share some common genetic factors, but unique genetic factors also underlie the different stages of substance use, as well as individual vulnerability for addiction to particular substances.[50]

The heterogeneity of substance use phenotypes and individual genetic variation present significant challenges for understanding the genetic and environmental factors that mediate the development of SUDs. Identifying and characterizing biologically relevant behavioral phenotypes will enhance the probability of identifying risk genes, relevant environmental and social risk and protective factors, development factors associated with SUD behavior, and, ultimately, objective diagnostic biomarkers.

Approaches

- Conduct longitudinal studies to examine the impact of drug use on development
- Improve standardization and depth of phenotypic and environmental characterization
- Support efforts to develop large data sets, integrating data across many scientific disciplines and data types to support more comprehensive characterization across stages of the SUD trajectory

A Look Inside the Teen Brain: the Adolescent Brain Cognitive Development (ABCD) Study

Decades of neuroscience research has shown that adolescence is a period of significant brain development and that experiences during this time can have a profound impact. For this reason, it is a crucial window during which a wide range of biological and environmental factors and health behaviors can influence and shape a person's cognitive development and associated life outcomes in both positive and negative ways. Experiences such as physical activity and sleep; stress; injuries from sports and other activities; substance use; mental illness; and socioeconomic, genetic, and developmental factors shape the developing brain. But because of their variety and complexity, our understanding of precisely how these experiences interact to affect brain development and social, behavioral, and health outcomes is still incomplete. To address this gap, we need to study a large and diverse group of children, starting early in adolescence, and follow them throughout the window of developmental vulnerability.

To this end, NIDA is leading a collaborative effort in partnership with NIAAA; NCI; the Collaborative Research on Addiction at NIH, or CRAN; and other NIH partners (NICHD, NIMH, NIMHD, NINDS, and OBSSR) on a new Adolescent Brain Cognitive Development (ABCD) study. This study is the largest-ever longitudinal brain imaging study of adolescents. ABCD will recruit 10,000 youth at age 9 or 10 and follow them over 10 years, into early adulthood, to determine how a wide range of behavioral, genetic, and environmental factors interact and influence brain structure and function as well as life and health outcomes. Studies will track mental health, substance use patterns, academic achievement, IQ, cognitive skills, and many other outcomes. The longitudinal design of the study will allow us to draw more meaningful conclusions and connections at the individual level, between key genetic and biological, behavioral, social, and environmental factors during adolescence.

Importantly, the size and scope of the ABCD study will allow scientists to answer pressing questions about the effects of biology, environment, and experience on the developing brain and the risks for specific health outcomes including substance use and other mental disorders. Also, the inclusion of roughly 800 twin pairs will yield invaluable data about the role of genetic versus environmental factors in development. The large data set will also allow scientists to answer pressing questions about the impact of substance use on physical health, psychological development, learning and memory, academic achievement, and other outcomes.

By leveraging recent advances in technology, this landmark study will help transform our understanding of genetic and environmental influences on brain development, structure, and function and also identify potential predictors of teen drug use. This information can then be used to improve our ability to predict, mitigate, or counteract the risk of substance use disorders among our nation's youth through more effective prevention messages and treatment interventions.

Objective 1.3

Establish the effects of drug use, addiction, and recovery on genes, molecules, cells, brain circuits, behavior, and health across the lifespan

Drug use has a broad range of direct and indirect consequences. The direct physiological effects on the user depend on the specific drug(s) used, dose, method of administration, and other factors. Acute effects can range from subtle molecular changes to overdose and death. While the major acute effects are known for many drugs, basic research is still necessary to understand the potential dangers of emerging drugs such as synthetic cannabinoids (e.g., K2, herbal incense) and synthetic cathinones (e.g., bath salts).

Chronic drug use can also have distinct effects on physical and mental health. Researchers are just beginning to understand the effects of chronic drug abuse on, for example, epigenetics, brain energetics, synaptic plasticity, and less-studied cell types, such as glia, that act to support neurons. All of these effects may vary across the trajectory of drug use and addiction. Drug use also has diverse indirect effects such as affecting a user's nutrition;[51] sleep and circadian rhythms;[52, 53] decision-making and impulsivity;[54] risk for trauma, violence, injury, and communicable diseases;[8, 10, 55–58] and outcomes such as educational attainment, employment, housing, relationships, and criminal justice involvement.[59–63] These consequences can all contribute to the trajectory of addiction and may need to be considered independently and collectively when developing treatment interventions.

Approaches

- Explore the epigenetic consequences of drug use, addiction, and recovery
- Use established or novel behavioral models of each stage of addiction to more comprehensively characterize effects on genes, molecules, cells, circuits, and overall health across the lifespan
- Investigate the causal role of changes to brain circuit function in addiction using advanced transgenic technologies (such as optogenetics and DREADDs) to target cell types
- Utilize advanced technologies (such as multi-electrode arrays, multi-angle cameras, and mobile sensing and analytics tools) to investigate complex brain circuits, networks, and behaviors linked to drug use and addiction

Leveraging Research Technologies

The last few years have brought a steady stream of dramatic advances in technologies that can impact the neuroscience field by enhancing our ability to visualize or manipulate functional brain circuits and decode the complex language of the brain. One of the best recent examples is optogenetics, a technology that combines advanced genetic and optical techniques to allow scientists to insert light-sensing proteins into neurons and then use pulses of light to turn specific neuronal pathways on or off.[64] By allowing precise optical control of cellular processes at high temporal (millisecond) and spatial (cell-specific) resolution, optogenetics has opened up completely new avenues for investigating biological systems in both healthy and diseased states.

New gene editing technologies hold even greater promise. Ever since the molecular basis of heredity was discovered, scientists have been looking for ways to edit the letters along the DNA double helix to both study the function of specific genes and to cure disease. Many such techniques have been developed over the years, but creating animals or cells with specific genetic modifications remained a tedious and expensive proposition until just 3 years ago, when a game-changing technology called CRISPR was developed.

CRISPR stands for clustered regularly interspaced short palindromic repeats. This refers to part of a very primitive bacterial defense system, which, as it turns out, can be easily adapted and coaxed to modify any desired gene for research or therapeutic purposes.

CRISPR technology has the potential to completely transform gene editing protocols. Because of its potential to help us understand complex biological systems, correct defective human genes, and eliminate disease, among other applications, CRISPR has swept through labs around the world.[6] Although more research needs to be done before it can be deployed ethically, safely, and efficiently in humans, it and related technologies are heralding exciting future discoveries in the study of addiction and related fields.

Eliminating Hidden Reservoirs of HIV Virus in the Brain

The brain is a major target organ for the HIV virus. This explains why AIDS is associated with significant brain pathology and a wide range of neurological symptoms, including HIV-associated dementia.[65] Many factors can influence the trajectory of these symptoms, but substance use, which commonly co-occurs with HIV infection, has been shown in many studies to hasten the progression of HIV infection and HIV-associated neurocognitive disorders. In turn, HIV-associated neurological dysfunction can increase the risk of SUDs.[66]

The introduction of antiretroviral therapy in the mid-1990s resulted in dramatic decreases in sickness and death in people infected with HIV. These drugs limit the HIV viral load and maintain a relatively healthy immune response, allowing the life expectancy of HIV-positive patients to approach that of the general population. Unfortunately, even with highly active antiretroviral therapy, HIV-1 viral proteins can still be expressed in so-called reservoir organs, which include the brain, causing persistent inflammation leading to continued neurological dysfunction and increased SUD risk.[67]

Thus, eradicating these hidden HIV reservoirs is absolutely critical to curtailing chronic brain inflammation and cutting the two-way connection between HIV infection and substance use. NIDA is actively encouraging researchers to explore the mechanisms responsible for the existence of HIV reservoirs as a way to identify additional vulnerabilities in the virus life cycle. To this end, NIDA is supporting basic studies of latency mechanisms behind HIV-1 reservoirs in a small pool of persistent, long-lived, and latently infected resting memory CD4 T cells; studies using nanotechnology to attack HIV where current medications do not penetrate; and investigations into the potential capability of anti-inflammatory drugs to attack latent viral reservoirs.

The knowledge we gain from these and related studies will lead to smarter approaches for targeting and purging HIV reservoirs, which could become a major component of an eventual cure for HIV.

Objective 1.4

Identify the bidirectional effects of drug use and common comorbidities

Addiction frequently co-occurs with other psychiatric disorders, infectious diseases, and pain conditions.[8, 10, 68, 69] The relationships between these comorbidities confer unique treatment needs on the respective patient populations. Comorbidities may also point to shared biological substrates, environmental influences, and social conditions that give rise to these disorders. For example, understanding the confluence of factors that contribute to the high rates of comorbid SUD and post-traumatic stress disorder among military populations is necessary to develop better-targeted prevention and treatment interventions for this high-risk group. Full characterization of the interactions between comorbid disorders will drive the development of improved treatment strategies for patients with complex SUD phenotypes.

Approaches

- Identify bidirectional risk factors for and impact of co-occurring psychiatric and physical health conditions (e.g., HIV, hepatitis C [HCV], pain, depression, insomnia) on addiction
- Evaluate the effectiveness of treatments for general health comorbidities—including the newly approved HCV antiviral—in individuals with problematic drug use and SUDs
- Identify the molecular, cellular, behavioral, and neurobiological interactions between pain and addiction
- Characterize the bidirectional effects of common comorbidities and recovery from SUDs

GOAL 2 Develop new and improved strategies to prevent drug use and its consequences

Considerable evidence has accumulated over the past four decades that substance use problems often can be prevented through interventions targeting one or more risk or protective factors. Interventions targeting child and adolescent risk factors for substance use disorders (SUDs) may reduce other behavioral health problems, such as aggression, and improve educational and later-life outcomes. Some interventions have been found to show continued effects long after intervention exposure and many deliver a significant return on investment in terms of reduced societal costs.[12,70,71]

Genetics have been shown to account for roughly half of the risk for SUDs.[50] Environmental influences include social as well as biological factors arising from prenatal and childhood environments that influence both gene expression and development, such as stress, nutrition, parental drug use, or illnesses (including pain) that affect an individual's likelihood of using drugs.[61, 72–74] Sociocultural environments (e.g., policy, peers, family, and communities) also play pivotal roles in the initiation of drug use, escalation of use, and SUD trajectories.[61,75]

An increased understanding of neurodevelopmental adaptations to the environment that influence risk of substance use is leading researchers to think of prevention as affecting not only behavior but also brain development and function, including neuroendocrine stress responses and neuroplasticity. For example, maltreated children in foster care receiving a prevention intervention for preschoolers not only showed improved behavioral functioning (leading to increased likelihood of successful transition into permanent homes) but also showed better stress regulation (measured by cortisol levels) approaching that of a control group of children in the general population.[76,77] Thus, we are entering an era when neurodevelopment can be directly targeted through prevention science.

Most substance use begins during adolescence, a time in which aspects of brain development, such as the slow maturation of the prefrontal cortex, interact synergistically with social pressures arising from new social roles, peer environments, insufficient or disrupted sleep, and stressful life transitions to heighten risk.[78] In addition, patterns of behaviors and interactions in family, school, and peer contexts become more established as the child moves into adolescence; consequently, while prevention interventions aimed at older children and teenagers can be effective, they have a greater challenge in positively influencing the decisions of youth who may already be on a risky life track.

Vulnerability for substance use and related problems has been shown to peak during critical life transitions, including biological transitions such as puberty and social/environmental transitions such as attending a new school, parental divorce or military deployment, or graduation.[72,79–82] Despite strong evidence supporting the effectiveness of prevention strategies targeted for both individuals and communities, relatively few effective interventions have been widely adopted or faithfully implemented, and thus their potential to positively impact public health has been limited.[83] Implementation research is therefore an important part of this overall prevention goal, as is capitalizing on the opportunities generated by health care reform. Unprecedented and rapid change in health care policy and technology has the potential to expand not only the reach of treatment but also to improve the delivery of evidence-based prevention interventions.

To design and deliver targeted prevention approaches to the individuals and communities who stand most to benefit from them, NIDA will support prevention research that builds on our growing experience in evaluating prevention interventions and that leverages the accumulating basic science on the developmental, biological, genetic, and neurobiological mechanisms underlying drug use and addiction. To facilitate the development of new prevention strategies, NIDA will support research to:

- **Objective 2.1:** Determine the mechanisms that underlie individual risk and resilience for addiction and common comorbidities
- **Objective 2.2:** Develop and test innovative prevention interventions that target mechanisms underlying risk factors
- **Objective 2.3:** Develop and test strategies for effectively and sustainably implementing evidence-based prevention interventions
- **Objective 2.4:** Develop and test novel strategies for preventing prescription opioid misuse and addiction

Objective 2.1

Determine the mechanisms that underlie individual risk and resilience for addiction and common comorbidities

To inform the development and implementation of effective prevention interventions for SUDs, it is important to better understand the mechanisms through which interventions work and for whom they are most effective. Determining the mechanistic effects that mediate effective interventions will provide an evidence base to guide efforts to refine and improve program components. Building this evidence base will require research on the individual predictors of intervention success and on the malleable mediators of intervention effects, as well as research to clarify which preventive components best predict intervention-related outcomes and for whom. Further research is needed to refine our understanding of modifiable risk and protective factors associated with life transitions and developmental periods to enhance the power of interventions. In addition, a greater understanding of the impact of preventive interventions on neurobiology is needed in order to identify the critical windows across the lifespan during which interventions may produce the greatest impact for specific populations.

This objective will build upon basic research to help determine the types of interventions that are most likely to be effective for specific individuals or subpopulations given underlying biological mechanisms of action.

Approaches

- Establish the mechanisms through which preventive interventions effectively influence the biological, behavioral, and social mediators of risk for SUDs
- Identify mediators of the effectiveness of prevention interventions for different populations and developmental stages
- Explore the common underlying mechanisms that lead to multiple problem behaviors including substance abuse

Objective 2.2

Develop and test innovative prevention interventions that target mechanisms underlying risk factors

Changes in technology and the social media landscape are presenting new opportunities to deliver innovative prevention interventions. In addition, the accumulating basic science of biological, environmental, and developmental interactions underlying substance use and addiction, combined with our increasing understanding of the mechanisms underlying behavior change and intervention effectiveness, will allow researchers to develop and test prevention interventions targeted to the mechanisms underlying risk and resilience for drug use and related disorders. For example, child maltreatment is one of the most powerful environmental risk factors for SUDs and other behavioral disorders.[84] The development of interventions that

identify and address the consequences of child abuse and neglect may offer effective prevention for a large population of vulnerable individuals. This objective includes integrating discoveries from the basic biological, behavioral, and social sciences to develop and test innovative preventive interventions that specifically target underlying mechanisms in drug abuse risk.

Priorities within this objective include developing and testing prevention interventions for known high-risk and vulnerable populations and for subgroups for which research gaps exist (e.g., older adults), and developing interventions to address emerging drug trends and drug use practices (e.g., e-cigarettes, synthetic drugs, dabbing) that have unique characteristics or confer unique risks. Novel intervention approaches, adaptive designs, and other methods for optimizing interventions at the individual and community level are also needed.

Approaches

- Integrate discoveries from the basic biological, behavioral, and social sciences to develop and test innovative preventive interventions that specifically target the underlying mechanisms of drug abuse risk and other related problems
- Build on developmental research to maximize the effectiveness of interventions at different critical developmental stages and transitions from infancy to adulthood
- Explore the potential of technology-based methods for delivering prevention interventions, such as smartphones, video games, and social media
- Develop and test effective preventive interventions targeted to factors underlying common comorbidities including mental illness, behavioral problems, and pain
- Develop and test preventive interventions for implementation in diverse clinical settings including emergency departments, primary care, hospital inpatient settings, high school and college health centers, and community coalitions

Objective 2.3

Develop and test strategies for effectively and sustainably implementing evidence-based prevention interventions

To increase the public health impact of effective prevention interventions, increased attention must be given to two types of implementation science: research that considers implementation and scale-up issues during intervention development and testing in order to increase the likelihood of uptake; and research to develop and test systematic, measurable, and replicable strategies for optimizing the adoption, uptake, and sustainability of evidence-based prevention interventions and practices with fidelity in real-world settings. NIDA will support research on the complex processes through which evidence-based interventions are adopted, implemented, and sustained at the community level, with a strong orientation toward devising empirically driven strategies for increasing their population impact.

Research is needed to test novel modes of intervention delivery, as well as to understand factors that influence the integration and sustainability of evidence-based prevention interventions across community and health care settings. This objective will also prioritize the development of new quantitative methods for data analysis and experimental design, as well as benefit-cost analyses to facilitate uptake and support for investing in prevention by policymakers and funders.

Approaches

- Identify obstacles to large-scale implementation of evidence-based prevention interventions and develop approaches to resolving those obstacles
- Identify the infrastructure and training needed to support large-scale adoption, implementation, and sustainability of evidence-based prevention interventions
- Identify ways the Affordable Care Act and related regulatory changes can best be leveraged to increase implementation of prevention interventions for substance use and related problems
- Explore the use of technology to improve the dissemination and sustainable implementation of evidence-based prevention interventions

Objective 2.4

Develop and test novel strategies for preventing prescription opioid misuse and addiction

An estimated 100 million U.S. adults suffer from chronic pain.[85] Over the last 16 years, there was a threefold increase in opioid prescribing, which was associated with a dramatic rise in opioid use disorders, overdose deaths, and cases of neonatal abstinence syndrome.[86,87] This effect was due in part to the limited options for effectively treating chronic pain. As summarized in a recent report from the NIH Pain Consortium, there is a pressing need for more research on the effectiveness and safety of using opioids to treat chronic pain as well as on optimal management and risk mitigation strategies.[88]

There are some patients who benefit from opioid medications, especially in the context of a broader pain treatment program. However, many other chronic pain patients are inappropriately prescribed opioid medications that may be ineffective or even harmful.[88] More research is needed to develop strategies to identify the patients for whom opioids are the most appropriate treatment, to develop new opioid drug formulations with reduced potential for abuse, and to develop more effective non-opioid pain treatment strategies. The U.S. Department of Health and Human Services is in the process of developing a National Pain Strategy[89] that outlines priorities in population-level research on pain and recommends specific steps to a) increase the precision of information about chronic pain prevalence overall, for specific types of pain, and in specific population groups; b) develop the capacity to gather information electronically about pain treatments and their usage, costs, effectiveness, and safety; and c) enable tracking changes in pain prevalence, impact, and treatment over time, allowing evaluation of population-level interventions and identification of emerging needs.

Approaches

- Develop and test non-opioid medication targets for chronic pain
- Develop and test adjunctive therapies that can reduce the dose of opioids to control pain
- Develop and test nonpharmacological pain treatment strategies such as neural stimulation therapies (e.g., transcranial magnetic stimulation, electrical deep brain stimulation), biofeedback, and behavioral treatments
- Identify and test strategies for improving opioid prescribing and patient management practices to reduce the development of opioid use disorders

Precision Medicine for Pain

Each year, about 100 million American adults experience chronic pain, costing the Nation between $560 billion and $635 billion.[85] Opioid pain relievers are among the most effective medications for the management of severe pain and are often used to treat chronic pain. However, the benefits of long-term opioid treatment are increasingly being questioned as patients face a significant risk of developing drug tolerance (needing higher doses) and hyperalgesia (increased pain sensitivity). Also, use of these medications can lead to dependence or even addiction, and they may trigger relapse in people who are recovering from SUDs. Over the past two decades, a steep rise in misuse of and addiction to opioid pain relievers has led to a dramatic increase in opioid use disorders as well as an epidemic of overdose deaths. As people with addictions to opioids seek cheaper alternatives, it has also led to a rise in heroin use and related deaths.

NIDA plays a central role in supporting research efforts aimed at developing safe and effective options for managing chronic pain while minimizing the risk of abuse. NIDA pursues this objective through research and development of non-opioid pain medications, abuse-deterrent formulations of existing medications, and user-friendly overdose reversal drug formulations (e.g., intranasal naloxone). NIDA is also committed to educating health care providers and the broader public about the proper use and potential risks of these medications.

NIDA supports a pharmacogenomics program that is developing ways to identify which pain management interventions are most effective for specific chronic pain patients and how to predict which patients might be at higher risk for opioid use disorders. Research has identified a number of genetic markers associated with risk for opioid addiction as well as pain sensitivity, including the μ opioid receptor-1 and cytochrome P450 2D6.[90] The ultimate goal of this research is to match pain treatment to a person's unique DNA profile and prescribe opioid pain relievers only to those who will benefit from them.

These efforts reflect a growing understanding at NIDA and across NIH that approaching health care in a patient-centered way, known as precision medicine, promises to spur significant, potentially transformative advances in clinical care and research.

GOAL 3 Develop new and improved treatments to help people with substance use disorders achieve and maintain a meaningful and sustained recovery

The last few decades have seen dramatic advances in our understanding of the biology of addiction, but the range of treatment options available for most substance use disorders (SUDs) remains limited. Pharmacotherapies approved by the U.S. Food and Drug Administration (FDA) exist for dependence on opioids (i.e., methadone, buprenorphine, and extended-release naltrexone), alcohol, and nicotine, and evidence-based psychosocial treatments (e.g., cognitive behavioral therapy, contingency management, etc.) are available for these and other SUDs[91,92], but the efficacy of these treatments is far from ideal. There is a clear need to develop better treatment strategies that target the biological substrates of addiction across stages, including detoxification, recovery maintenance, and relapse prevention.

SUDs are chronic conditions that often require long-term management. The chronic nature of the disorder means that relapsing is common, with recurrence rates similar to those for other well-characterized chronic medical illnesses that have both physiological and behavioral components—such as diabetes, hypertension, and asthma.[93] SUDs can be managed successfully in many cases, but available treatments are ineffective for others. In addition, the vast majority of individuals who have SUDs never seek treatment.[1]

There are many new approaches that show promise for the treatment of SUDs in preclinical studies including novel pharmacotherapies, behavioral therapies, vaccines, biofeedback, and direct manipulation of brain activity via transcranial magnetic stimulation (TMS) and electrical deep brain stimulation.[94–98] Translating these promising interventions into clinical practice will require testing their efficacy in target populations in clinical trials. However, a key challenge in this area is the reticence of pharmaceutical companies to invest in developing treatments for addiction. This is due in part to the perception

that the market for such treatments is small and in part to difficulties conducting clinical trials in patients with multiple comorbidities. In addition, the only end point currently accepted by the FDA for clinical trials examining therapeutics for SUDs is abstinence. This represents a particularly high bar, which discourages investment by the private sector.[99] NIDA, together with the FDA and our academic and industrial partners, is working towards validating end points other than abstinence, and this will remain a strategic priority over the next 5 years.

Targeting the Brain's Circuits to Treat SUDs: Transcranial Magnetic Stimulation

All mental and behavioral phenomena—whether healthy or disordered—result from electric currents coursing through neural circuits in the brain. Thus, it should be possible, at least in theory, to disrupt and perhaps even correct a disease process by activating or inhibiting specific brain circuits.

TMS, first developed in 1985, uses localized magnetic pulses to activate targeted regions of the brain. In October 2008, the FDA approved TMS as a noninvasive method of brain stimulation for treatment of major depression among patients who do not respond to at least one antidepressant medication. TMS is also being studied as a treatment for many other neuropsychiatric disorders.

Fortunately, we now have an increased understanding of the brain circuits that become disordered in individuals with SUDs. These include circuits governing impulse control, motivation, reward-dependent learning, and emotional processing.

Growing evidence suggests that TMS may be helpful in the treatment of SUDs, particularly if the pulses are administered in rapid succession. This technique, referred to as repetitive TMS (rTMS), enables longer-lasting changes in brain activity. For example, two of four controlled clinical trials using rTMS to reduce nicotine craving found decreased cigarette smoking, and a trial in cocaine users found decreased cocaine use after treatment.[100]

We still have much more to learn about how to optimize rTMS treatment: what its duration should be, whether it can reduce cue-induced craving, and whether it can be combined with other treatments. We also still do not fully understand how rTMS achieves its effects in treating SUDs, so it is still considered experimental. As we learn more about brain circuit changes in the brains of addicted individuals, it could turn out to be a promising noninvasive and nonpharmacological treatment approach.

The ongoing transformation of the health care system also presents significant opportunities for advancing treatment for SUDs. Health reform initiatives are promoting the integration of behavioral health care into general health services. In addition, new payment models—including shared savings programs and the hospital readmission penalty—are creating financial incentives for addressing broader issues, including SUDs, that contribute to treatment success and long-term outcomes. Medical costs for treating patients with chronic physical health conditions can be two to three times higher in patients with comorbid behavioral health disorders[101], and untreated SUDs are associated with poorer adherence to treatment plans and medications, leading to worse outcomes.[102] However, less than 12 percent of people with SUDs receive treatment, and only a fraction of those receive care that is adequate, making addressing SUDs a prime target for reducing health care costs.[1] Research can help to define how best to prevent substance use, identify individuals with problematic substance use or SUDs, and engage patients in appropriate treatment in general health care and integrated care settings.

Another element of the changing health care landscape that has the power to affect SUD treatment is the rapid development and adoption of technologies including electronic health records, telehealth, and mobile health technologies. These technologies have the power to revolutionize health services research and to drive new treatment delivery models by supporting more effective integration of care, extending the reach of the SUD treatment workforce, enabling real-time patient monitoring and support, delivering technology-based intervention, and engaging patients who are hesitant to participate in the traditional behavioral health treatment system. Research is needed to inform how best to leverage these new technologies to improve patient outcomes.

Ongoing reform efforts within the criminal justice system also present new opportunities for improving SUD treatment. It is estimated that one half of all prisoners meet the diagnostic criteria for drug abuse or dependence, yet less than 20 percent of prisoners with drug abuse or dependence receive treatment while incarcerated.[103] Left untreated, drug-addicted offenders often relapse to drug use and return to criminal behavior. This represents a significant opportunity to intervene with a high-risk population. More research is needed to develop improved prevention and treatment models within the criminal justice system that fit the chronic nature of SUDs and ensure a continuity of treatment services upon community reentry. In addition, integrated implementation strategies are needed not only to incorporate the best criminal justice practices and therapeutic services, but also to use the best organizational practices to deliver them.

A primary goal of NIDA research is the amelioration of the health burden caused by addiction; the development of effective interventions is vital to the realization of this goal. To facilitate the development of innovative intervention strategies, NIDA will support research to:

- **Objective 3.1:** Develop and test novel treatments based on the science of addiction
- **Objective 3.2:** Develop and test metrics for measuring the quality and efficacy of treatment
- **Objective 3.3:** Identify biomarkers that predict response to treatment and risk for relapse
- **Objective 3.4:** Develop and test strategies for effectively and sustainably implementing evidence-based treatments

Juvenile Justice: A Key Intervention Point

Drug use and involvement with the criminal and juvenile justice systems go hand in hand, and the number of incarcerated drug offenders continues to grow. There are many competing theories about how to best address this persistent and costly phenomenon, but the scientific understanding of addiction as a brain disorder should help us see that punishment alone cannot be effective at addressing SUDs. Instituting effective treatment programs for offenders whose criminal behavior is directly related to drug use is urgently needed as part of a humane and comprehensive public health and safety intervention. This rationale only strengthens when we consider that incarceration provides a unique opportunity to reach those who would otherwise not seek treatment.

NIDA funds a broad portfolio of research addressing adult SUD issues within the criminal justice system, but the ethical case for robust treatment options is particularly compelling when it comes to incarcerated adolescents. About half of all teens who enter the juvenile justice system need treatment for SUDs, and the remaining half would no doubt benefit from a drug use prevention intervention.[104] While effective interventions exist for youth with substance use problems in general, the juvenile justice system has been slow to embrace evidence-based principles and practices; service delivery is typically inconsistent and continuity of care following release into the community remains a serious challenge.

To begin addressing these critical needs, NIDA has spearheaded the Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS), a $22.5 million, 5-year cooperative study designed to support research on the implementation of services to improve the continuum of SUD and HIV prevention and treatment interventions for youth under juvenile justice supervision. Collectively, the cooperative includes three key components: (1) a set of integrated, large-scale implementation research studies; (2) a large-scale national survey; and (3) two pilot implementation studies.

These complementary efforts are aimed at increasing the capacity of the juvenile justice system to address youth substance use. The large-scale implementation study is a randomized controlled trial designed to identify the most effective strategies to promote adoption of evidence-based prevention and treatment interventions in 36 juvenile justice systems across the country. The JJ-TRIALS survey is a tool for

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measuring the degree to which evidence-based practices are used throughout the U.S. juvenile justice system. Lastly, JJ-TRIALS pilot implementation studies will examine how well the strategies identified in the large-scale implementation study generalize to juvenile justice partnerships in other service sectors (e.g., public health departments to target HIV, the education system to target prevention services).

This initiative has the potential to enhance the implementation of SUD treatment in a context where youth engage multiple systems that must collaborate to ensure their complex needs are met. The JJ-TRIALS could become the foundation for future work exploring important questions about other systems affecting juvenile care, like coordinating treatment for co-occurring mental and SUDs, addressing family-level needs, and better utilizing technology and other system infrastructure in facilitating coordination among service providers.

Objective 3.1

Develop and test novel treatments based on the science of addiction

Recent advances in our understanding of the genetic, epigenetic, and neurobiological mediators of addiction have led to the identification of a range of potential therapeutic targets. New interventions are particularly needed for SUDs, such as cocaine, methamphetamine, and cannabis use disorders[91], for which there are currently no FDA-approved medications. In addition, developing new and improved treatment options for opioid use disorders remains a high priority due to the scope of the current opioid overdose epidemic.[47] NIDA will focus on supporting a robust translational pipeline of compounds, biologics, and nonpharmacological interventions (e.g., TMS, behavioral interventions) to be developed as potential treatments for SUDs.

President Obama's new Precision Medicine Initiative aims to develop the research infrastructure to begin to delineate individual biological factors that contribute to treatment outcomes. This initiative will set the groundwork for developing treatment strategies based on a person's unique DNA profile to achieve the greatest health benefit with fewer side effects (pharmacogenomics). Research has identified genetic variations that influence response to drugs as well as risk for SUDs, including genes for enzymes that metabolize drugs, neurotransmitter receptors and transporters, and enzymes that mediate neurotransmitter synthesis or degradation.[50,105,106] Understanding how genetic variations contribute to response to treatment will support the development of better-targeted therapeutic interventions.

Approaches

- Build upon discoveries from basic science to develop and test new medications and behavioral treatment interventions that specifically target the underlying neurobiological mechanisms of SUDs
- Develop and test novel nonpharmacological approaches to treat SUDs
- Expand testing of pharmacogenomic approaches for treating SUDs
- Explore how health care technologies can be used to improve patient identification, diagnosis, and personalized treatment

Objective 3.2

Develop and test metrics for measuring the quality and efficacy of treatment

One of the principles of current health reform efforts is that health care may be improved through the development and use of clinical quality measures. New health care payment and delivery models that create financial incentives based on quality performance measures are emerging. Efforts are underway to incorporate these types of measures into a "learning health care system" that continuously monitors performance and strives to rapidly adjust practices to improve outcomes.

In 2006, the Institute of Medicine recommended developing and implementing a quality measurement and reporting infrastructure as part of an overall strategy for enhancing the care provided in the field of SUD treatment.[107] The creation of valid and reliable quality measures that can be monitored and acted upon to drive improvements in identification and treatment of people with SUDs is a critical mechanism through which the behavioral health field can contribute to the ongoing evolution of the health care system.

Currently, almost all clinical quality measures used to evaluate addiction treatment are process measures that evaluate the services provided—for example, whether or not a patient was counseled about the medications available for opioid use disorder treatment. There is a significant need to develop and test outcome measures that evaluate patient response to treatment.

In addition to use in the health care system, valid outcome measures that can serve as end-point measures for clinical trials of therapeutics for SUDs are also urgently needed.[108] Over the next 5 years, NIDA will prioritize the development of metrics that measure the quality and efficacy of addiction treatments, leveraging existing measurement standards—such as the NIH Patient Reported Outcomes Measurement Information System (PROMIS®)—when possible (www.nihpromis.org/about/overview).

Approaches

- Identify target metrics that are effective indicators of long-term treatment efficacy
- Develop and test new end-point measures (other than abstinence) for clinical trials of SUD therapeutics
- Develop and test clinical quality measures for implementation in diverse health care settings
- Determine the influence of health care provider training and experience on patient outcomes

Objective 3.3

Identify biomarkers that predict response to treatment and risk for relapse

An impediment to understanding addiction as a brain disorder, and to its successful treatment, is the current lack of biological markers that can be measured to accurately determine the relative states of impairment and health across the trajectory of SUDs. In addition, behavioral markers such as impulsivity, emotional regulation, and sensitivity to reward may be used to predict response to treatment. NIDA will continue to support research to identify such biological and behavioral markers that predict treatment response and relapse risk. Reliable metrics will enable providers to more accurately predict risk for and diagnose an SUD, predict which therapeutic intervention may be most effective, or intervene early in people at risk for relapse. Identification of mechanistic biomarkers of SUD risk will also serve to illuminate targets and pathways for development of therapeutics and will facilitate tracking treatment response to allow for faster testing and validation of medications and other interventions.

Approaches

- Correlate findings from -omics studies (i.e., genomics, epigenomics, proteomics, metabolomics) to elucidate mechanistic pathways and target proteins or molecules that may be linked with the biological mechanisms of SUDs at specific stages
- Develop and test mobile sensing strategies as biomarkers for drug taking, recovery, and relapse risk

Objective 3.4

Develop and test strategies for effectively and sustainably implementing evidence-based treatments

Validated treatment strategies for SUDs have great potential to make a positive impact on public health. The size of this impact, however, is limited by the inconsistent use of evidence-based interventions in real-world settings—the "evidence-to-practice gap." A 2012 NIDA workgroup report outlined deficiencies in delivery of evidence-based treatments in SUD treatment centers, which included lack of medication-assisted treatment, recovery services, mental health assessments, and testing for infectious diseases (HIV, hepatitis C, etc.), as well as lack of fidelity to evidence-based practices in delivery of psychosocial interventions, among others[109] (www.drugabuse.gov/sites/default/files/files/evidence-based_treatments_in_real_world_settings_workgroup_report.pdf).

Research is needed to identify specific barriers to and facilitators of implementation and to explore approaches to support sustainable implementation of evidence-based practices—for example, research that addresses how various business practices, workforce strategies (e.g., health educators, peer support, etc.), service delivery models, coordinated care models, and screening and referral processes can improve treatment delivery and patient retention and outcomes. Targeted research is also needed to develop implementation strategies that address delivery-system-specific needs, including those of the criminal justice system, primary care, and integrated treatment systems. To address this need, NIDA will support research to develop and test strategies for effectively and sustainably implementing evidence-based treatments for SUDs in diverse health care delivery settings.

Approaches

- Identify the factors that influence effective and sustainable dissemination and implementation of evidence-based practices for treatment of SUDs and common comorbidities
- Develop and validate novel implementation strategies for delivering evidence-based SUD treatment and integrated treatment services in diverse health care settings
- Develop and test innovative approaches to leverage technology to support implementation of evidence-based practices

Improving Treatment with Electronic Health Record Technology

About 10 percent of people in need of treatment for an SUD receive specialty treatment.[1] Of those who are treated for an opioid use disorder, less than 30 percent receive medication-assisted treatments (MAT)—buprenorphine, methadone, or extended-release naltrexone (Vivitrol®)—even though there is strong evidence they are effective.[110] The two major questions in the addiction treatment field are:

- *How can we get more people with opioid use disorders to engage in treatment?*
- *How can we make sure the treatment they receive is based on the best available science?*

The growing adoption of electronic health records (EHRs) provides an important tool to address this problem.

People with SUDs are often seen by clinicians (i.e., their primary care doctor) in general medical settings, but visits typically focus on managing other illnesses. Substance use is rarely discussed or addressed in such visits. The NIDA Center for Clinical Trials Network, in consultation with the Office of the National Coordinator for Health IT, the Health Resources and Services Administration, and the Substance Abuse and Mental Health Services Administration, is developing a Clinical Decision Support (CDS) tool that can be incorporated into EHRs to help primary care providers identify patients with opioid use disorders and determine the best treatments for them. The CDS will include guidance on how to screen for and assess SUDs and will help the health care provider develop a plan of action tailored to meet the needs of the patient, taking into consideration the patient's motivation and treatment preferences and any co-occurring health conditions.

This effort will encourage the general health care system to identify patients in need of treatment, promote the use of evidence-based treatments like MAT, and foster the collection of standardized clinical data related to substance use in EHRs.

GOAL 4 Increase the public health impact of NIDA research and programs

Substance use disorders (SUDs) and their consequences present a significant and ongoing public health burden in our nation. While it is important to support scientific research that will increase our understanding of the SUD disease processes and ultimately lead to better prevention and treatment options, it is also crucial to understand that there are many people in need of help right now. An estimated 7.1 million individuals in the United States are dependent on or abuse illicit drugs, yet only about 15 percent receive treatment.[1] In addition, more than 25 percent of Americans, an estimated 66.9 million people, currently use tobacco products; despite significant declines in cigarette smoking, it is still the leading cause of preventable death in the United States, accounting for more than 480,000 deaths every year.[1,4]

A range of public health issues are associated with the current crisis of opioid abuse, including opioid use disorders, opioid overdoses, neonatal abstinence syndrome, and increased spread of infectious diseases like HIV and hepatitis C (HCV).[8–11,47] Science can help to inform these issues as well as other public health challenges including the significant unmet need for SUD treatment, changes in state policies related to marijuana, emerging drug trends including synthetic cannabinoids and cathinones, and the emergence of electronic cigarettes and vaporizers.

Right now there are unprecedented opportunities for advancing SUD treatment across the Nation. The combined effects of the Affordable Care Act, the Excellence in Mental Health Act, and requirements for parity of insurance coverage for behavioral health treatment are leading to a significant expansion in access to prevention and treatment services for SUDs and are creating financial incentives for integrating care for behavioral health disorders within the general health care system.[111] These changes, along with recent advances in addiction treatment and criminal justice reforms, present a unique opportunity for advancing the SUD treatment field.

In addition, the rapid acceleration in the development and adoption of health care technologies—including electronic health records and mobile apps and sensors—has the potential to revolutionize health care as well as research. These advances will facilitate health information exchange, real-time patient monitoring and outreach, more efficient coordination of patient care, use of real-time analytics to drive a "learning health care system," new approaches for implementing evidence-based practices, use of biosensors to predict and intervene in advance of a relapse, and collation of large clinical data sets for pragmatic trials and population studies.

Mobile Health: New Applications for Consumer Technologies

The mobile health (mHealth) industry is growing rapidly with new technologies that have the power to revolutionize health care. From automated text messaging services that educate parents and teachers about how to talk to children about the dangers of drugs to counseling apps that provide real-time support for patients in need, these technologies present incredible opportunities for preventing and treating SUDs.

One example is a mobile app developed by researchers at the University of Wisconsin, Madison, called Addiction-Comprehensive Health Enhancement Support System (A-CHESS). A-CHESS is designed to help patients transition from treatment into a stable recovery by enhancing their coping skills, providing a social support network, and linking them to aftercare services. The app includes:

- programmed routine check-ins with a care manager
- self-monitoring and feedback
- access to a "panic button" that immediately links the patient to a counselor
- social support through an online bulletin board or text messaging to other A-CHESS users
- GPS that alerts the patient to nearby resources and possible triggers (e.g., old hangouts)
- reminders for medication, appointments, and treatment milestones
- guided relaxation exercises

Importantly, these technologies have the potential to reach people who cannot or will not participate in the traditional treatment system, whether because of cost, lack of treatment providers in the area, or fear of stigma or discrimination. Technologies including telehealth and behavioral intervention software tools can also be used to support more efficient use of the SUD treatment workforce. The mHealth field is rapidly evolving, and NIDA will continue to support research on how to harness these technologies to more effectively and efficiently prevent and treat SUDs.

NIDA serves a number of roles relevant to public health, including supporting health services and epidemiology research, educating the public and relevant stakeholders on the science of drug use and addiction, helping to inform science-based decision-making, and engaging in strategic partnerships to translate scientific advances into public health gains. Science can help to inform many important questions, including:

- How can limited resources be most effectively used?
- How can prevention and treatment programs be better implemented?
- How can society best reduce harms associated with drug use, such as drugged driving and transmission of infectious diseases?
- What impacts are various policies likely to have?
- How can we best leverage technology?
- How can we identify and intervene with high-risk individuals and populations?
- Which health care models and payment systems promote the highest quality care?

To promote the use of science-informed decision-making to improve public health, NIDA will:

- **Objective 4.1:** Determine the impact of drug use and addiction on individuals, families, peers, and society
- **Objective 4.2:** Assess the impact of federal-, state-, and systems-level policies related to drug use and substance use disorders on public health and well-being
- **Objective 4.3:** Increase strategic partnerships with the community to improve dissemination and implementation of evidence-based research findings into policy and practice

Objective 4.1

Determine the impact of drug use and addiction on individuals, families, peers, and society

The effects of drug use, including nicotine, affect not just the individual but also his or her family, friends, and peers. Families and friends can be negatively impacted by drug use not just from the stress of seeing a loved one suffer through addiction but also through financial impacts. SUDs commonly affect the structure of a family because of divorce or the need to fill different roles to compensate for neglect of responsibilities by the drug user.[61] There is also an increased risk for interpersonal violence and child abuse and neglect (both physical and emotional), and these factors can lead to diminished attachments to parents and others, impaired self-regulation and problem-solving, decreased development of prosocial attitudes and behaviors, and impairment of healthy development. Indeed, parental drug use can have profound effects on children, from direct effects of using drugs while pregnant (e.g., neonatal abstinence syndrome) to impacts on perceptions of normative behaviors. Children of parents who abuse drugs have a greater risk for SUDs, depression, exposure to violence, and other health outcomes.[112]

Drug use, including tobacco, also has significant effects on society, including public health outcomes related to chronic disease (cancer, chronic obstructive pulmonary disease [COPD]) and the spread of infectious diseases (HIV and HCV); [8,10] public safety hazards such as crime, violence, and drugged driving;[62] and a large economic burden associated with increased health care costs, lost productivity, and criminal justice costs.[3] Understanding these consequences and the factors that influence their expression is critical for developing effective prevention, treatment, and mitigation strategies; for guiding development of laws and policies related to drug use; and for targeting limited resources to the efforts that will have the most potent effects.

Approaches

- Determine the impact of drug use and SUDs on public health outcomes
- Clarify the impact of drug use and addiction on families and peers
- Measure the societal costs associated with drug use and addiction

Studying Why People Use Tobacco to Inform Public Policy

Over the last several decades, dramatic changes in attitudes and behaviors have resulted in significant declines in cigarette use. Still, smoking continues to be the leading cause of preventable disease, disability, and death with nearly half a million people dying each year in the United States.[4] In 2011, NIDA and NIH began collaborating with the U.S. Food and Drug Administration (FDA) Center for Tobacco Products to develop the Population Assessment of Tobacco and Health (PATH) Study.

The PATH Study is a household-based, nationally representative, longitudinal cohort study of nearly 46,000 adults and youth in the United States. Interviewers are meeting with each person once a year for at least 3 years. The study will provide comprehensive data on tobacco use behaviors, including patterns of use, attitudes, beliefs, exposures, and related health outcomes among the U.S. population. Data collection began in September 2013 and will continue into 2016. These data will help inform FDA's regulatory decisions and actions to further reduce tobacco-related death and disease in the future.

Objective 4.2

Assess the impact of federal-, state-, and systems-level policies related to drug use and substance use disorders on public health and well-being

Diverse federal, state, and local laws and policies related to substance use and SUDs have the potential to affect public health and safety. This includes laws and policies that affect health care reimbursement, access to treatments, criminal sentencing, clean needle distribution, naloxone distribution, good Samaritan laws, e-cigarette regulations, marijuana legalization (for medical and/or recreational purposes), drug testing, eligibility for social services, drugged driving, and alcohol and tobacco taxes and regulations. There is a significant need for research on these and other relevant policies to understand their effects on public health and safety, to assess their cost effectiveness, and to describe any unintended consequences to help inform future decision-making.

Approaches

- Determine how laws and policies affect drug use trends and prevalence of SUDs
- Identify impacts of laws and policies on key health and social indicators, such as rates of use of other drugs, tobacco, and alcohol; corollary risk and protective health behaviors; transmitted infections including HIV and HCV; comorbid health conditions and outcomes (cancer, COPD, mental health); truancy, academic performance, and school dropout; crime and criminal justice outcomes; accidents associated with drugged driving; and employment outcomes
- Track the impact of laws and policies on social norms, attitudes, beliefs, perceptions of harm, and disapproval associated with drug use
- Measure the economic impact of laws and policies including costs related to health care, criminal justice, and workplace productivity

Objective 4.3

Increase strategic partnerships with the community to improve dissemination and implementation of evidence-based research findings into policy and practice

As discussed in Goals 2 and 3, there is a significant research-to-practice gap in the implementation of evidence-based prevention and treatment strategies. Implementation science develops and tests strategies for increasing effective and sustainable uptake of scientific advances by service and treatment providers in real-world settings. To accomplish this, strong partnerships with organizations that have the power to affect real-world implementation are needed.

Health care providers, payers, federal and state agencies, state Medicaid directors, public health agencies, educators, community coalitions, and others need to be engaged early and often throughout the development and testing of prevention and treatment interventions to ensure that real-world barriers (e.g., workforce, billing) are taken into consideration. These collaborations should also help researchers prioritize efforts to address critical ongoing barriers to effective prevention and treatment of SUDs. International collaborations are also important for building research capacity in other countries and leveraging the global network of scientific experts on addiction to ensure that we all learn from one another's successes and failures and generate knowledge that will benefit everyone.

Approaches

- Support the development of models to scale up evidence-based prevention and treatment interventions and implementation strategies
- Explore nontraditional methods for addressing current barriers to effective prevention and treatment, such as workforce shortages and engagement of nontreatment seekers
- Develop educational materials and training tools, including clinical decision support, to support effective dissemination of evidence-based practices
- Develop new methods for assessing service delivery outcomes of care in diverse settings in real time

Real-World Impact: Training Clinicians

Many health care providers are hesitant to address SUDs and related issues, such as the risk for misusing prescription pain relievers. This is often because clinicians are not adequately trained to address these issues during medical school and because drug use can be a sensitive topic that many people are uncomfortable discussing. U.S. medical schools offer only minimal training in pain management, for example, leaving many doctors uncertain of how to treat patients with pain.[85] This lack of training contributes to the overprescribing of highly addictive opioids. Research shows that most people who misuse these medications get them from legitimate prescriptions—either their own or those of friends or family members.[1]

To address these problems, NIDA established the NIDAMED initiative to educate health care providers on how to identify, prevent, and treat SUDs and how to safely prescribe medications for pain. With the help of Medscape Education and funding from the White House Office of National Drug Control Policy, NIDA developed continuing medical education (CME) courses that provide practical guidance for physicians and other clinicians in screening pain patients for SUD risk factors before prescribing and in identifying when patients are misusing their medications. The courses use videos that model effective communication about sensitive issues without losing sight of addressing the patient's pain. As of October 2, 2015, more than 113,000 clinicians had completed these courses for CME credit. Also, the American Association of Nurse Practitioners, the American Academy of Physicians Assistants, and the American Academy of Family Physicians offered these CMEs to their members for credit.

NIDAMED is currently partnering with a coalition of professional health care organizations along with experts in the addiction and clinical implementation field to improve adult and adolescent patient outcomes related to SUDs. The coalition includes the following:

- American Academy of Pediatrics
- California Academy of Family Physicians
- American Society of Addiction Medicine
- American Osteopathic Association
- American Association of Nurse Practitioners
- American Academy of Physicians Assistants

The coalition is creating a CME that will train health care providers on how to prevent SUDs in adolescent patients. It will focus on prescription drug misuse and marijuana and tobacco use, as well as use of other drugs.

NIDAMED enables physicians to be the first line of defense against drug use and addiction and to increase awareness of the likely impact of substance use on a patient's overall health.

High-Risk, High-Reward Research: Avenir Awards

When making tough decisions about how to spend precious research dollars, institutions often naturally lean toward projects with a reasonable chance of success and shy away from more risky proposals. But the fact is that some of the biggest research payoffs may actually flow from out-of-the-box, untested, high-risk ideas. To capture those ideas, we need to be creative and flexible in our funding mechanisms.

The NIDA Avant-Garde Award Program for HIV/AIDS and Drug Use Research is one such mechanism. It was created to support highly innovative investigators with groundbreaking ideas that are likely to open new areas of research on the prevention and treatment of HIV/AIDS among drug users. Although it is open to investigators at all career stages, the Avant-Garde Award has not attracted many in the early stages of their careers who may not have the data needed for an NIH Research Project Grant (R01). This deficit called for some programmatic tweaking, which led to NIDA's creation of two Avenir (meaning "future" in French) Award Programs: the Avenir Award Program for Research on Substance Abuse and HIV/AIDS (www.grants.nih.gov/grants/guide/rfa-files/RFA-DA-15-007.html) and the Avenir Award Program for Genetics or Epigenetics of Substance Abuse (www.grants.nih.gov/grants/guide/rfa-files/RFA-DA-15-006.html). These programs complement Avant-Garde by focusing on exceptionally creative early-stage investigators who propose trailblazing—and possibly transformative—approaches to these two major problem areas in biomedical and behavioral research.

The Avenir Award Program for Research on Substance Abuse and HIV/AIDS (DP2) supports highly innovative research aimed at improving prevention and treatment, long-term retention in care, and ultimately, eradication of HIV within at-risk, substance-using populations. In 2015, NIDA funded four new Avenir Awards for Research on Substance Abuse and HIV/AIDS. These projects will use a wide range of approaches, including:

1. Exploring interventions to reduce HIV transmission among people who inject drugs
2. Using high-resolution computer modeling to develop community-specific responses to HIV transmission among people who inject drugs
3. Examining the potential for a new single-dose antibody therapy to suppress viral replication in HIV-infected people, which would be highly beneficial for substance users who have trouble adhering to current HIV treatments
4. Integrating neurobiological and behavioral research techniques to advance our understanding of HIV-related decision-making in drug users

The Avenir Award Program for Genetics or Epigenetics of Substance Abuse (DP2) is funding projects in the following areas:

1. Drug-related behaviors and how they alter epigenetic modifications in the brain, to develop more effective epigenetic-based addiction treatment and prevention strategies
2. Epigenetic mechanisms underlying nicotine dependence, to provide a foundation for developing new treatments to help people stop smoking
3. Development of novel technologies and methods for genetic and epigenetic analysis
4. Integration of epigenetics and genetic analyses

Priority Focus Areas

The four main goals listed above outline the broad scope of NIDA's strategic objectives over the next 5 years. Across these goals and objectives, four priority focus areas have been identified that present unique opportunities to leverage over that time frame. These areas include:

1. **Understanding the complex interactions of factors influencing drug use trajectories**
2. **Accelerating development of treatments**
3. **Addressing real-world complexities**
4. **Advancing bidirectional translation**

1. Understanding the complex interactions of factors influencing drug use trajectories

Behaviors such as drug use and addiction are mediated by numerous biological, environmental, social, and developmental factors. Understanding the interactions among these factors and how they contribute to the risk for addiction and other negative consequences of drug use is critical for developing better prevention and treatment strategies. Basic and clinical addiction research have made significant progress in the identification of discrete genetic, epigenetic, neuro-circuitry, and behavioral factors that contribute to substance use disorders (SUDs).[40] Moving forward, the integration of knowledge across scales and domains related to the complex expression of phenotypes will allow for a deeper and more clinically meaningful understanding of addiction, which, in turn, can translate into better prevention and treatment interventions.

Advances in informatics and information technology are enabling more sophisticated types of analyses than ever before. Effectively leveraging these advances will require coordinated efforts, including:

- infrastructure development
- multidisciplinary workforce training
- culture change related to data sharing
- consensus-based data standardization
- support for large-scale data collection, curation, and maintenance

To achieve real progress toward understanding the human brain and how it is affected by drugs, it is vital to develop more powerful analytical methods and visualization tools that can help capture the richness of data being generated from genetic, epigenetic, molecular, proteomic, metabolomic, brain imaging, behavioral, clinical, social, and environmental studies. Neuroscience is fast approaching a data analysis bottleneck.[113] Dramatic advances in sequencing technologies, for example, have reached the point where it is now far cheaper to sequence whole genomes than to analyze the results. As a result, we are taking advantage of smaller and smaller fractions of the high density of data derived from various methodologies. A long-term effort is needed to develop the infrastructure necessary to analyze complex systems (drawing from mathematics, statistics, engineering, computer science, and bioinformatics) in ways that allow researchers to investigate behaviors of nonlinear, highly interacting systems. Such analytical and modeling tools are urgently required to take full advantage of the emerging data sets and to address multifaceted questions, such as how genes linked to addiction influence brain function and the response to drug use; how orchestrated genetic networks drive complex, adaptive brain functions; and how social and environmental stimuli can interact with those networks to perturb their balance.

Over the next 5 years, NIDA will capitalize on emerging technologies and discoveries to facilitate integration and analysis of diverse data sources, including genomic, epigenomic, behavioral, neurobiological, environmental, and other phenotypic data associated with the stages of drug use and addiction. These efforts will focus on developing data sets and tools with the power to reveal hidden associations across organizational, temporal, and spatial scales and yield critical insights about brain function and development, genetic influence on brain and behavior development, and the biological precursors to and correlates of SUDs. These efforts will include:

The Adolescent Brain Cognitive Development (ABCD) Study

This landmark 10-year study led by NIDA in partnership with NIAAA; NCI; the Collaborative Research on Addiction at NIH, or CRAN; and other NIH partners (NICHD, NIMH, NIMHD, NINDS, and OBSSR) will establish a large cohort of youth to prospectively examine neurodevelopmental outcomes using brain imaging, genetics, and varied measures of physical health and development, psychosocial development, cognition (e.g., information processing, learning, memory, decision-making), academic achievement, motivation, and emotional regulation. Youth will be recruited at approximate ages 9 or 10 and followed into early adulthood, the period of highest risk for substance use and SUDs. Objectives of the study include:

- Identifying individual developmental trajectories (e.g., brain, cognitive, emotional, academic) and the factors that can affect them
- Developing national standards of normal brain development in youth
- Examining the role of genetic versus environmental factors on development, enriched by comparisons of twin participants (800 pairs are expected to be included in the study)
- Exploring the effects of physical activity and sleep, as well as sports injuries and other injuries on brain development and other outcomes
- Evaluating the onset and progression of mental disorders, factors that influence their course or severity, and the relationship between mental disorders and substance use
- Providing knowledge of how exposure to different substances such as alcohol, marijuana, nicotine, caffeine, and others, individually or in combination, affects various developmental outcomes (and vice versa)
- Providing rapid and open access to de-identified data to enable scientists to address unforeseen scientific questions over the course of the study, maximizing and extending the impact of this scientific investment

Findings from the ABCD study will greatly increase our understanding of environmental, social, and genetic factors relevant to brain and cognitive development and their role in the initiation of substance use and the progression to SUD, which can inform the development of substance use prevention and treatment strategies.

The Addictome Project

This initiative aims to integrate diverse data types to enable meaningful analyses, assimilating a diverse, interoperable collection of multiscale data sets that can be mined by the scientific community and visualized in a user-friendly framework to support discovery of novel relationships and scientific knowledge related to addiction. The Addictome will be a collection of numerous data types from diverse sources representing internal and external factors that contribute to an individual's risk for addiction across the lifespan. It will provide the infrastructure tools necessary to enable investigation into how these diverse factors interact within and across individuals to influence drug experimentation, escalation, and diverse substance use trajectories. This project will be aligned with the Trans-NIH Big Data to Knowledge initiative.

It is also critical to ensure that, once created, these databases are effectively used. As a part of this effort, NIDA will work to:

- Develop standard data formats and common data elements for a user-friendly framework
- Ensure that addiction scientists are trained in the statistical and analytical methods needed to analyze these data sets
- Provide incentives for contributing data to this initiative
- Increase support for secondary data analyses

Gene x Environment x Development Interplay (GxExD) Research

Understanding how environmental exposures impact genetic and epigenetic factors to influence the risk for developing SUDs across development is critical for creating and improving prevention and treatment strategies—especially for SUDs for which there are limited effective therapeutic interventions available. The primary challenge of GxExD research is to determine how small genetic effects across many genes combine to contribute to the overall risk for SUDs and how these genetic effects change with varying environmental exposures across human development.

A number of single-gene variants that contribute to SUD risk have been identified. In addition, research has successfully identified some environmental contributors to risk. For example, when a person experiences extreme or prolonged stress, changes in the epigenetic profile can make him or her more susceptible to drug taking and addiction.[114] The nearly infinite biological complexity associated with individual genetics, variation in environmental exposures, and diversity in human behavioral responses make GxExD research particularly challenging. However, new advances in genetic and epigenetic technology coupled with increasing and evolving computational power are allowing such challenges to become increasingly tractable. Using these technologies to study complex GxExD interactions gives us the power to transform our fundamental understanding of how drug use and addiction evolve.

2. Accelerating development of treatments

The SUD treatment field has seen some important successes, but significant challenges remain. There are currently three medications approved by the U.S. Food and Drug Administration (FDA) to treat opioid addiction: buprenorphine, methadone, and extended-release naltrexone.[91] While these have represented meaningful advances in the ability to treat opioid use disorders, the efficacy of these medications is far from ideal. In addition, while there are evidence-based psychosocial treatments (e.g., cognitive-behavioral therapy, contingency management interventions, etc.) available for the treatment of cocaine, methamphetamine, or cannabis use disorders, there are no approved medications for these SUDs. Moreover, many larger pharmaceutical companies are reticent to enter the addiction market because of the perception of a small market size, the difficulties in executing clinical trials in patients with SUDs (who frequently suffer from multiple comorbidities and who often do not adhere to the treatment protocol), and the high regulatory bar required to obtain approval by the FDA (i.e., the focus on abstinence instead of harm reduction).[99]

To accelerate development of new medications for SUDs, NIDA supports a dual strategy. The first is a "repurposing" strategy that focuses on medications already approved for other indications that may also show potential benefit for treating or preventing SUDs. This approach aims to leverage existing safety profiles and pharmacology data to lower development costs and shorten the timeline for obtaining FDA approval. The second is to translate basic knowledge of the molecular pathways and brain circuits involved in SUDs to develop new approaches that modulate specific targets and networks. In this context, novel therapeutic approaches include pharmacotherapies as well as biologics (e.g., vaccines, immunotherapies, peptides) and nonpharmacological interventions such as transcranial magnetic stimulation, deep brain stimulation, and neurofeedback, which modify the activity of specific brain regions and, thus, may have fewer adverse effects.

NIDA will continue to prioritize efforts to de-risk medication development and foster strategic partnerships to accelerate the development of therapeutics for SUDs using the combined strengths and resources of NIDA and outside organizations, including academic institutions, pharmaceutical and biotechnology companies, private and public foundations, and small businesses. In addition, efforts will focus on defining alternative end points other than abstinence, such as decreased drug use, that can be linked to improved patient outcomes to reduce the regulatory bar to obtain approval of new therapeutics. For example, a recent publication found that reduced use of cocaine decreased endothelial dysfunction, a marker of heart disease risk that is characteristic of chronic cocaine use.[115]

Treating Addictions with Antibodies

Can we prevent a drug from affecting the brain of the person who takes it? One promising approach is to tap into the well-known ability of antibodies in the immune system to recognize, stop, and get rid of foreign agents. Anti-addiction vaccines aimed at eliciting antibodies that block the effects of a specific drug have great potential for treating SUDs, and researchers have been exploring the feasibility of this approach against drugs such as nicotine, cocaine, heroin, and methamphetamine for several years.

The biggest challenge thus far has been getting an immune response strong enough to effectively neutralize the drug in the bloodstream before it enters the brain. NIDA continues to invest in research to enhance the potency of these vaccines, but we are also investing in an alternative approach called passive immunization. This approach bypasses the person's immune response by using a monoclonal antibody that is made in a lab. An anti-methamphetamine monoclonal antibody (ch-mAb7F9) is in development, and the results are promising. The first-ever Phase I, randomized clinical trial of this approach found that ch-mAb7F9 was safe and well-tolerated, and that it remained at high enough levels in the blood to be effective for an average of 3 weeks.[116] While these preliminary results are encouraging, more studies are needed to further assess its safety and side effects in active methamphetamine users.

The concept of ch-mAb7F9 is exciting because it offers specific advantages for addiction therapy over other vaccines. For example, the user's immune system does not need to be functioning, making this type of therapy uniquely suited to patients with HIV and other conditions that suppress the immune system. Also, compared with vaccines, monoclonal antibodies can easily reach very high concentrations that can last much longer, and the dosing can be more precisely controlled. When combined, these properties can provide around-the-clock protection from methamphetamine's effects, making people much less vulnerable to relapse and thus more likely to succeed with recovery.

Methamphetamine use disorder causes serious medical, social, and economic harm, yet there are currently no FDA-approved medications for its treatment. If successful, therapies like ch-mAb7F9—either alone or in combination with other treatments—have the potential to revolutionize how we treat, and maybe even someday prevent, addiction to methamphetamine and other drugs of abuse.

3. Addressing real-world complexities

The specific symptoms experienced by people with SUDs are shaped by complex, interacting factors that range from co-occurring physical and behavioral health conditions to social and environmental influences. In addition, while much of the research focuses on the effects of taking a single drug, we know that most drug use and SUDs involve polydrug use, including alcohol and tobacco use. Further, different stages of life, such as adolescence, pregnancy, and old age, confer unique risk factors and treatment needs. Finally, when effective evidence-based prevention and treatment strategies are developed, there is often a significant research-to-practice gap in the implementation of these interventions. A broadening of research focus is necessary to include the context of such interacting complexities to develop and effectively disseminate interventions that meet the diverse needs associated with this variability in substance-use-related phenotypes.

Substance use, including tobacco use, and SUDs frequently occur in people with psychiatric and physical health comorbidities. These conditions can often arise from shared causal factors, and these comorbidities can interact to affect symptom profiles, illness trajectory, and treatment outcomes.[69,117] As the field moves toward an integrative view of SUDs, phenotypes should be

defined in a way that captures these underlying causes. Rather than considering all SUDs together, varied SUD phenotypes should be separated based on functional domains that can be defined biologically. Indeed, defining the pathway from gene variation to molecular profile, to neuron function and brain circuit activity, and then to disordered behavior will enable a deeper understanding of addiction and reveal new targets for prevention and treatment intervention.

The severity of any co-occurring condition can influence the course of another, which highlights the importance of effectively integrating treatments. Psychiatric disorders frequently occur along with SUDs and, in the case of nicotine, contribute significantly to shorter life expectancies among this population. In addition, SUDs are associated with increased risk of physical health comorbidities, including HIV, cancer, chronic pain conditions, and cardiovascular and cardiopulmonary diseases.[118] Recent health care reform efforts are prioritizing integrated medical care for people with SUDs, and more research is needed to inform the development of treatment delivery strategies that simultaneously address SUDs and co-occurring conditions.

The complexity of interacting biological, environmental, and social factors that contribute to and sustain SUDs presents significant opportunities for the application of precision medicine. An individual's environment, experience, and biology combine to determine their risk for developing an SUD, the trajectory the SUD will take, and the interventions that will be most effective for treating it. This is the inspiration behind the President Obama's Precision Medicine Initiative, which will provide a foundation for the development of personalized interventions addressing the multiplicity of individual phenotypes.

More focused research is also needed to help address the significant research-to-practice gap in the implementation of evidence-based prevention and treatment interventions. Closing the gap between research discovery and clinical and community practice is both a complex challenge and an absolute necessity if we are to ensure that all populations benefit from the Nation's investments in scientific discoveries. Research is needed to better understand the barriers to successful and sustainable implementation of evidence-based practices and to develop implementation strategies that effectively overcome these barriers. Conversely, there is also a need for research that addresses how to reduce the use of strategies and procedures that are not evidence based that may be harmful or wasteful.

NIDA will prioritize research that focuses on addressing real-world complexities, such as:

- Understanding the common underlying substrates and biological mechanisms that contribute to common comorbidities
- Research that incorporates real-world complexities including common comorbidities, pregnancy, development and aging, environmental stress, polysubstance use, etc.
- Development of prevention and treatment interventions that account for individual differences in biological, environmental, and social factors that impact SUD trajectories and phenotypes (precision medicine)
- Development, validation, and use of animal models that address real-world complexities
- Strategies to improve the effective and sustainable implementation of evidence-based prevention and treatment interventions (implementation science)

4. Advancing bidirectional translation

One core component of NIDA's mission is supporting research that will ultimately improve individual and public health. To support this goal, NIDA is fostering a strong bidirectional translational pipeline spanning basic neuroscience to clinical and applied research that is focused on the neurobiological substrates of addiction. Efforts are focused on integrating and coordinating human and basic research spanning all stages of drug use (i.e., initiation through recovery) and stages of development (i.e., from childhood through senescence), and across scales (i.e., molecular to societal).

Basic research should identify potential mechanisms and processes that may provide targets for intervention—including new molecular, brain circuit, and behavioral targets—which should then rapidly be tested in humans. Clinical research findings should be translated in applied, patient-oriented, and population-based research to facilitate broad implementation of best practices and improve public health. Importantly, insights from clinical and applied research should be modeled in basic research to identify and understand the biological mechanisms underlying the various phases of addiction.

Human and animal studies that use directly comparable outcome measures and testing conditions offer a powerful translational opportunity. A key integrative interface between clinical and basic studies is provided by human laboratory studies, including those with healthy volunteers. A recent reorganization of NIDA's divisions and branches was undertaken to foster bidirectional communication and interaction between clinical, applied, and basic research efforts. NIDA's ongoing efforts in this area will promote strong collaborations across basic and clinical researchers to advance this goal.

Cross-Cutting Themes

Throughout the strategic planning process, a number of cross-cutting themes emerged that are relevant across multiple goals and objectives. NIDA will work to ensure that these themes are addressed across institute programs and initiatives. These cross-cutting elements include:

- advancing basic research on neuroscience and biology
- leveraging technology
- driving innovation
- increasing scientific rigor and reproducibility
- building a strong, diverse, multidisciplinary scientific workforce
- promoting collaboration
- encouraging data and resource sharing (data harmonization)
- supporting health equality
- increasing the real-world relevance of research (translation)

Advancing Basic Research on Neuroscience and Biology

Advancing fundamental knowledge of basic biological, and especially neurobiological, processes is critical for advancing our understanding of the effects of drugs and in guiding the design of interventions to prevent and treat substance use disorders (SUDs). SUDs are complex disorders involving disruption of brain circuits involved in reward, decision-making, learning, and self-control. They are mediated by complex biological, social, environmental, and developmental factors that dynamically interact to influence risk, trajectory, and outcomes. Understanding this complexity will require drawing upon multiple disciplines across biomedicine, including neuroscience, genetics/epigenetics, behavioral and social sciences, development research, and information sciences.

Leveraging Technology

The last few years have seen tremendous advances in the development and implementation of technologies that have great promise for accelerating research on drug use and addiction. Particularly prominent are technologies for gene sequencing, epigenetic analyses, neuronal cell classification, brain imaging, and modulation of brain circuits. Also relevant is the expanding access to increasingly larger databases of genetic, epigenetic, transcriptomic, and clinical health data—through electronic health records and mobile health technologies—along with rapid advances in analytic, computational, and information technologies. Programs such as the BRAIN Initiative, the NIH Blueprint, and the NIH Common Fund are helping to drive accelerated technology development. NIDA will actively follow these advances and look for opportunities to capitalize on these developments to advance research on drug use and addiction.

Beyond Simply DNA: Epigenetics

It has become increasingly clear in the past two decades that the roots of inheritance extend beyond the genome and its simple four-letter code. A top priority across all biomedical research disciplines is studying an additional form of inheritance known as *epigenetics*, so-named because it operates on top of (*epi*, in Greek) simple genetics, affecting which genes actually get expressed. Its mechanisms remain a complex puzzle that many scientists are working hard to piece together.

We now know that the epigenetic changes affecting cellular patterns of gene expression are a direct response to and reflection of that cell's history. The epigenome is constantly changing in response to signals coming from inside the cell, from neighboring cells, or from the outside world. In this way, the specific modifications along the DNA molecule or on the proteins that package it (i.e., histones) constitute a kind of cellular memory of a person's experiences, good and bad, throughout his or her lifetime.

Importantly, these epigenetic marks can be not only mapped and characterized but also manipulated to better understand and, in theory, treat various disorders, including addiction.

The long-lasting nature of the behavioral changes seen in SUDs suggests that changes in patterns of gene expression, like those resulting from epigenetic modifications, are occurring in the brain. Independent lines of research have clearly shown that these processes play a crucial role in mediating the lasting effects of drugs on the brain. For instance, we now have robust evidence—albeit mostly from animal studies—that repeated exposure to drugs of abuse can induce changes in the brain's reward regions through various modes of epigenetic regulation. Furthermore, in some cases, researchers have been able to demonstrate a direct link between those epigenetic changes, gene expression, and addiction-related behavioral problems.[119]

Studies of epigenetic mechanisms in addiction are providing an unprecedented view of the range of genes and noncoding regions of DNA that are affected by repeated drug exposure and the precise molecular basis of that effect. Exciting new research is being conducted to validate key aspects of this work in human addiction and evaluate whether we can mine this information to develop new diagnostic tests and more effective treatments for SUDs.

Driving Innovation

The biomedical research workforce in this country includes a tremendous number of talented and dedicated scientists with innovative ideas for how to advance research. NIDA will work to encourage and reward innovation to drive advances in addiction research by (1) promoting interdisciplinary collaborations, (2) encouraging research and development through our small business innovation research program, (3) crowdsourcing the development of novel technologies and solutions through challenge grants, (4) supporting innovative researchers through novel mechanisms including our Avenir Awards Program, and (5) supporting training in cutting-edge areas important for driving innovation (e.g., data science).

Increasing Scientific Rigor and Reproducibility

Reliable and reproducible research findings are essential to the advancement of science. Over the last few years, multiple studies have reported a troubling lack of reproducibility of biomedical research findings.[120–122] Though part of this lack of reproducibility could reflect biological diversity, other factors that are likely to contribute include: selective reporting of data, invalid statistical methods, substandard laboratory techniques, insufficient transparency in reporting key methodologies and findings, and a failure to train students in ethical scientific practices. NIDA is committed to the responsible stewardship of public funds and will focus on enhancing the reliability of the research we support. To this end, NIDA will actively contribute to the NIH-wide Rigor and Reproducibility Initiative, participate in relevant activities of scientific organizations focused on enhancing reproducibility through education and outreach, and make concentrated efforts to improve both the quality and credibility of addiction research.

Building a Strong, Diverse, Multidisciplinary Scientific Workforce

The entire biomedical research enterprise relies on the creativity, innovation, and dedication of the Nation's scientific workforce. NIH and NIDA are committed to supporting a sustainable and robust workforce of neuroscientists, clinicians, chemists, physicists, behavioral and social scientists, bioengineers, statisticians, economists, mathematicians, health services researchers, and others who are equipped to address the greatest challenges and opportunities in biomedical research. Attracting and retaining a diverse, well-trained, and multidisciplinary workforce is a key to achieving our overall mission and addressing the challenges of addiction research. Efforts will focus on increasing the number of scientists with the multidisciplinary training necessary to address the complexities of addiction research; supporting the development of a high-quality, diverse, and sustainable scientific workforce; enhancing recruitment and mentoring of underrepresented investigators; and improving mentoring of young scientists.

Promoting Collaboration

Fulfilling NIDA's mission will require effective partnerships with and between stakeholders throughout the community, including collaborations between scientists, health care providers, engineers, informaticists, health care payers, pharmaceutical and biotechnology companies, public health organizations, patients and families, people in recovery, community prevention organizations, educators, federal and state agencies, and others. NIDA will facilitate collaboration among researchers in disparate fields and between researchers and the community. In addition, NIDA will work to maximize the impact of our research by working directly with diverse stakeholders to improve dissemination of NIDA research findings, support more rapid uptake of evidence-based practices, facilitate critical connections among areas of research, improve translation of basic findings to clinical interventions, and drive evidence-based decision-making across the community.

Encouraging Data and Resource Sharing (Data Harmonization)

Data sharing is an essential element of applying the power of data science and information technology (Big Data) for SUD research. Harnessing large quantities of data generated by researchers across the world has numerous methodological and economic advantages and provides tremendous opportunities for gaining new insight into addiction. To realize this benefit, however, there are many challenges to overcome. In particular, scientists and users from diverse areas need to be able to find data easily and to analyze them in new ways. Combining data from various sources and formats requires implementation of data standards as much as possible, which can be achieved via usage of common data elements, shared ontologies, and data dictionaries. Operational challenges related to data curation, development of advanced analysis tools (including machine learning and artificial intelligence techniques) and visualization strategies, and establishment of a culture of data sharing and open access within the scientific community need to be addressed. NIDA will work to develop standard practices and approaches that create incentives for sharing data and for secondary analysis of existing data sets.

Big Data for Addiction Science

Rapid progress in addiction research over the past few years has been fueled in part by technological advances, particularly next-generation sequencing, genomics, epigenetics, epidemiology, and neuroimaging. These advances have enhanced our understanding of the biological, developmental, and environmental factors that affect brain function in health and disease. Big Data is now providing unprecedented new opportunities to maximize the value of research results, giving researchers the ability to analyze huge amounts of data in new ways—turning vast data sets of complex information into knowledge.

Big Data is more than just large data sets; it refers to the challenges and opportunities presented by combining and analyzing different types of complex data in an integrated way. In research on SUDs, these data sources include imaging, phenotypic, molecular, exposure, clinical, health, behavioral, and many other types of data generated by researchers, hospitals, and mobile devices around the world. These data have the power to reveal new treatments, determine the genetic and environmental causes of SUDs, support the development of precision medicine in health care, and so much more.

There are certainly challenges to overcome, such as:

- how and where to store massive data sets
- how to integrate and harmonize data
- how to ensure data quality and consistency
- how to facilitate efficient use of available data
- how to foster a culture of open science and data sharing
- how to ensure privacy and confidentiality

NIDA and the NIH Big Data to Knowledge program are committed to addressing these challenges and helping the biomedical research community harness Big Data's full potential.

Supporting Health Equality

NIDA is committed to addressing health disparities, studying unique SUD issues of underrepresented populations, and supporting health equality research across the lifespan. This requires considering the impact of age, sex, sexual and gender identity, race, ethnicity, culture, and socioeconomic status on substance use and SUDs. NIDA will work to ensure that these factors are adequately addressed in the research we support.

Improving Outcomes by Considering Sex and Gender Differences

Historically, females have been underrepresented in scientific research. For instance, preclinical research often studies only male animals and cell lines. It is often assumed that results can be generalized to females, but this assumption is faulty. The same is true of human research and includes the field of addiction.[123] At NIDA, research across all program divisions is showing that outcomes are not always the same in males and females. Some are stronger in one sex than the other, some occur only in one sex, and still other outcomes are opposite between the sexes.

There is a large body of SUD prevention and treatment research reporting outcomes that vary by sex. It is important to understand the mechanisms that underlie these differences to develop interventions targeted to males and females, which can improve outcomes in both sexes. Beyond the genetic differences between males and females, other mechanisms may include cultural, psychosocial, and environmental factors; sexual dimorphisms in the brain; and epigenetics.

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NIDA will continue to support research targeted to understanding sex differences in both animal models and clinical research. This research includes the role of menstrual cycles and their associated hormones, pregnancy and the postpartum period, and factors such as intimate partner violence and trauma that are experienced mostly by women.

As we enhance our research on sex differences, we must also consider the role of gender factors—roles and expectations of males and females that are culturally and socially based. With respect to drug abuse, such factors can be reflected in differential access to drugs, reasons for using drugs, and access and barriers to treatment.

Sex is the most fundamental genetic difference; every cell has a sex. From this perspective, sex differences are the low-hanging fruit for achieving precision medicine. In June 2015, the NIH announced a new requirement to report data for both males and females in all human and vertebrate animal research effective January 25, 2016.[124] This represents a crucial cultural shift, which will greatly improve the health of both women and men, including those with SUDs.

Increasing the Real-World Relevance of Research (Translation)

NIDA is committed to making our sponsored research more relevant and applicable to real-world settings by proactively tackling relatively neglected and challenging issues such as polydrug use (which will require the development of validated animal models), nontreatment-seeking populations, patients with complexities (e.g., older adults; those who are incarcerated, pregnant, or in the military; and those with psychiatric and physical health comorbidities), and the impact of social factors (e.g., poverty, racism, housing and educational inequality, etc.).

Translation, Implementation, and Dissemination

Another main element of NIDA's mission is ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disorder. Addiction science can only improve public health if research findings effectively reach the people who can benefit from them and if the public's understanding of drug abuse is changed by new knowledge. One of NIDA's central roles is to be the trusted source of data related to drug use and addiction and to ensure that new findings are rapidly and effectively disseminated to the field and to the wider public.

A crucial aspect of this mandate is to promote wider recognition of addiction as a chronic, relapsing brain disorder. Addiction is a disorder that powerfully compromises executive function circuits that mediate self-control and decision-making; failure to understand this often results in stigma against people with substance use disorders (SUDs). This stigma has contributed to the slow adoption of effective treatments for addiction, including medication-assisted treatments for opioid use disorders, such as methadone and buprenorphine.[125] It has also impeded implementation of evidence-based harm reduction approaches such as needle exchange programs to prevent the spread of HIV and hepatitis C.[126] Effective dissemination of research findings can facilitate evidence-based decision-making and drive improvements in public health.

NIDA's communication efforts are targeted to a broad range of stakeholders, including health care providers, teens, parents, educators, community organizations, policymakers, and others. Our NIDAMED initiative and Blending Initiative develop educational materials that include continuing medical education courses to train health care providers on evidence-based practices for screening individuals for risky substance use, prescribing for pain, and treating adolescents with SUDs.

NIDA strives to make addiction research more accessible to people in the community by strategically leveraging social media, blogs, and the news media to promote new findings, inform the public about emerging drug trends, and educate the community on addiction science. NIDA also engages in various forms of outreach targeted to adolescents, including our popular teen-oriented Drugs and Health Blog, our annual National Drug and Alcohol Facts Week℠ events that engage participating schools across the country, and Drugs & Alcohol Chat Day, in which NIDA scientists answer questions from middle- and high-school students in an all-day, real-time virtual chat.

While adolescents are at the greatest risk for drug use, it can be difficult to reach this audience directly; therefore, NIDA works to educate various teen influencers including parents, teachers, and the media. NIDA produces materials aimed at helping parents and teachers communicate with children and teens about drugs, such as web-based FAQs and our *Family Checkup* resource.

Approaches

- Use evidence-based communication strategies to disseminate relevant findings from scientific research to all stakeholders
- Provide clear, comprehensive, and up-to-date scientific information to guide policymaking related to drug use and related disorders

Trans-NIH Initiatives

Collaborative Research on Addiction at NIH (CRAN)

The mission of the NIH partnership, Collaborative Research on Addiction at NIH (CRAN), is to provide a strong collaborative framework to enable NIDA, the National Institute on Alcohol Abuse and Alcoholism, and the National Cancer Institute (NCI) to integrate resources and expertise to advance substance use and addiction research and to improve public health outcomes.

HIV/AIDS Research at NIH

The Office of AIDS Research (OAR) coordinates the scientific, budgetary, legislative, and policy elements of the NIH HIV/AIDS research program. Through its annual comprehensive trans-NIH planning, budgeting, and portfolio assessment processes, OAR sets scientific priorities, enhances collaboration, and ensures that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools in the global fight against AIDS. New strategic priorities were announced in August 2015 that will guide NIH and NIDA funding related to HIV and AIDS research (www.grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html).

NIH Blueprint for Neuroscience Research

The NIH Blueprint is a collaborative framework that includes the NIH Office of the Director and the 15 NIH institutes (including NIDA) and centers that support research on the nervous system (https://neuroscienceblueprint.nih.gov/about/blueprint-facts). By pooling resources and expertise, the Blueprint identifies cross-cutting areas of research and confronts challenges too large for any single institute or center. NIDA plays a lead role in a number of NIH Blueprint projects that contribute to our strategic goals and objectives:

A The **Human Connectome Project**, an effort to map the connections within the healthy brain, is expected to help answer questions about how genes influence brain connectivity and how this, in turn, relates to mood, personality, and behavior (www.neuroscienceblueprint.nih.gov/connectome/index.htm). The investigators will collect brain imaging data and genetic and behavioral data from 1,200 adults. They are working to optimize brain imaging techniques to see the brain's wiring in unprecedented detail.

B The **Blueprint Neurotherapeutics Network** is helping small laboratories develop new drugs for nervous system disorders (www.neuroscienceblueprint.nih.gov/bpdrugs/index.htm). The Network provides research funding and access to millions of dollars' worth of services and expertise to assist in every step of the drug development process, from laboratory studies to preparation for clinical trials. Project teams across the United States have received funding to pursue drugs for treatment of conditions from vision loss to neurodegenerative disease and depression. NIDA is coordinating a smoking cessation project utilizing orexin receptor antagonists.

C The **Neuroscience Information Framework (NIF)**, which NIDA led the effort to establish, is an online portal for neuroscience information that includes a customized search engine, a curated registry of resources, and direct access to more than 100 online databases (www.neuinfo.org). NIF advances neuroscience research by enabling discovery and access to public research data and tools worldwide through an open-source, networked environment.

D **Blueprint Training Initiatives**, for which NIDA has also taken a leadership role, provide support for undergraduate and graduate student research training in the areas of computational neuroscience and multimodal neuroimaging (www.neuroscienceblueprint.nih.gov/training.htm). These two programs were extended for another funding round due to their demonstrated highly successful outcomes.

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative

The BRAIN initiative, launched by President Obama in 2013, is a coordinated effort among public and private organizations aimed at revolutionizing our understanding of the human brain (www.braininitiative.nih.gov/index.htm). Significant breakthroughs in how we treat neurological and psychiatric disease will require a new generation of tools to enable researchers to investigate the functions of the brain in much greater detail and at faster speeds. This initiative will accelerate technology development at the intersections of nanoscience, imaging, engineering, informatics, and other rapidly emerging fields of science to achieve this goal.

NIH Big Data to Knowledge (BD2K) Initiative

The Big Data to Knowledge (BD2K) Initiative is a trans-NIH initiative established to enable biomedical research as a digital research enterprise, to facilitate discovery and support new knowledge, and to maximize community engagement. BD2K is working to enhance the utility of biomedical Big Data by:

- Facilitating broad use of biomedical data by making them discoverable, accessible, and citable
- Conducting research to develop methods, software, and tools to analyze biomedical Big Data
- Enhancing training necessary for biomedical Big Data science
- Supporting a data ecosystem that accelerates discovery as part of a digital enterprise

The NIH Common Fund

The NIH Common Fund provides a strategic and nimble approach to address key roadblocks in biomedical research that impede basic scientific discovery and its translation into improved human health, and to capitalize on emerging opportunities to catalyze the rate of progress across multiple biomedical fields (www.commonfund.nih.gov). The Common Fund supports 32 programs (www.commonfund.nih.gov/initiativeslist); NIDA plays key roles in:

A **The Epigenomics Program.** This program is aimed at generating new research tools, technologies, and data sets to accelerate our understanding of how genome-wide chemical modifications to DNA and DNA-associated proteins regulate gene activity without altering the DNA sequence itself, and what role these modifications play in health and disease.

B **The 4D Nucleome Program.** It is estimated that each human cell contains approximately 2 meters (6.5 feet) of DNA, squeezed inside the cell's microscopic nucleus in tightly controlled arrangement. This program aims to develop technologies, resources, and data to understand the principles underlying the organization of DNA in space and time, the role nuclear organization plays in gene expression and cellular function, and how changes in nuclear organization affect normal development as well as various diseases.

C **The Genotype-Tissue Expression Program.** This program examines human gene expression and regulation in multiple tissues, providing valuable insights into the mechanisms of gene regulation. Genetic variation between individuals will be examined for correlation with differences in gene expression level to identify regions of the genome that influence if and how much a gene is expressed. These types of studies are important for determining the role that genetics plays along the substance use disorder (SUD) trajectory.

D **The Illuminating the Druggable Genome Program.** The goal of this program is to improve our understanding of the properties and functions of proteins that are commonly targeted for drug development: G-protein-coupled receptors, nuclear receptors, ion channels, and protein kinases. The program is creating a data resource center that will catalog known information about these proteins to help identify and prioritize targets for further study, and it will develop the technologies necessary to elucidate their function.

E **The Extracellular RNA Communication Program.** This program aims to discover fundamental biological principles about the mechanisms of extracellular ribonucleic acid (exRNA) generation, secretion, and transport; to identify and develop a catalog of exRNAs found in normal human body fluids; and to investigate the potential for using exRNAs in the clinic as therapeutic molecules or biomarkers of disease (www.commonfund.nih.gov/Exrna/index).

F **The Science of Behavior Change Program.** This program seeks to promote basic research on the initiation, personalization, and maintenance of behavior change. Unhealthy behaviors—such as smoking, drug and alcohol abuse, overeating, and a sedentary lifestyle—account for approximately 40 percent of the risk associated with preventable premature death in the United States (www.commonfund.nih.gov/behaviorchange/index). By integrating work across disciplines, this effort seeks to improve our understanding of basic mechanisms of human behavior change across a broad array of health-related behaviors and to use this knowledge to develop more effective behavioral interventions.

The NIH Pain Consortium

The NIH Pain Consortium was established to enhance pain research and promote collaboration among researchers across the many NIH institutes and centers that have programs and activities addressing pain. The Pain Consortium works to develop a comprehensive multidisciplinary pain research agenda for the NIH and to increase visibility for pain research both within NIH and with external stakeholders.

Marijuana Research at NIH

Interest in the potential therapeutic effects of marijuana and its constituents has been growing rapidly, partially in response to media attention surrounding the use of cannabidiol (CBD) in young children with intractable seizure disorders.[127] To date, 23 states and the District of Columbia have legalized marijuana for medicinal use; another 15 states have specifically legalized CBD for medicinal use. While there is significant preliminary research supporting the potential therapeutic value of marijuana-derived compounds for a number of conditions, there is not yet sufficient evidence to support new drug approval by the U.S. Food and Drug Administration. There is a pressing need for rigorous clinical research in this area.

As part of NIDA's mission, we support research on both the adverse effects of marijuana use and the potential therapeutic value of marijuana and its components for the treatment of SUDs and pain. Research on the therapeutic potential for other health conditions is supported by other NIH institutes as it aligns with their mission. For example, the efficacy of marijuana-derived compounds, such as CBD, for the treatment of epilepsy is studied by the National Institute on Neurological Disorders and Stroke; potential uses in cancer treatment are studied by NCI; and so on. NIDA provides marijuana for research through the NIDA Drug Supply Program and will continue to coordinate with other NIH institutes and centers to support research in this area. For example, in 2015 NIDA partnered with six other NIH institutes to develop a program announcement on developing the therapeutic potential of the endocannabinoid system for pain treatment (www.grants.nih.gov/grants/guide/pa-files/PA-15-188.html).

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