



Mindful
Continuing Education

Addiction in America: Introduction, Overview, and Neurobiology



CHAPTER 1.

INTRODUCTION AND OVERVIEW

OF THE REPORT

Chapter 1 Preview

The United States has a serious substance misuse problem. Substance misuse is the use of alcohol or drugs in a manner, situation, amount, or frequency that could cause harm to the user or to those around them. Alcohol and drug misuse and related substance use disorders affect millions of Americans and impose enormous costs on our society. In 2015, 66.7 million people in the United States reported binge drinking in the past month and 27.1 million people were current users of illicit drugs or misused prescription drugs.³ 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, increased spread of infectious disease, loss of productivity, reduced quality of life, increased crime and violence, increased motor vehicle crashes, abuse and neglect of children, and health care costs.

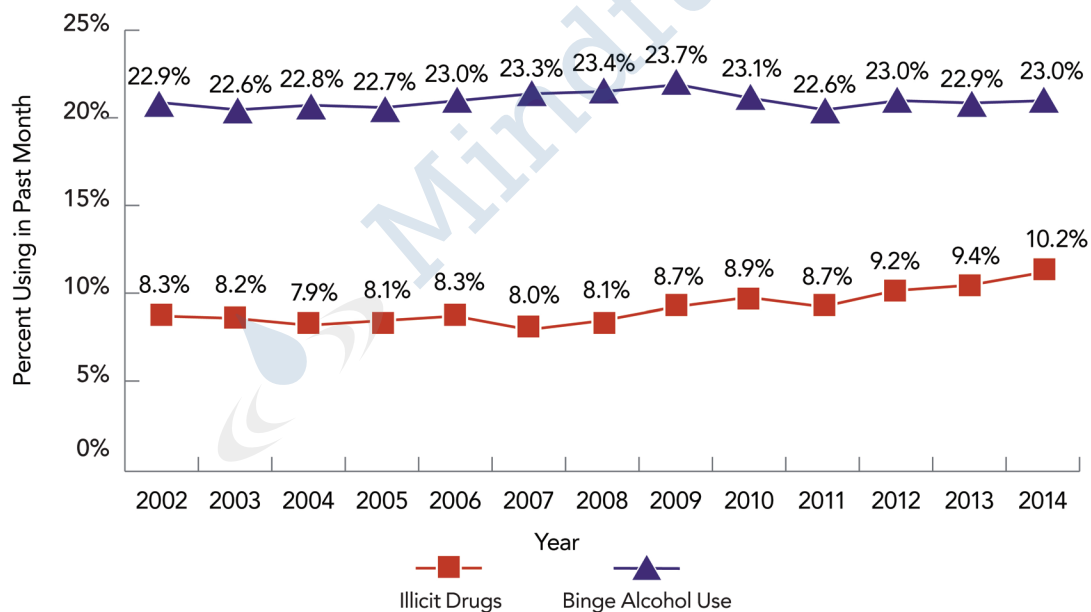
The most devastating consequences are seen in the tens of thousands of lives that are lost each year as a result of substance misuse. Alcohol misuse contributes to 88,000 deaths in the United States each year; 1 in 10 deaths among working adults are due to alcohol misuse.⁶ In addition, in 2014 there were 47,055 drug overdose deaths including 28,647 people who died from a drug overdose involving some type of opioid, including prescription pain relievers and heroin—more than in any previous year on record.⁷

Even though the United States spends more than any other country on health care, it ranks 27th in life expectancy, which has plateaued or decreased for some segments of the population at a time when life expectancy continues to increase in other developed countries—and the difference is largely due to substance misuse and associated physical and mental health problems. For example, recent research has shown an unprecedented increase in mortality among middle-aged White Americans between 1999 and 2014 that was largely driven by alcohol and drug misuse and suicides, although this trend was not seen within other racial and ethnic populations such as Blacks and Hispanics.⁸ An analysis from the Centers for Disease Control and Prevention (CDC) demonstrated that alcohol and drug misuse accounted for a roughly 4-month decline in life expectancy among White Americans; no other cause of death had a larger negative impact in this population.⁹

Substance misuse and substance use disorders also have serious economic consequences, costing more than \$400 billion annually in crime, health, and lost productivity.^{10,11} These costs are of a similar order of magnitude to those associated with other serious health problems such as diabetes, which is estimated to cost the United States \$245 billion each year.¹² Alcohol misuse and alcohol use disorders alone costs the United States approximately \$249 billion in lost productivity, health care expenses, law enforcement, and other criminal justice costs.¹⁰ The costs associated with drug use disorders and use of illegal drugs and non-prescribed medications were estimated to be more than \$193 billion in 2007.¹¹

Despite decades of expense and effort focused on a criminal justice–based model for addressing substance use-related problems, substance misuse remains a national public health crisis that continues to rob the United States of its most valuable asset: its people. In fact, high annual rates of past-month illicit drug use and binge drinking among people aged 12 years and older from 2002 through 2014 (Figure 1.1) emphasize the importance of implementing evidence-based public-health-focused strategies to prevent and treat alcohol and drug problems in the United States.¹³ A public health approach seeks to improve the health and safety of the population by addressing underlying social, environmental, and economic determinants of substance misuse and its consequences, to improve the health, safety, and well-being of the entire population.

Figure 1.1: Past Month Rates of Substance Use Among People Aged 12 or Older: Percentages, 2002-2014, 2014 National Survey on Drug Use and Health (NSDUH)



Notes: *The National Survey on Drug Use and Health (NSDUH)* obtains information on nine categories of illicit drugs: marijuana (including hashish), cocaine (including crack), heroin, hallucinogens, and inhalants, as well as the nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives; see the section on nonmedical use of psychotherapeutic drugs for the definition of nonmedical use. Estimates of “illicit drug use” reported from NSDUH reflect the use of these nine drug categories. Difference between the Illicit Drug Use estimate for 2002-2013 and the 2014 estimate is statistically significant at the .05 level for all years against 2014. Binge drinking for NSDUH data collected in 2014 is defined as five or more drinks on the same occasion on at least one day in the past 30 days. There was no significant difference between 2002-2013 against 2014. In 2015, changes were made to the NSDUH questionnaire and data collection procedures that do not allow comparisons between 2015 and previous years for a number of outcomes.

Source: Center for Behavioral Health Statistics and Quality, (2015).¹³

This *Surgeon General's Report* has been created because of the important health and social problems associated with alcohol and drug misuse in America. As described in this *Report*, a comprehensive approach is needed to address substance use problems in the United States that includes several key components:

- Enhanced public education to improve awareness about substance use problems and demand for more effective policies and practices to address them;
- Widespread implementation of evidence-based prevention policies and programs to prevent substance misuse and related harms;
- Improved access to evidence-based treatment services, integrated with mainstream health care, for those at risk for or affected by substance use disorders;
- Recovery support services (RSS) to assist individuals in maintaining remission and preventing relapse; and
- Research-informed public policies and financing strategies to ensure that substance misuse and use disorder services are accessible, compassionate, efficient, and sustainable.

Recognizing these needs, the *Report* explains the neurobiological basis for substance use disorders and provides the biological, psychological, and social frameworks for improving diagnosis, prevention, and treatment of alcohol and drug misuse. It also describes evidence-based prevention strategies, such as public policies that can reduce substance misuse problems (e.g., driving under the influence [DUI]); effective treatment strategies, including medications and behavioral therapies for treating substance use disorders; and RSS for people who have completed treatment. Additionally, the *Report* describes recent changes in health care financing, including changes in health insurance regulations, which support the integration of clinical prevention and treatment services for substance use disorders into mainstream health care practice, and defines a research agenda for addressing alcohol and drug misuse as medical conditions.

Thus, this first *Surgeon General's Report on Alcohol, Drugs, and Health* is not issued simply because of the prevalence of substance misuse or even the related devastating harms and costs, but also to help inform policymakers, health care professionals, and the general public about effective, practical, and sustainable strategies to address these problems. These strategies have the potential to substantially reduce substance misuse and related problems; promote early intervention for substance misuse and substance use disorders; and improve the availability of high-quality treatment and RSS for persons with substance use disorders.



KEY TERMS

The Public Health System. The Public Health System is defined as “all public, private, and voluntary entities that contribute to the delivery of essential public health services within a jurisdiction” and includes state and local public health agencies, public safety agencies, health care providers, human service and charity organizations, recreation and arts-related organizations, economic and philanthropic organizations, and education and youth development organizations.²

The Health Care System. The World Health Organization defines a health care system as (1) all the activities whose primary purpose is to promote, restore, and/or maintain health, and (2) the people, institutions, and resources, arranged together in accordance with established policies, to improve the health of the population they serve. The health care system is made up of diverse health care organizations ranging from primary care, specialty substance use disorder treatment (including residential and outpatient settings), mental health care, infectious disease clinics, school clinics, community health centers, hospitals, emergency departments, and others.⁵

A Public Health Model for Addressing Substance Misuse and Related Consequences

A public health systems approach to substance misuse and its consequences, including substance use disorders, aims to:

- Define the problem through the systematic collection of data on the scope, characteristics, and consequences of substance misuse;
- Identify the risk and protective factors that increase or decrease the risk for substance misuse and its consequences, and the factors that could be modified through interventions;
- Work across the public and private sector to develop and test interventions that address social, environmental, or economic determinants of substance misuse and related health consequences;
- Support broad implementation of effective prevention and treatment interventions and recovery supports in a wide range of settings; and
- Monitor the impact of these interventions on substance misuse and related problems as well as on risk and protective factors.

A healthy community is one with not just a strong health care system but also a strong public health educational system, safe streets, effective public transportation and affordable, high quality food and housing – where all individuals have opportunities to thrive. Thus, community leaders should work together to mobilize the capacities of health care organizations, social service organizations, educational systems, community-based organizations, government health agencies, religious institutions, law enforcement, local businesses, researchers, and other public, private, and voluntary entities that can contribute to the above aims. Everyone has a role to play in addressing substance misuse and its consequences and thereby improving the public health.

Substances Discussed in this Report

This *Report* defines a **substance** as a psychoactive compound with the potential to cause health and social problems, including substance use disorders (and their most severe manifestation, addiction). These substances can be divided into three major categories: Alcohol, Illicit Drugs (a category that includes prescription drugs used nonmedically), and Over-the-Counter Drugs. Some specific examples of the substances included in each of these categories are included in [Table 1.1](#). Over-the-Counter Drugs are not discussed in this *Report*, but are included in [Appendix D](#).

Although different in many respects, the substances discussed in this *Report* share three features that make them important to public health and safety. *First, many people use and misuse these substances: 66.7 million individuals in the United States aged 12 or older admitted to binge drinking in the past month and 27.1 million people aged 12 or older used an illicit drug in the past month.*³

Table 1.1: Categories and Examples of Substances

Substance Category	Representative Examples
Alcohol	<ul style="list-style-type: none"> • Beer • Wine • Malt liquor • Distilled spirits
Illicit Drugs	<ul style="list-style-type: none"> • Cocaine, including crack • Heroin • Hallucinogens, including LSD, PCP, ecstasy, peyote, mescaline, psilocybin • Methamphetamines, including crystal meth • Marijuana, including hashish* • Synthetic drugs, including K2, Spice, and "bath salts"*** • Prescription-type medications that are used for nonmedical purposes <ul style="list-style-type: none"> ○ Pain Relievers - Synthetic, semi-synthetic, and non-synthetic opioid medications, including fentanyl, codeine, oxycodone, hydrocodone, and tramadol products ○ Tranquilizers, including benzodiazepines, meprobamate products, and muscle relaxants ○ Stimulants and Methamphetamine, including amphetamine, dextroamphetamine, and phentermine products; mazindol products; and methylphenidate or dexmethylphenidate products ○ Sedatives, including temazepam, flurazepam, or triazolam and any barbiturates
Over-the-Counter Drugs and Other Substances	<ul style="list-style-type: none"> • Cough and cold medicines** • Inhalants, including amyl nitrite, cleaning fluids, gasoline and lighter gases, anesthetics, solvents, spray paint, nitrous oxide

Notes: The Report discusses the substances known to have a significant public health impact. These substances are also included in NSDUH. Additionally, NSDUH includes tobacco products (cigarettes, smokeless tobacco, cigars, and pipe tobacco); however, tobacco products are not discussed in this Report at length because they have been covered extensively in other Surgeon General's Reports.¹⁴⁻¹⁷

* As of June 2016, 25 states and the District of Columbia have legalized medical marijuana use, four states have legalized retail marijuana sales, and the District of Columbia has legalized personal use and home cultivation (both medical and recreational). It should be noted that none of the permitted uses under state laws alter the status of marijuana and its constituent compounds as illicit drugs under Schedule I of the federal Controlled Substances Act.

*Second, individuals can use these substances in a manner that causes harm to the user or those around them. This is called **substance misuse** and often results in health or social problems, referred to in this Report as **substance misuse problems**. Misuse can be of low severity and temporary, but it can also result in serious, enduring, and costly consequences due to motor vehicle crashes,^{18,19} intimate partner and sexual violence,²⁰ child abuse and neglect,²¹ suicide attempts and fatalities,²² overdose deaths,²³ various forms of cancer²⁴ (e.g., breast cancer in women),²⁵ heart and liver diseases,²⁶ HIV/AIDS,²⁷ and problems related to drinking or using drugs during pregnancy, such as fetal alcohol spectrum disorders (FASDs) or neonatal abstinence syndrome (NAS).²⁸*

*Third, prolonged, repeated misuse of any of these substances can produce changes to the brain that can lead to a **substance use disorder**, an independent illness that significantly impairs health and function and may require specialty treatment. Disorders can range from mild to severe. Severe and chronic substance use disorders are commonly referred to as **addictions**.*

Key Terms Used in the Report

Addiction: The most severe form of substance use disorder, associated with compulsive or uncontrolled use of one or more substances. Addiction is a chronic brain disease that has the potential for both recurrence (relapse) and recovery.

Substance: A psychoactive compound with the potential to cause health and social problems, including substance use disorders (and their most severe manifestation, addiction). For a list of substance categories included in this Report see [Table 1.1](#). Note: Cigarettes and other tobacco products are only briefly discussed here due to extensive coverage in prior Surgeon General's Reports.¹⁴⁻¹⁷

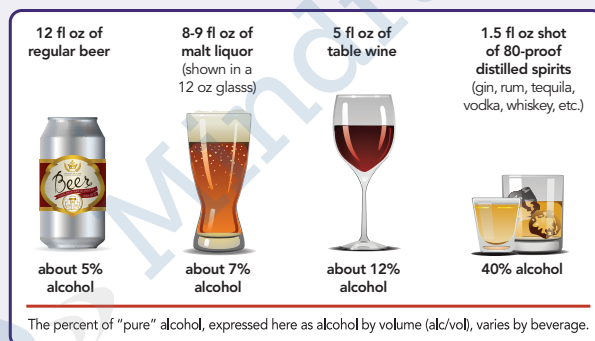
Substance Use: The use—even one time—of any of the substances in this Report.

Substance Misuse: The use of any substance in a manner, situation, amount, or frequency that can cause harm to users or to those around them. For some substances or individuals, any use would constitute misuse (e.g., underage drinking, injection drug use).

Binge Drinking: Binge drinking for men is drinking 5 or more standard alcoholic drinks, and for women, 4 or more standard alcoholic drinks on the same occasion on at least 1 day in the past 30 days.

Heavy Drinking: Defined by the CDC as consuming 8 or more drinks per week for women, and 15 or more drinks per week for men, and by the Substance Abuse and Mental Health Services Administration (SAMHSA), for research purposes, as binge drinking on 5 or more days in the past 30 days.

Standard Drink: Based on the *2015-2020 Dietary Guidelines for Americans*, a standard drink is defined as shown in the graphic below. All of these drinks contain 14 grams (0.6 ounces) of pure alcohol.



Source: U.S. Department of Health and Human Services and U.S. Department of Agriculture, (2015).²⁹

Substance Misuse Problems or Consequences: Any health or social problem that results from substance misuse. Substance misuse problems or consequences may affect the substance user or those around them, and they may be acute (e.g., an argument or fight, a motor vehicle crash, an overdose) or chronic (e.g., a long-term substance-related medical, family, or employment problem, or chronic medical condition, such as various cancers, heart disease, and liver disease). These problems may occur at any age and are more likely to occur with greater frequency of substance misuse.

Substance Use Disorder: A medical illness caused by repeated misuse of a substance or substances. According to the Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*,³⁰ substance use disorders are characterized by clinically significant impairments in health, social function, and impaired control over substance use and are diagnosed through assessing cognitive, behavioral, and psychological symptoms. Substance use disorders range from mild to severe and from temporary to chronic. They typically develop gradually over time with repeated misuse, leading to changes in brain circuits governing incentive salience (the

ability of substance-associated cues to trigger substance seeking), reward, stress, and executive functions like decision making and self-control. Multiple factors influence whether and how rapidly a person will develop a substance use disorder. These factors include the substance itself; the genetic vulnerability of the user; and the amount, frequency, and duration of the misuse. Note: A severe substance use disorder is commonly called an addiction.

Relapse: The return to drug use after a significant period of abstinence.

Recovery: A process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential. Even individuals with severe and chronic substance use disorders can, with help, overcome their substance use disorder and regain health and social function. This is called remission. When those positive changes and values become part of a voluntarily adopted lifestyle, that is called “being in recovery.” Although abstinence from all substance misuse is a cardinal feature of a recovery lifestyle, it is not the only healthy, pro-social feature.

Prevalence of Substance Use, Misuse Problems, and Disorders

How widespread are substance use, misuse, and substance use disorders in the United States? The annual *National Survey on Drug Use and Health* (NSDUH) gathers data on the scope and prevalence of substance use, misuse, and related disorders, as well as utilization of substance use disorder treatment, among Americans aged 12 and older, representing more than 265 million people. [Table 1.2](#) provides selected findings from the 2015 NSDUH. The table provides only general statistics for the United States as a whole; readers are urged to consult NSDUH’s detailed tables³ for subpopulation estimates.

Over 175 million persons aged 12 and older (65.7 percent of this population) reported alcohol use in the past year, with over 66 million (24.9 percent) reporting binge drinking in the past month ([Table 1.2](#)). More than 36 million (13.5 percent) reported using marijuana in the past year, 12.5 million reported misusing prescription pain relievers, and over 300,000 reported using heroin in the past year. Almost 8 percent of the population met diagnostic criteria for a substance use disorder for alcohol or illicit drugs, and another 1 percent met diagnostic criteria for both an alcohol and illicit drug use disorder. Although 20.8 million people (7.8 percent of the population) met the diagnostic criteria for a substance use disorder in 2015, only 2.2 million individuals (10.4 percent) received any type of treatment. Of those treated, 63.7 percent received treatment in specialty substance use disorder treatment programs.³



KEY TERMS

Prevalence. The proportion of a population who have (or had) a specific characteristic—for example, an illness, condition, behavior, or risk factor—in a given time period.

Several specific findings shown in [Table 1.2](#) bear emphasis. Past year misuse of prescription psychotherapeutic drugs was reported by 18.9 million individuals in 2015 (7.1 percent of the population).³ Within this category, prescribed opioid pain relievers (e.g., OxyContin®, Vicodin®, Lortab®) accounted for 12.5 million people, followed by tranquilizers, such as Xanax®, reported by 6.1 million people; stimulants, such as Adderall® or Ritalin®, reported by 5.3 million people; and sedatives, such as Valium®, reported by 1.5 million people.³

Substance Use Disorder Treatment Programs

Historically, treatment services were designed for people with severe substance use disorders (addictions), and programs were generally referred to as “specialty addiction treatment programs.” Today, individuals with mild to severe substance use disorders may receive treatment. These treatments are delivered by specialty programs, as well as by more generalist providers (e.g., primary care and general mental health providers). Not everyone with a substance use disorder will need ongoing treatment; many will require only a brief intervention and monitoring. Because treatments vary substantially in level of specialization, content, duration, and setting, and because those receiving services may differ substantially in the severity, duration, and complexity of their substance use disorder, this *Report* uses the phrase “substance use disorder treatment” as the generic term to capture the broad spectrum of advice, therapies, services, and monitoring provided to the group of individuals with mild to severe substance use disorders. The programs and services that provide specialty treatment are referred to as “substance use disorder treatment programs or services.”

The prevalence of past 30-day use of “any illicit drugs” (a broad category including marijuana/hashish, cocaine/crack, heroin, hallucinogens, inhalants, and prescription psychotherapeutic medications used nonmedically) rose from 9.4 percent in 2013 to 10.2 percent in 2014 among persons aged 12 and older ([Figure 1.2](#)). This 2014 prevalence rate for illicit drugs is significantly higher than it was in any year from 2002 to 2013. However, no significant changes were observed that year specifically in the use of prescription psychotherapeutic drugs, cocaine, or hallucinogens, suggesting that the observed increase was primarily related to increased use of marijuana. Marijuana was the most frequently used illicit drug (35.1 million past year users).³¹ The rate for past month marijuana use in 2014 was significantly higher than it was in any year from 2002 to 2013, with the prevalence of past 30-day marijuana use rising from 7.5 percent in 2013 to 8.4 percent in 2014.¹³ (Note: In 2015, changes were made to the NSDUH questionnaire and data collection procedures that do not allow for the presentation of trend data beyond 2014. For more information, see *Summary of the Effects of the 2015 NSDUH Questionnaire Redesign: Implications for Data Users*.³²)

Demographics of Substance Use

[Table 1.3](#) and [Table 1.4](#) show substance use by demographic characteristics. Prevalence of substance misuse and substance use disorders differs by race and ethnicity and gender, and these factors can also influence access to health care and substance use disorder treatment. Past year alcohol use for men was 68.6 percent and for women it was 62.9 percent. Past month binge alcohol use was 29.6 percent for men and 20.5 percent for women. The prevalence of past month binge alcohol use was 24.1 percent for American Indians or Alaska Natives, 25.7 percent for Hispanics or Latinos, and 26.0 for Whites. Prevalence of an alcohol use disorder was 7.8 percent for men and 4.1 percent for women. The prevalence of an illicit drug use disorder was 3.8 percent for men and 2.0 percent for women.

Table 1.2: Past Year Substance Use, Past Year Initiation of Substance Use, and Met Diagnostic Criteria for a Substance Use Disorder in the Past Year Among Persons Aged 12 Years or Older for Specific Substances: Numbers in Millions and Percentages, 2015 National Survey on Drug Use and Health (NSDUH)

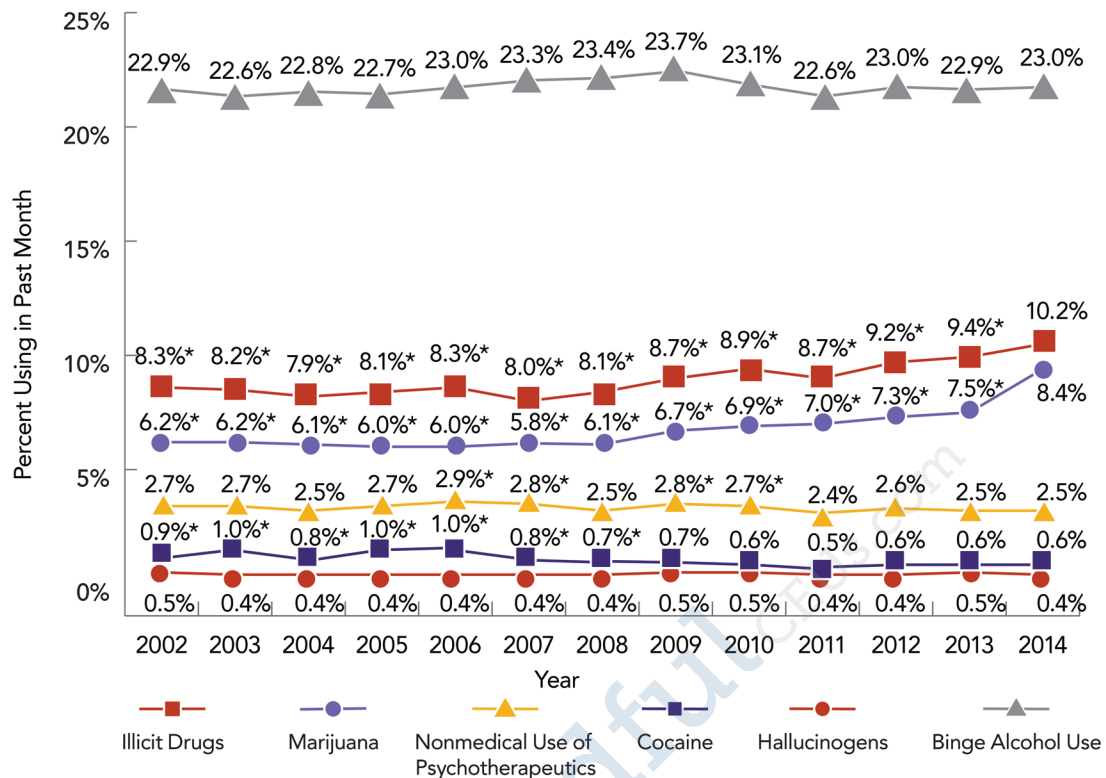
Substance	Past Year Use or Misuse ^v		Past Year Initiation Among Total Population ^{vi}		Met Diagnostic Criteria for a Substance Use Disorder ^{vi,vii}	
	#	%	#	%	#	%
Alcohol	175.8	65.7	4.8	1.8	15.7	5.9
Drinking Pattern						
Binge Drinking ⁱ	66.7	24.9	da	da	da	da
Heavy Drinking ⁱ	17.3	6.5	da	da	da	da
Any Illicit Drugⁱⁱ	47.7	17.8	nr	nr	7.7	2.9
Cocaine/Crack	36.0	1.8	1.0	0.4	0.9	0.3
Heroin	0.8	0.3	0.1	0.1	0.6	0.2
Hallucinogens	4.7	1.8	1.2	0.4	0.3	0.1
Marijuana ⁱⁱⁱ	36.0	13.5	2.6	1.0	4.0	1.5
Inhalants	1.8	0.7	0.6	0.2	0.1	0.0
Misuse of Psychotherapeutics ^{iv}	18.9	7.1	nr	nr	2.7	1.0
Pain Relievers	12.5	4.7	2.1	0.8	2.0	0.8
Tranquilizers	6.1	2.3	1.4	0.5	0.7	0.3
Stimulants	5.3	2.0	1.3	0.5	0.4	0.2
Sedatives	1.5	0.6	0.4	0.2	0.2	0.1
Alcohol or Any Illicit Drugsⁱ	182.3	68.1	nr	nr	20.8	7.8
Alcohol and Any Illicit Drugsⁱⁱ	41.3	15.4	nr	nr	2.7	1.0

Notes: Past year initiates are defined as persons who used the substance(s) for the first time in the 12 months before the date of interview. The "nr = not reported due to measurement issues" notation indicates that the estimate could be calculated based on available data but is not calculated due to potential measurement issues. The "da" indication means does not apply.

- i. Binge and heavy drinking, as defined by SAMHSA, are reported only for the period of 30 days before the interview date. SAMHSA defines binge use of alcohol for males and females as "drinking five (males)/four (females) or more drinks on the same occasion (i.e., at the same time or within a couple of hours of each other) on at least 1 day in the past 30 days" and heavy use of alcohol for both males and females as "binge drinking on each of 5 or more days in the past 30 days."
- ii. Illicit drug use includes the misuse of prescription psychotherapeutics or the use of marijuana, cocaine (including crack), heroin, hallucinogens, inhalants, or methamphetamine.
- iii. As of June 2016, 25 states and the District of Columbia have legalized medical marijuana use. Four states have legalized retail marijuana sales; the District of Columbia has legalized personal use and home cultivation (both medical and recreational). It should be noted that none of the permitted uses under state laws alter the status of marijuana and its constituent compounds as illicit drugs under Schedule I of the federal Controlled Substances Act.
- iv. Misuse of prescription-type psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives and does not include over-the-counter drugs.
- v. Estimates of misuse of psychotherapeutics and stimulants include data from new methamphetamine items added in 2005 and 2006 and are not comparable with estimates presented in NSDUH reports before 2007. See Section B.4.8 in Appendix B of the Results from the 2008 NSDUH.
- vi. Estimates of misuse of psychotherapeutics and stimulants do not include data from new methamphetamine items added in 2005 and 2006.
- vii. Diagnostic criteria for a substance use disorder is based on definitions found in the Fourth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: Center for Behavioral Health Statistics and Quality, (2016).³

Figure 1.2: Trends in Binge Drinking and Past 30-Day Use of Illicit Drugs among Persons Aged 12 Years or Older, 2014 National Survey on Drug Use and Health (NSDUH)



Notes: *Difference between this estimate and the 2014 estimate is statistically significant at the .05 level. Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription psychotherapeutics used non-medically. Nonmedical use of prescription psychotherapeutics includes the nonmedical use of pain relievers, tranquilizers, stimulants, or sedatives. In 2015, changes were made to the NSDUH questionnaire and data collection procedures that do not allow comparisons between 2015 and previous years for a number of outcomes.

Source: Center for Behavioral Health Statistics and Quality, (2015).¹³

Relevance of Substance Use and Misuse

It is sometimes thought that concern over substance use and misuse should be secondary to the *real* issue of substance use disorders and especially their severest manifestation, addiction, which has captured media headlines and has been linked to many health and social problems. This is an important misconception. Individuals with substance use disorders have elevated rates of substance misuse-related health and social problems and costs, but as shown in the last columns of [Table 1.2](#), [Table 1.3](#), and [Table 1.4](#), many people who misuse substances do not meet the diagnostic criteria for a substance use disorder. For example, binge drinking at least once during the past month was self-reported by over 66 million individuals. By definition, those episodes have the potential for producing harm to the user and/or to those around them, through increases in motor vehicle crashes, violence, and alcohol-poisonings.³³ Similarly, in 2015, 12.5 million individuals misused a pain reliever in the past year—setting the stage for a potential overdose—but only 2.9 million met diagnostic criteria for a prescription medication disorder.³

Table 1.3: Past Year Alcohol Use, Past Month Binge Alcohol Use, and Met Diagnostic Criteria for a Substance Use Disorder in the Past Year Among Persons Aged 12 Years or Older: Numbers in Millions and Percentages, 2015 National Survey on Drug Use and Health (NSDUH)

Demographic Group	Past Year Alcohol Use		Past Month Binge Alcohol Use ⁱⁱ		Met Diagnostic Criteria for a Substance Use Disorder in Past Year ⁱ	
	#	%	#	%	#	%
Alcohol						
Male	89.0	68.6	38.4	29.6	10.1	7.8
Female	86.9	62.9	28.3	20.5	5.6	4.1
White	119.9	70.3	44.4	26.0	10.4	6.1
Black or African American	18.6	58.0	7.5	23.4	1.6	4.9
American Indian or Alaska Native	0.7	51.4	0.3	24.1	0.1	9.7
Native Hawaiian or Other Pacific Islander	0.4	51.1	0.1	17.8	0.04	5.4
Asian	7.8	53.1	2.1	14.0	0.5	3.2
Two or More Races	2.7	57.8	1.1	22.9	0.3	6.2
Hispanic or Latino	25.7	59.0	11.2	25.7	2.8	6.4

Table 1.4: Past Year Substance Use, Past 30-Day Illicit Drug Use, and Met Diagnostic Criteria for a Substance Use Disorder in the Past Year Among Persons Aged 12 Years or Older: Numbers in Millions and Percentages, 2015 National Survey on Drug Use and Health (NSDUH)

Demographic Group	Past Year Use		Past 30-Day Illicit Drug Use		Met Diagnostic Criteria for a Substance Use Disorder in Past Year ⁱ	
	#	%	#	%	#	%
Any Illicit Drugⁱⁱⁱ						
Male	26.6	20.5	16.2	12.5	5.0	3.8
Female	21.2	15.3	10.9	7.9	2.8	2.0
White	30.5	17.9	17.4	10.2	4.8	2.8
Black or African American	6.6	20.7	4.0	12.5	1.1	3.5
American Indian or Alaska Native	0.3	22.9	0.2	14.2	0.06	4.1
Native Hawaiian or Other Pacific Islander	0.1	20.5	0.07	9.8	0.03	4.5
Asian	1.4	9.2	0.6	4.0	0.2	1.2
Two or More Races	1.3	27.1	0.8	17.2	0.2	4.9
Hispanic or Latino	7.4	17.2	4.0	9.2	1.3	3.0

- i. Diagnostic criteria for a substance use disorder is based on definitions found in the Fourth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).
- ii. Binge drinking, as defined by SAMHSA, are reported only for the period of 30 days before the interview date. SAMHSA defines binge use of alcohol for males and females as "drinking five (males)/four (females) or more drinks on the same occasion (i.e., at the same time or within a couple of hours of each other) on at least 1 day in the past 30 days.
- iii. Illicit drugs include marijuana/hashish, cocaine (including crack), heroin, hallucinogens, inhalants, or misuse of prescription-type psychotherapeutics, including data from original methamphetamine questions but not including new methamphetamine items added in 2005 and 2006.

The clear implications of these data are that a comprehensive approach to reducing the misuse of alcohol and drugs—one that includes the implementation of effective prevention programs and policy strategies as well as high-quality treatment services—is needed to reduce the problems and costs of substance misuse in the United States. In fact, greater impact is likely to be achieved by reducing substance misuse in the general population—that is, among people who are *not* addicted—than among those with severe substance use problems. Of course, efforts to reduce general population rates of substance use and misuse are also likely to reduce rates of substance use disorders, because substance use disorders typically develop over time following repeated episodes of misuse (often at escalating rates) that result in the progressive changes to brain circuitry that underlie addiction.



FOR MORE ON THIS TOPIC

See Chapter 2 - *The Neurobiology of Substance Use, Misuse, and Addiction.*

Costs and Impact of Substance Use and Misuse

Alcohol misuse, illicit drug use, misuse of medications, and substance use disorders are estimated to cost the United States more than \$400 billion in lost workplace productivity (in part, due to premature mortality), health care expenses, law enforcement and other criminal justice costs (e.g., drug-related crimes), and losses from motor vehicle crashes.^{10,11} Furthermore, about three quarters of the costs associated with alcohol use were due to binge drinking, and about 40 percent of those costs were paid by government, emphasizing the huge cost of alcohol misuse to taxpayers.³⁴

These costs are not unique to the United States. A 2010 study examined the global burden of disability attributable to substance misuse problems and disorders, focusing particularly on lost ability to work and years of life lost to premature mortality. Costs were calculated for 20 age groups and both sexes in 187 countries.³⁵ Mental and substance use disorders were the leading causes of years lived with disability worldwide, largely because these problems strike individuals early in their lives and can continue—especially if untreated—for long periods.

In addition to the costs to society, substance misuse can have many direct and indirect health and personal consequences for individuals. The direct effects on the user depend on the specific substances used, how much and how often they are used, how they are taken (e.g., orally vs. injected), and other factors. Acute effects can range from changes in mood and basic body functions, such as heart rate or blood pressure, to overdose and death. Alcohol misuse and drug use can also have long-term effects on physical and mental health and can lead to substance use disorders. For example, drug use is associated with chronic pain conditions and cardiovascular and cardiopulmonary diseases.^{36,37} Alcohol misuse is associated with liver and pancreatic diseases, hypertension, reproductive system disorders, trauma, stroke, FASD, and cancers of the oral cavity, esophagus, larynx, pharynx, liver, colon, and rectum.^{26,28} For breast cancer, studies have shown that even moderate drinking may increase the risk.²⁵ Although alcohol consumption is associated with adverse health effects as noted above, the *2015-2020 Dietary Guidelines for*

Americans indicate that moderate alcohol use can be part of a healthy diet, but only when used by adults of legal drinking age.ⁱ

In addition, alcohol and drug use by pregnant women can have profound effects on the developing fetus. Alcohol use during pregnancy can lead to a wide range of disabilities in children, the most severe of which is FASD, characterized by intellectual disabilities, speech and language delays, poor social skills, and sometimes facial deformities. Use of drugs, such as opioids during pregnancy, can result in NAS, a drug-withdrawal syndrome requiring medical intervention and extended hospital stay for newborns. Use of some drugs, such as cocaine, during pregnancy may also lead to premature birth or miscarriage. In addition, substance use during pregnancy may interfere with a child's brain development and result in later consequences for mental functioning and behavior.

Substance misuse also can affect a user's nutrition and sleep, as well as increase the risk for trauma, violence, injury, and contraction of communicable diseases, such as HIV/AIDS and Hepatitis C. These consequences can all contribute to the spectrum of public health consequences of substance misuse and need to be considered both independently and collectively when developing and implementing clinical and public health interventions.

Substance misuse problems can also result in other serious and sometimes fatal health problems and extraordinary costs; they may also lead to unexpected death from other causes. Three examples of these serious, sometimes lethal, problems related to substance misuse are highlighted below.

Driving Under the Influence

In 2014, 9,967 people were killed in motor vehicle crashes while driving under the influence of alcohol, representing nearly one third (31 percent) of all traffic-related fatalities in the United States.³⁸ DUI continues to be among the most frequent causes for arrests every year.³⁹ But at approximately 1.3 million per year, these arrests represent only about 1 percent of the actual alcohol-impaired driving incidents reported in national surveys, suggesting that there are many more people who drive while impaired that have not been arrested, putting themselves and others at high risk of being harmed.^{18,40} In addition to the deaths that result from DUI, the National Highway Traffic Safety Administration (NHTSA) estimates that DUI costs the United States more than \$44 billion each year in prosecution, higher insurance rates, higher taxes, medical claims, and property damage.⁴¹

As important as they are, these statistics account for only alcohol-related driving impairment and fail to measure other impairing substances. A study by NHTSA tested oral fluid and blood specimens from a random sample of drivers at the roadside (during daytime on Friday or nighttime Friday to Sunday) and

i Moderate alcohol use is defined by the *2015-2020 Dietary Guidelines for Americans* as up to 1 drink per day for women and up to 2 drinks per day for men—and only by adults of legal drinking age. Many individuals should not consume alcohol, including individuals who are taking certain over-the-counter or prescription medications or who have certain medical conditions, those who are recovering from an alcohol use disorder or are unable to control the amount they drink, and anyone younger than age 21 years. In addition, drinking during pregnancy may result in negative behavioral or neurological consequences in the offspring.

found 12 to 15 percent had used one or more illegal substances.⁴² Drivers tested positive for drugs in approximately 16 percent of all motor vehicle crashes.⁴³

Overdose Deaths

Overdose deaths are typically caused by consuming substances at high intensity and/or by consuming combinations of substances such as alcohol, sedatives, tranquilizers, and opioid pain relievers to the point where critical areas in the brain that control breathing, heart rate, and body temperature stop functioning.

Alcohol Overdose (Alcohol Poisoning)

The CDC reports more than 2,200 alcohol overdose deaths in the United States each year—an average of six deaths every day.⁴⁴ More than three quarters (76 percent) of alcohol overdose deaths occur among adults between ages 35 and 64, and 76 percent of those who die from alcohol overdose are men.

Drug Overdose (Illicit and Prescription Drugs)

Opioid analgesic pain relievers are now the most prescribed class of medications in the United States, with more than 289 million prescriptions written each year.^{45,46} The increase in prescriptions of opioid pain relievers has been accompanied by dramatic increases in misuse ([Table 1.1](#)) and by a more than 200 percent increase in the number of emergency department visits from 2005 to 2011.⁴⁷ In 2014, 47,055 drug overdose deaths occurred in the United States, and 61 percent of these deaths were the result of opioid use, including prescription opioids and heroin.⁷ Heroin overdoses have more than tripled from 2010 to 2014.⁷ Heroin overdoses were more than five times higher in 2014 (10,574) than ten years before in 2004 (1,878). Additionally, rates of cocaine overdose were higher in 2014 than in the previous six years (5,415 deaths from cocaine overdose). In 2014, there were 17,465 overdoses from illicit drugs and 25,760 overdoses from prescription drugs.⁴⁸ Drug overdose deaths also occur as a result of the illicit manufacturing and distribution of synthetic opioids, such as fentanyl, and the illegal diversion of prescription opioids. Illicit fentanyl, for example, is often combined with heroin or counterfeit prescription drugs or sold as heroin, and may be contributing to recent increases in drug overdose deaths.^{7,49}



KEY CONCEPT

The Opioid Crisis. Over-prescription of powerful opioid pain relievers beginning in the 1990s led to a rapid escalation of use and misuse of these substances by a broad demographic of men and women across the country.¹ This led to a resurgence of heroin use, as some users transitioned to using this cheaper street cousin of expensive prescription opioids. As a result, the number of people dying from opioid overdoses soared—increasing nearly four-fold between 1999 and 2014.⁴

Intimate Partner Violence, Sexual Assault, and Rape

Intimate partner violence, sexual assault, and rape are crimes with long-lasting effects on victims and great cost to society.^{50,51} These crimes happen to both women and men and are often associated with substance use. A recent national survey found that 22 percent of women and 14 percent of men reported experiencing severe physical violence from an intimate partner in their lifetimes.⁵² In this survey, 19.3 percent of women and 1.7 percent of men reported being raped in their lifetimes, while 43.9 percent of women and 23.4 percent of men reported some other form of sexual violence in their lifetimes.⁵² Substance misuse is often related to these crimes.

Numerous studies have found a high correlation between substance use and intimate partner violence,⁵³⁻⁵⁶ although this does not mean that substance use causes intimate partner violence. In addition to evidence from the criminal justice arena, recent systematic reviews have found that substance use is both a risk factor for and a consequence of intimate partner violence.⁵⁷⁻⁵⁹

A recent survey of sexual assault and sexual misconduct on college campuses found that use of alcohol and drugs are important risk factors for nonconsensual sexual contact among undergraduate, graduate, and professional students.²⁰ It is clear that substance use and intimate partner violence and sexual assault are closely linked; however, more research is needed on the nature of the relationship between substance use and these forms of violence to determine how substance use contributes to the perpetration of violence and victimization and how violence contributes to subsequent substance use among both perpetrators and victims.

Vulnerability to Substance Misuse Problems and Disorders

Risk and Protective Factors: Keys to Vulnerability

Substance misuse problems and substance use disorders are not inevitable. An individual's vulnerability may be partly predicted by assessing the nature and number of their community, caregiver/family, and individual-level risk and protective factors.

Significant community-level risk factors for substance misuse and use disorders include easy access to inexpensive alcohol and other substances. Caregiver/family-level risk factors include low parental monitoring, a family history of substance use or mental disorders, and high levels of family conflict or violence. At the individual level, major risk factors include current mental disorders, low involvement in school, a history of abuse and neglect, and a history of substance use during adolescence, among others.⁶⁰

Community-level protective factors include higher cost for alcohol and other drugs (often achieved by increasing taxes on these products); regulating the number and concentration of retailers selling various substances (e.g., density of alcohol outlets or marijuana dispensaries); preventing illegal alcohol and other drug sales by enforcing existing laws and holding retailers accountable for harms caused by illegal sales (e.g., commercial host [dram shop] liability); availability of healthy recreational and social activities; and other population-level policies and their enforcement.⁶¹ Caregiver/family-level protective factors include support and regular monitoring by parents.⁶⁰ Some important individual-level protective factors include involvement in school, engagement in healthy recreational and social activities, and good coping skills.⁶⁰

Three important points about vulnerability should be highlighted. First, no single individual or community-level factor determines whether an individual will develop a substance misuse problem or disorder. Second, most risk and protective factors can be modified through preventive programs and



FOR MORE ON THIS TOPIC

See Chapter 3 - *Prevention Programs and Policies*.

policies to reduce vulnerability. Third, although substance misuse problems and disorders may occur at any age, adolescence and young adulthood are particularly critical at-risk periods. Research now indicates that the majority of those who meet criteria for a substance use disorder in their lifetime

started using substances during adolescence and met the criteria by age 20 to 25.⁶²⁻⁶⁴ One likely reason for this vulnerability in adolescence and young adulthood is that alcohol and other substances have particularly potent effects on developing brain circuits, and recent scientific findings indicate that brain development is not complete until approximately age 21 to 23 in women and 23 to 25 in men.⁶⁵⁻⁶⁷ Among the last brain regions to reach maturity is the prefrontal cortex, the brain region primarily responsible for “adult” abilities, such as delay of reward, extended reasoning, and impulse control. This area of the brain is one of the most affected regions in a substance use disorder.

Substance misuse can begin at any age. Therefore, it is important to focus on prevention of substance misuse across the lifespan as well as the prevention of substance use disorders.

Diagnosing a Substance Use Disorder

Changes in Understanding and Diagnosis of Substance Use Disorders

Repeated, regular misuse of any of the substances listed in [Figure 1.2](#) may lead to the development of a substance use disorder. Severe substance use disorders are characterized by compulsive use of substance(s) and impaired control of substance use. Substance use disorder diagnoses are based on criteria specified in the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Much of the substance use disorder data included in this *Report* is based on definitions included in the DSM-IV, which described two distinct disorders: substance abuse and substance dependence, with specific diagnostic criteria for each. Anyone meeting one or more of the abuse criteria—which focused largely on the negative consequences associated with substance misuse, such as being unable to fulfill family or work obligations, experiencing legal trouble, or engaging in hazardous behavior as a result of drug use—would receive the “abuse” diagnosis. Anyone with three or more of the dependence criteria, which included symptoms of drug tolerance, withdrawal, escalating and uncontrolled substance use, and the use of the substance to the exclusion of other activities, would receive the “dependence” diagnosis. Notably, addiction is not listed as a formal diagnosis in the DSM. However, substance



FOR MORE ON THIS TOPIC

See Chapter 2 - *The Neurobiology of Substance Use, Misuse, and Addiction*.



KEY CONCEPT

Misuse versus Abuse. This *Report* uses the term substance misuse, a term that is roughly equivalent to substance abuse. Substance abuse, an older diagnostic term, was defined as use that is unsafe (e.g., drunk or drugged driving), use that leads a person to fail to fulfill responsibilities or gets them in legal trouble, or use that continues despite causing persistent interpersonal problems like fights with a spouse.

However, “substance abuse” is increasingly avoided by professionals because it can be shaming. Instead, substance misuse is now the preferred term. Although misuse is not a diagnostic term, it generally suggests use in a manner that could cause harm to the user or those around them.

dependence was often used interchangeably with addiction, and tolerance and withdrawal were considered, by many, cardinal features of addiction.

The DSM-5, which is the fifth and current version of the DSM, integrates the two DSM-IV disorders, substance abuse and substance dependence, into a single disorder called *substance use disorder* with *mild*, *moderate*, and *severe* sub-classifications. Individuals are evaluated for a substance use disorder based on 10 or 11 (depending on the substance) equally weighted diagnostic criteria ([Table 1.5](#)). Most of these overlap with those used to diagnose DSM-IV dependence and abuse. Individuals exhibiting fewer than two of the symptoms are not considered to have a substance use disorder. Those exhibiting two or three symptoms are considered to have a “mild” disorder, four or five symptoms constitutes a “moderate” disorder, and six or more symptoms is considered a “severe” substance use disorder.³⁰ In this *Report*, addiction is used to refer to substance use disorders at the severe end of the spectrum and are characterized by compulsive substance use and impaired control over use.

KEY TERMS
<p>Tolerance. Alteration of the body's responsiveness to alcohol or a drug such that higher doses are required to produce the same effect achieved during initial use.</p>
<p>Withdrawal. A set of symptoms that are experienced when discontinuing use of a substance to which a person has become dependent or addicted, which can include negative emotions such as stress, anxiety, or depression, as well as physical effects such as nausea, vomiting, muscle aches, and cramping, among others. Withdrawal symptoms often lead a person to use the substance again.</p>

Table 1.5: Criteria for Diagnosing Substance Use Disorders

Diagnostic Criteria for Substance Use Disorders
Using in larger amounts or for longer than intended
Wanting to cut down or stop using, but not managing to
Spending a lot of time to get, use, or recover from use
Craving
Inability to manage commitments due to use
Continuing to use, even when it causes problems in relationships
Giving up important activities because of use
Continuing to use, even when it puts you in danger
Continuing to use, even when physical or psychological problems may be made worse by use
Increasing tolerance
Withdrawal symptoms

Notes: Fewer than 2 symptoms = no disorder; 2-3 = mild disorder; 4-5 = moderate disorder; 6 or more = severe disorder.

Source: American Psychiatric Association, (2013).³⁰

Implications of the New Diagnostic Criteria

The new diagnostic criteria are likely to reduce the “all or nothing” thinking that has characterized the substance use field. Tolerance and withdrawal remain major clinical symptoms, but they are no longer the deciding factor in whether an individual “has an addiction.” Substance use disorders, including addiction, can occur with *all* substances listed in [Table 1.1](#), *not* just those that are able to produce

What is an Intervention?

Intervention here and throughout this *Report* means a professionally delivered program, service, or policy designed to prevent substance misuse or treat an individual's substance use disorder. It does not refer to an arranged meeting or confrontation intended to persuade a friend or loved one to quit their substance misuse or enter treatment—the type of “intervention” sometimes depicted on television. Planned surprise confrontations of the latter variety—a model developed in the 1960s, sometimes called the “Johnson Intervention”—have not been demonstrated to be an effective way to engage people in treatment.⁶⁸ Confrontational approaches in general, though once the norm even in many behavioral treatment settings, have not been found effective and may backfire by heightening resistance and diminishing self-esteem on the part of the targeted individual.⁶⁹

tolerance and withdrawal. It is also important to understand that substance use disorders do not occur immediately but over time, with repeated misuse and development of more symptoms. This means that it is both possible and highly advisable to identify emerging substance use disorders, and to use evidence-based early interventions to stop the addiction process before the disorder becomes more chronic, complex, and difficult to treat.

This type of proactive clinical monitoring and management is already done within general health care settings to address other potentially progressive illnesses that are brought about by unhealthy behaviors.⁷⁰ For example, patients with high blood pressure may be told to adjust their activity and stress in order to reduce the progression of hypertension. Typically, these individuals are also clinically monitored for key symptoms to ensure that symptoms do not worsen.

There are compelling reasons to apply similar procedures in emerging cases of substance misuse. Routine screening for alcohol and other substance use should be conducted in primary care settings to identify early symptoms of a substance use disorder (especially among those with known risk and few protective factors). This should be followed by informed clinical guidance on reducing the frequency and amount of substance use, family education to support lifestyle changes, and regular monitoring.

Research has shown that substance use disorders are similar in course, management, and outcome to other chronic illnesses, such as hypertension, diabetes, and asthma.⁷¹ Unfortunately, substance use disorders have not been treated, monitored, or managed like other chronic illnesses, nor has care for these conditions been covered by insurance to the same degree. Nonetheless, it is possible to adopt the same type of chronic care management approach to the treatment of substance use disorders as is now used to manage most other chronic illnesses.⁷⁰⁻⁷² Evidence-based behavioral interventions, medications, social support services, clinical monitoring, and RSS make this type of chronic care management possible, often by the same health care teams that currently treat other chronic illnesses.



FOR MORE ON THIS TOPIC

See Chapter 6 - *Health Care Systems and Substance Use Disorders*.



FOR MORE ON THIS TOPIC

See Chapter 4 - *Early Intervention, Treatment, and Management of Substance Use Disorders* and Chapter 6 - *Health Care Systems and Substance Use Disorders*.

Evidence also shows that such an approach will improve the effectiveness of treatments for substance use disorders. Remission of substance use and even full recovery can now be achieved if evidence-based care is provided for adequate periods of time, by properly trained health care professionals, and augmented by supportive monitoring, RSS, and social services. This fact is supported by a national survey showing that there are more than 25 million individuals who once had a problem with alcohol or drugs who no longer do.⁷³

The Separation of Substance Use Treatment and General Health Care

Until quite recently, substance misuse problems and substance use disorders were viewed as social problems, best managed at the individual and family levels, and sometimes through the existing social infrastructure—such as schools and places of worship, and, when necessary, through civil and criminal justice interventions.⁷⁴ In the 1970s, when rates of substance misuse increased, including by college students and Vietnam War veterans, most families and traditional social services were not prepared to handle this problem.⁷⁵ Despite a compelling national need for treatment, the existing health care system was neither trained to care for nor especially eager to accept patients with substance use disorders.

For these reasons, a new system of substance use disorder treatment programs was created, but with administration, regulation, and financing placed outside mainstream health care.^{74,75} This meant that with the exception of detoxification in hospital-based settings, virtually all treatment was delivered by programs that were geographically, financially, culturally, and organizationally separate from mainstream health care. Of equal historical importance was the decision to focus treatment only on addiction. This left few provisions for detecting or intervening clinically with the far more prevalent cases of early-onset, mild, or moderate substance use disorders.

Creating this system of substance use disorder treatment programs was a critical element in addressing the burgeoning substance use disorder problems in our nation. However, that separation also created unintended and enduring impediments to the quality and range of care options. For example, separate systems for substance use disorder treatment and other health care needs may have exacerbated the negative public attitudes toward people with substance use disorders. Additionally, the pharmaceutical industry was hesitant to invest in the development of new medications for individuals with substance use disorders, because they were not convinced that a market for these medications existed. Consequently, until the 1990s, few U.S. Food and Drug Administration (FDA) approved medications were available to treat addictions.^{76,77}

Meanwhile, despite numerous research studies documenting high prevalence rates of substance use disorders among patients in emergency departments, hospitals, and general medical care settings, mainstream health care generally failed to recognize or address substance use disorders.⁷⁸ In fact, a recent study by the CDC found that in 2011, only 1 in 6 United States adults and 1 in 4 binge drinkers had *ever* been asked by a health professional about their drinking behavior.⁷⁹ Furthermore, the percent of adult binge drinkers who had been asked about their drinking had not changed since 1997, reflecting the challenges involved in fostering implementation of screening and counseling services for alcohol

misuse in clinical settings. This has been a costly mistake, with often deadly consequences. A recent study showed that the presence of a substance use disorder often doubles the odds for the subsequent development of chronic and expensive medical illnesses, such as arthritis, chronic pain, heart disease, stroke, hypertension, diabetes, and asthma.⁸⁰

In this regard, fatal medication errors due to unforeseen interactions between a prescribed medication for a diagnosed medical condition and unscreened, unaddressed patient substance use increased ten-fold over the past 20 years.⁸¹ To address this problem, researchers suggested “...(1) screening patients for use...of alcohol and/or street drugs; (2) taking extra precautions when prescribing medicines with known dangerous interactions with alcohol and/or street drugs; and (3) teaching the patient the risks of mixing medicines with alcohol and/or street drugs.”⁸¹ Similar recommendations focusing on prescribed opioids have been issued by the CDC to curb the rise in opioid overdose deaths.⁸² Again, screening for substance use and substance use disorders before and during the course of opioid prescribing, combined with patient education, are recommended.⁸²

Yet despite these and other indications of extreme threats to health care quality, safety, effectiveness, and cost containment, as of this writing, few general health care organizations screen for, or offer services for, the early identification and treatment of substance use disorders. Moreover, few medical, nursing, dental, or pharmacy schools teach their students about substance use disorders,⁸³⁻⁸⁶ and, until recently, few insurers offered adequate reimbursement for treatment of substance use disorders.^{87,88}

Recent Changes in Health Care Policy and Law

The longstanding separation of substance use disorders from the rest of health care began to change with enactment of the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA) and the Affordable Care Act in 2010.^{89,90} MHPAEA requires that the financial requirements and treatment limitations imposed by health plans and insurers for substance use disorders be no more restrictive than the financial requirements and treatment limitations they impose for medical and surgical conditions. The Affordable Care Act requires the majority of United States health plans and insurers to offer prevention, screening, brief interventions, and other forms of treatment for substance use disorders.⁸⁹

It is difficult to overstate the importance of these two Acts for creating a public health-oriented approach to reducing substance misuse and related disorders. These laws and related changes in health care financing are creating incentives for health care organizations to integrate substance use disorder treatment with general health care. Many questions remain, but those questions are no longer *whether* but *how* this much-needed integration will occur. These changes combine to create a new, challenging but exceptionally promising era for the prevention and treatment of substance use disorders and set the context for this *Report*.



FOR MORE ON THIS TOPIC

See Chapter 6 - *Health Care Systems and Substance Use Disorders*.

Marijuana: A Changing Legal and Research Environment

Although this *Report* does not examine the issue of marijuana legalization, its continually evolving legal status is worth mentioning because of implications for both research and policy. As mentioned elsewhere, marijuana is the most commonly used illicit drug in the United States, with 22.2 million people aged 12 or older using it in the past year.³ In recent years marijuana use has become more socially acceptable among both adults and youth, while perceptions of risk among adolescents of the drug's harms have been declining over the past 13 years.⁹¹

As use of marijuana and its constituent components and derivatives becomes more widely accepted, it is critical to strengthen understanding of the effects and consequences for individual users and for public health and safety. Conducting such research can be complex as laws and policies vary significantly from state to state. For example, some states use a decriminalization model, which means production and sale of marijuana are still illegal and no legal marijuana farms, distributors, companies, stores, or advertising are permitted. Through ballot initiatives, other states have “legalized” marijuana use, which means they allow the production and sales of marijuana for personal use. Additionally, some states have legalized marijuana for medical purposes, and this group includes a wide variety of different models dictating how therapeutic marijuana is dispensed. The impacts of state laws regarding therapeutic and recreational marijuana are still being evaluated, although the differences make comparisons between states challenging.⁹²

As of June 2016, 25 states and the District of Columbia have legalized medical marijuana use. Four states have legalized retail sales; the District of Columbia has legalized personal use and home cultivation (both medical and recreational), with more states expecting to do so. None of the permitted uses under state laws alters the status of marijuana and its constituent compounds as illicit drugs under Schedule I of the federal Controlled Substances Act.⁹³ It should also be noted that use for recreational purposes has not been legalized by any jurisdiction for people under age 21, and few jurisdictions have legalized medical marijuana for young people. While laws are changing, so too is the drug itself with average potency more than doubling over the past decade (1998 to 2008).⁹⁴ The ways marijuana is used are also changing – in addition to smoking, consuming edible forms like baked goods and candies, using vaporizing devices, and using high-potency extracts and oils (e.g., “dabbing”) are becoming increasingly common.⁹⁵ Because these products and methods are unregulated even in states that have legalized marijuana use, users may not have accurate information about dosage or potency, which can lead and has led to serious consequences such as hospitalizations for psychosis and other overdose-related symptoms.⁹⁵ Marijuana use can also impair driving skills and, while estimates vary, is linked to a roughly two-fold increase in accident risk.⁹⁶⁻⁹⁸ The risk is compounded when marijuana is used with alcohol.^{96,99}

There is a growing body of research suggesting the potential therapeutic value of marijuana's constituent cannabinoid chemicals in numerous health conditions including pain, nausea, epilepsy, obesity, wasting disease, addiction, autoimmune disorders, and other conditions. Given the possibilities around therapeutic use, it is necessary to continue to explore ways of easing existing barriers to research. Marijuana has more than 100 constituent cannabinoid compounds, with cannabidiol (CBD) and tetrahydrocannabinol (THC, the chemical responsible for most of marijuana's intoxicating effects) being the most well-studied. Evidence collected so far in clinical investigations of the marijuana plant is still insufficient to meet

FDA standards for a finding of safety and efficacy for any therapeutic indications. However, the FDA has approved three medications containing synthetically derived cannabinoids: Marinol capsules and Syndros oral solution (both containing dronabinol, which is identical in chemical structure to THC), and Cesamet capsules (containing nabilone, which is similar in structure to THC) for severe nausea and vomiting in certain circumstances, for instance in AIDS patients. Recognizing the potential therapeutic importance of compounds found in marijuana, the FDA has granted Fast Track designation to four development programs of products that contain marijuana constituents or their synthetic equivalents. The therapeutic areas in which products are being developed granted Fast Track by FDA include the treatment of pain in patients with advanced cancer; treatment of Dravet syndrome (two programs), a rare and catastrophic treatment-resistant form of childhood epilepsy; and treatment of neonatal hypoxic ischemic encephalopathy, brain injury resulting from oxygen deprivation during birth.

Additionally, there are clinical investigations for the treatment of refractory seizure syndromes, including Lennox Gastaut Syndrome, and for treatment of post-traumatic stress disorder (PTSD). However, further exploration of these issues always requires consideration of the serious health and safety risks associated with marijuana use. Research shows that risks can include respiratory illnesses, dependence, mental health-related problems, and other issues affecting public health such as impaired driving. Within this context of changing marijuana policies at the state level, research is needed on the impact of different models of legalization and how to minimize harm based on what has been learned from legal substances subject to misuse, such as alcohol and tobacco. Continued assessment of barriers to research and surveillance will help build the best scientific foundation to support good public policy while also protecting the public health.

Purpose, Focus, and Format of the *Report*

The Audience

This *Report* is intended for individuals, families, community members, educators, health care professionals, public health practitioners, advocates, public policymakers, and researchers who are looking for effective, sustainable solutions to the problems created by alcohol and other substances. To meet those needs, the *Report* reviews and synthesizes the most important and reliable scientific findings in key topic areas and distills those findings into recommendations for:

- Improving public awareness of substance misuse and related problems;
- Reducing negative attitudes related to substance use disorders;
- Closing the gap between what is known to reduce substance misuse at the population level and within specific subgroups, and the implementation of these effective programs, policies, and environmental strategies at the federal, state, and community levels;
- Understanding the need for and effectiveness of programs for high-risk populations;
- Expanding the capacity of health care systems to deliver evidence-based substance use disorder treatment;
- Integrating financing and health care system models to facilitate access and affordability of care for substance use disorders;

- Continuing to build the science base of effective prevention, treatment, and recovery practices and policies; and
- Engaging stakeholders in reducing substance use and misuse problems and protecting the health of all individuals across the lifespan.

Because of the broad audience, the *Report* is purposely written in accessible language without excessive scientific jargon. The *Report* also focuses on current issues and practical questions that trouble so many people:

- What are the health and social impacts of alcohol and drug use and misuse in the United States? What key factors influence these behaviors?
- What are the major substance misuse problems facing the United States?
- What causes substance use disorders and why do they change people so dramatically?
- Can substance misuse problems and disorders be prevented? How?
- What constitutes effective treatment?
- Can addicted individuals recover? What will it take to manage their disorders and sustain recovery?

Topics Covered in the *Report*

Individual chapters in the *Report* review the science associated with the major substance use, misuse, and disorder issues for specific topics. Tobacco, also an addictive substance, is mentioned only briefly, because problems associated with tobacco use and nicotine addiction have been covered extensively in other Surgeon General's Reports.^{14-16,100-103}

Because of the broad audience and the practical emphasis, the *Report* is intentionally selective rather than exhaustive, emphasizing findings that have the potential for the greatest public health impact and the greatest potential for action. For readers wanting greater scientific detail or more specific information, detailed research reports, as well as supplemental resource materials, are supplied in references, in the Appendices, and in special emphasis boxes throughout the *Report*.

Scientific Standards Used to Develop the *Report*

Findings cited in all of the chapters came from electronic database searches of research articles published in English. Within those searches, priority was given to systematic literature reviews and to findings that were replicated by multiple controlled trials. However, many important issues in prevention, treatment, recovery, and health care systems have not yet been examined in rigorous controlled trials, or are not appropriate for such research designs. In these cases, the best available evidence was cited and labeled according to the reporting conventions published by the CDC:¹⁰⁴

- *Well-supported*: Evidence derived from multiple controlled trials or large-scale population studies.
- *Supported*: Evidence derived from rigorous but fewer or smaller trials or restricted samples.
- *Promising*: Findings that do not derive from rigorously controlled studies but that nonetheless make practical or clinical sense and are widely practiced.

In cases in which evidence was based on findings of neurobiological research, the CDC standards were adapted.

A summary of the key findings appears at the beginning of each chapter. The key findings highlight what is currently known from available research about the chapter topic, as well as the strength of the evidence. As with the rest of the *Report*, the key findings are not intended to be exhaustive, but are instead considered the important “take-aways” from each chapter. Readers interested in a fuller discussion of the topics are encouraged to read the chapters in their entirety.

Addressing Substance Use in Specific Populations

As indicated, the chapters are designed to prioritize best available research findings that apply most broadly across different substances and across various subgroups, while also identifying program and policy interventions that have strong evidence for particular substances (e.g., alcohol), when available. The rationale for this decision is that the available research suggests that the genetic, neurobiological, and environmental processes underlying substance use, misuse, and disorders are largely similar across most known substances and unrelated to the age, sex, race and ethnicity, gender identity, or culture of the individual. The available research also clearly indicates that many of the interventions, including population-level policies, focused programs, behavioral therapies, medications, and social services shown to be effective in one subgroup are *generally* effective for other subgroups. Put differently, it is reasonable to assume that the findings presented in this *Report* are relevant for many substance use types and patterns; for most age, gender, racial and ethnic, and cultural subgroups; and for many special needs subgroups (e.g., those with co-occurring mental or physical illnesses; those involved with the criminal justice system).

However, this general statement has some important caveats. First, the statement depends heavily on the phrase “available research.” There is insufficient research examining subgroup differences in the neurobiology of substance use disorders and in interventions aimed at preventing, treating, and promoting recovery from substance use disorders. Additional research designed to examine these differences and to test interventions in specific populations is needed.

A second caveat is that individual variability in response to standard prevention, treatment, and recovery support interventions is common throughout health care. Individuals with the same disease often react quite differently to the same medicine or behavioral intervention. Accordingly, general health care has moved toward “personalized medicine,” an individualized treatment regimen derived from specific information about the individual’s genetics and stage of illness, as well as lifestyle, language, culture, and personal preferences. Personalized care is not common in the substance use disorder field because many prevention, treatment, and recovery regimens were created as standardized “programs” rather than individualized protocols.

The third caveat to the statement on general research findings is that even if research has shown that certain medications, therapies, or recovery support services are likely to be *effective*, this does not mean that they will be *adequate*, especially for groups with specific needs. For example, a medication that is effective in blocking the rewarding effects of opioid use will not fully address the multiple, complex problems of those with opioid use disorders, nor address any co-occurring health conditions such as depression or HIV/AIDS.

CHAPTER 2.

THE NEUROBIOLOGY OF SUBSTANCE USE, MISUSE, AND ADDICTION

Chapter 2 Preview

A substantial body of research has accumulated over several decades and transformed our understanding of substance use and its effects on the brain. This knowledge has opened the door to new ways of thinking about prevention and treatment of substance use disorders.

This chapter describes the neurobiological framework underlying substance use and why some people transition from using or misusing alcohol or drugs to a substance use disorder—including its most severe form, addiction. The chapter explains how these substances produce changes in brain structure and function that promote and sustain addiction and contribute to relapse. The chapter also addresses similarities and differences in how the various classes of addictive substances affect the brain and behavior and provides a brief overview of key factors that influence risk for substance use disorders.

An Evolving Understanding of Substance Use Disorders

Scientific breakthroughs have revolutionized the understanding of substance use disorders. For example, severe substance use disorders, commonly called *addictions*, were once viewed largely as a moral failing or character flaw, but are now understood to be chronic illnesses characterized by clinically significant impairments in health, social function, and voluntary control over substance use.³ Although the mechanisms may be different, addiction has many features in common with disorders such as diabetes, asthma, and hypertension. All of these disorders are chronic, subject to relapse, and influenced by genetic, developmental, behavioral, social, and environmental factors. In all of these disorders, affected individuals may have difficulty in complying with the prescribed treatment.⁴

This evolving understanding of substance use disorders as medical conditions has had important implications for prevention and treatment. Research demonstrating that addiction is driven by changes in the brain has helped to reduce the negative attitudes associated with substance use disorders and provided support for integrating treatment for substance use disorders into mainstream health care. Moreover, research on the basic neurobiology of addiction has already resulted in several effective

KEY FINDINGS*

- Well-supported scientific evidence shows that addiction to alcohol or drugs is a chronic brain disease that has potential for recurrence and recovery.
- Well-supported evidence suggests that the addiction process involves a three-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. This cycle becomes more severe as a person continues substance use and as it produces dramatic changes in brain function that reduce a person's ability to control his or her substance use.
- Well-supported scientific evidence shows that disruptions in three areas of the brain are particularly important in the onset, development, and maintenance of substance use disorders: the basal ganglia, the extended amygdala, and the prefrontal cortex. These disruptions: (1) enable substance-associated cues to trigger substance seeking (i.e., they increase incentive salience); (2) reduce sensitivity of brain systems involved in the experience of pleasure or reward, and heighten activation of brain stress systems; and (3) reduce functioning of brain executive control systems, which are involved in the ability to make decisions and regulate one's actions, emotions, and impulses.
- Supported scientific evidence shows that these changes in the brain persist long after substance use stops. It is not yet known how much these changes may be reversed or how long that process may take.
- Well-supported scientific evidence shows that adolescence is a critical "at-risk period" for substance use and addiction. All addictive drugs, including alcohol and marijuana, have especially harmful effects on the adolescent brain, which is still undergoing significant development.

* Well-supported: when evidence is derived from multiple rigorous human and nonhuman studies; Supported: when evidence is derived from rigorous but fewer human and nonhuman studies.

medications for the treatment of alcohol, opioid, and nicotine use disorders, and clinical trials are ongoing to test other potential new treatments.⁵

All addictive substances have powerful effects on the brain. These effects account for the euphoric or intensely pleasurable feelings that people experience during their initial use of alcohol or other substances, and these feelings motivate people to use those substances again and again, despite the risks for significant harms.



FOR MORE ON THIS TOPIC

See the section on "Factors that Increase Risk for Substance Use, Misuse, and Addiction" later in this chapter.

As individuals continue to misuse alcohol or other substances, progressive changes, called *neuroadaptations*, occur in the structure and function of the brain. These neuroadaptations compromise brain function and also drive the transition from controlled, occasional substance use to chronic misuse, which can be difficult to control. Moreover, these brain changes

endure long after an individual stops using substances. They may produce continued, periodic craving for the substance that can lead to relapse: More than 60 percent of people treated for a substance use disorder experience relapse within the first year after they are discharged from treatment,^{4,6} and a person can remain at increased risk of relapse for many years.^{7,8}

However, addiction is not an inevitable consequence of substance use. Whether an individual ever uses alcohol or another substance, and whether that initial use progresses to a substance use disorder of any severity, depends on a number of factors. These include: a person's genetic makeup and other individual

biological factors; the age when use begins; psychological factors related to a person's unique history and personality; and environmental factors, such as the availability of drugs, family and peer dynamics, financial resources, cultural norms, exposure to stress, and access to social support.⁹ Some of these factors increase risk for substance use, misuse, and use disorders, whereas other factors provide buffers against those risks. Nonetheless, specific combinations of factors can drive the emergence and continuation of substance misuse and the progression to a disorder or an addiction.



FOR MORE ON THIS TOPIC

See Chapter 3 - *Prevention Programs and Policies*.

Conducting Research on the Neurobiology of Substance Use, Misuse, and Addiction

Until recently, much of our knowledge about the neurobiology of substance use, misuse, and addiction came from the study of laboratory animals. Although no animal model fully reflects the human experience, animal studies let researchers investigate addiction under highly controlled conditions that may not be possible or ethical to replicate in humans. These types of studies have greatly helped to answer questions about how particular genes, developmental processes, and environmental factors, such as stressors, affect substance-taking behavior.



KEY TERMS

Neurobiology. The study of the anatomy, function, and diseases of the brain and nervous system.

Neurobiology studies in animals have historically focused on what happens in the brain right after taking an addictive substance (this is called the acute impact), but research has shifted to the study of how ongoing, long-term (or chronic) substance use changes the brain. One of the main goals of this research is to understand at the most basic level the mechanisms through which substance use alters brain structure and function and drives the transition from occasional use to misuse, addiction, and relapse.¹⁰

A growing body of substance use research conducted with humans is complementing the work in animals. For example, human studies have benefited greatly from the use of brain-imaging technologies, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans. These technologies allow researchers to “see” inside the living human brain so that they can investigate and characterize the biochemical, functional, and structural changes in the brain that result from alcohol and drug use. The technologies also allow them to understand how differences in brain structure and function may contribute to substance use, misuse, and addiction.

Animal and human studies build on and inform each other, and in combination provide a more complete picture of the neurobiology of addiction. The rest of this chapter weaves together the most compelling data from both types of studies to describe a neurobiological framework for addiction.

A Basic Primer on the Human Brain

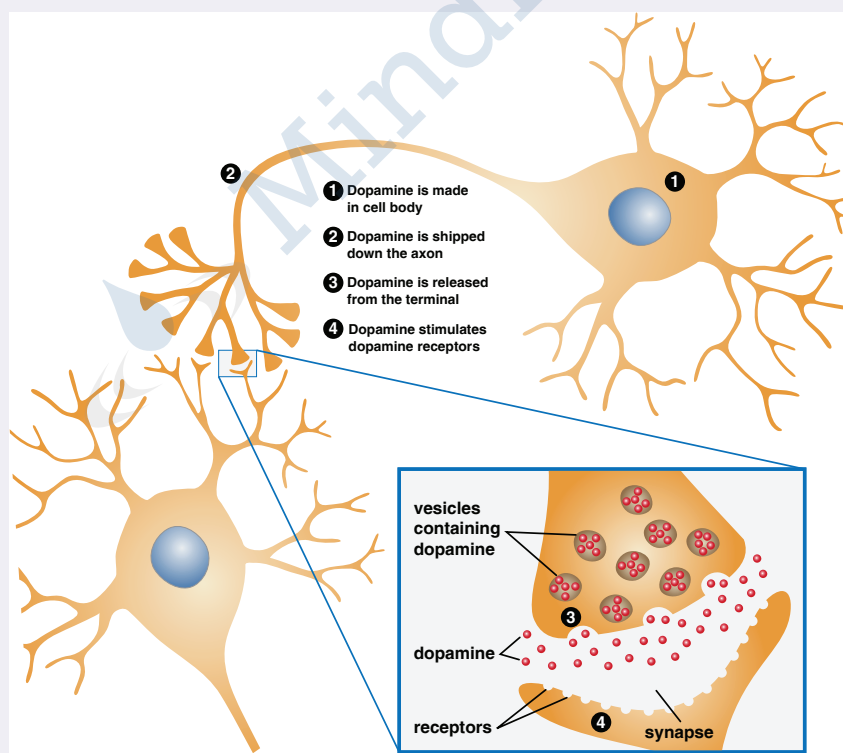
To understand how addictive substances affect the brain, it is important to first understand the basic biology of healthy brain function. The brain is an amazingly complex organ that is constantly at work. Within the brain, a mix of chemical and electrical processes controls the body's most basic functions, like breathing and digestion. These processes also control how people react to the multitudes of sounds, smells, and other sensory stimuli around them, and they organize and direct individuals' highest thinking and emotive powers so that they can interact with other people, carry out daily activities, and make complex decisions.

The brain is made of an estimated 86 billion nerve cells—called neurons—as well as other cell types. Each neuron has a cell body, an axon, and dendrites (Figure 2.1). The cell body and its nucleus control the neuron's activities. The axon extends out from the cell body and transmits messages to other neurons. Dendrites branch out from the cell body and receive messages from the axons of other neurons.

Neurons communicate with one another through chemical messengers called neurotransmitters. The neurotransmitters cross a tiny gap, or synapse, between neurons and attach to receptors on the receiving neuron. Some neurotransmitters are inhibitory—they make it less likely that the receiving neuron will carry out some action. Others are excitatory, meaning that they stimulate neuronal function, priming it to send signals to other neurons.

Neurons are organized in clusters that perform specific functions (described as networks or circuits). For example, some networks are involved with thinking, learning, emotions, and memory. Other networks communicate with muscles, stimulating them into action. Still others receive and interpret stimuli from the sensory organs, such as the eyes and ears, or the skin. The addiction cycle disrupts the normal functions of some of these neuronal networks.

Figure 2.1: A Neuron and its Parts

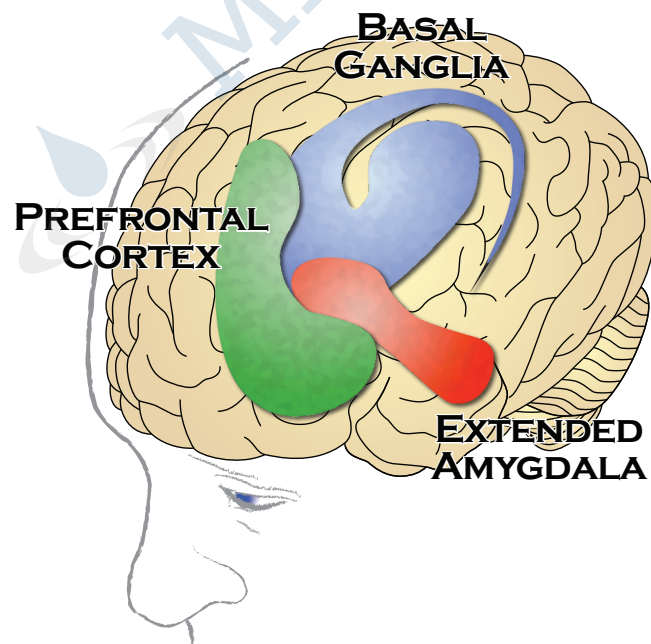


The Primary Brain Regions Involved in Substance Use Disorders

The brain has many regions that are interconnected with one another, forming dynamic networks that are responsible for specific functions, such as attention, self-regulation, perception, language, reward, emotion, and movement, along with many other functions. This chapter focuses on three regions that are the key components of networks that are intimately involved in the development and persistence of substance use disorders: the **basal ganglia**, the **extended amygdala**, and the **prefrontal cortex** (Figure 2.2). The basal ganglia control the rewarding, or pleasurable, effects of substance use and are also responsible for the formation of habitual substance taking. The extended amygdala is involved in stress and the feelings of unease, anxiety, and irritability that typically accompany substance withdrawal. The prefrontal cortex is involved in executive function (i.e., the ability to organize thoughts and activities, prioritize tasks, manage time, and make decisions), including exerting control over substance taking.

These brain areas and their associated networks are not solely involved in substance use disorders. Indeed, these systems are broadly integrated and serve many critical roles in helping humans and other animals survive. For example, when people engage in certain activities, such as consuming food or having sex, chemicals within the basal ganglia produce feelings of pleasure. This reward motivates individuals to continue to engage in these activities, thereby ensuring the survival of the species. Likewise, in the face of danger, activation of the brain's stress systems within the extended amygdala drives "fight or flight" responses. These responses, too, are critical for survival. As described in more detail below, these and other survival systems are "hijacked" by addictive substances.

Figure 2.2: Areas of the Human Brain that Are Especially Important in Addiction



The Basal Ganglia

The basal ganglia are a group of structures located deep within the brain that play an important role in keeping body movements smooth and coordinated. They are also involved in learning routine behaviors and forming habits. Two sub-regions of the basal ganglia are particularly important in substance use disorders:

- The nucleus accumbens, which is involved in motivation and the experience of reward, and
- The dorsal striatum, which is involved in forming habits and other routine behaviors.¹¹

The Extended Amygdala

The extended amygdala and its sub-regions, located beneath the basal ganglia, regulate the brain's reactions to stress-including behavioral responses like “fight or flight” and negative emotions like unease, anxiety, and irritability. This region also interacts with the hypothalamus, an area of the brain that controls activity of multiple hormone-producing glands, such as the pituitary gland at the base of the brain and the adrenal glands at the top of each kidney. These glands, in turn, control reactions to stress and regulate many other bodily processes.¹²

The Prefrontal Cortex

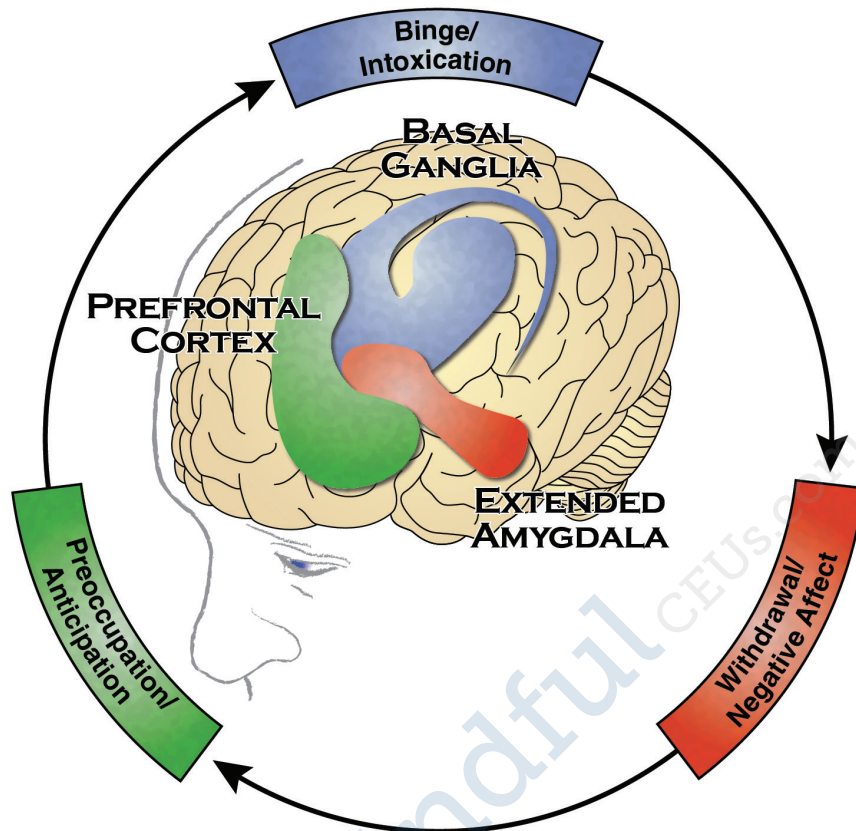
The prefrontal cortex is located at the very front of the brain, over the eyes, and is responsible for complex cognitive processes described as “executive function.” Executive function is the ability to organize thoughts and activities, prioritize tasks, manage time, make decisions, and regulate one's actions, emotions, and impulses.¹³

The Addiction Cycle

Addiction can be described as a repeating cycle with three stages. Each stage is particularly associated with one of the brain regions described above—basal ganglia, extended amygdala, and prefrontal cortex ([Figure 2.3](#)).¹⁰ This three-stage model draws on decades of human and animal research and provides a useful way to understand the symptoms of addiction, how it can be prevented and treated, and how people can recover from it.¹⁴ The three stages of addiction are:

- **Binge/Intoxication**, the stage at which an individual consumes an intoxicating substance and experiences its rewarding or pleasurable effects;
- **Withdrawal/Negative Affect**, the stage at which an individual experiences a negative emotional state in the absence of the substance; and
- **Preoccupation/Anticipation**, the stage at which one seeks substances again after a period of abstinence.

Figure 2.3: The Three Stages of the Addiction Cycle and the Brain Regions Associated with Them



The three stages are linked to and feed on each other, but they also involve different brain regions, circuits (or networks), and neurotransmitters and result in specific kinds of changes in the brain. A person may go through this three-stage cycle over the course of weeks or months or progress through it several times in a day. There may be variation in how people progress through the cycle and the intensity with which they experience each of the stages. Nonetheless, the addiction cycle tends to intensify over time, leading to greater physical and psychological harm.¹⁰

The following sections describe each of the stages in more detail. But first, it is necessary to explain four behaviors that are central to the addiction cycle: impulsivity, positive reinforcement, negative reinforcement, and compulsivity.

For many people, initial substance use involves an element of impulsivity, or acting without foresight or regard for the consequences. For example, an adolescent may impulsively take a first drink, smoke a cigarette, begin experimenting with marijuana, or succumb to peer pressure to try a party drug. If the experience is pleasurable, this feeling positively reinforces the substance use, making the person more likely to take the substance again.

Another person may take a substance to relieve negative feelings such as stress, anxiety, or depression. In this case, the temporary relief the substance brings from the negative feelings negatively reinforces

substance use, increasing the likelihood that the person will use again. Importantly, positive and negative reinforcement need not be driven solely by the effects of the drugs. Many other environmental and social stimuli can reinforce a behavior. For example, the approval of peers positively reinforces substance use for some people. Likewise, if drinking or using drugs with others provides relief from social isolation, substance use behavior could be negatively reinforced.

The positively reinforcing effects of substances tend to diminish with repeated use. This is called tolerance and may lead to use of the substance in greater amounts and/or more frequently in an attempt to experience the initial level of reinforcement. Eventually, in the absence of the substance, a person may experience negative emotions such as stress, anxiety, or depression, or feel physically ill. This is called withdrawal, which often leads the person to use the substance again to relieve the withdrawal symptoms.

As use becomes an ingrained behavior, impulsivity shifts to compulsivity, and the primary drivers of repeated substance use shift from positive reinforcement (feeling pleasure) to negative reinforcement (feeling relief), as the person seeks to stop the negative feelings and physical illness that accompany withdrawal.¹⁵ Eventually, the person begins taking the substance not to get “high,” but rather to escape the “low” feelings to which, ironically, chronic drug use has contributed. Compulsive substance seeking is a key characteristic of addiction, as is the loss of control over use. Compulsivity helps to explain why many people with addiction experience relapses after attempting to abstain from or reduce use.

The following sections provide more detail about each of the three stages—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—and the neurobiological processes underlying them.

Binge/Intoxication Stage: Basal Ganglia

The binge/intoxication stage of the addiction cycle is the stage at which an individual consumes the substance of choice. This stage heavily involves the basal ganglia (Figure 2.4) and its two key brain subregions, the nucleus accumbens and the dorsal striatum. In this stage, substances affect the brain in several ways.



KEY TERMS

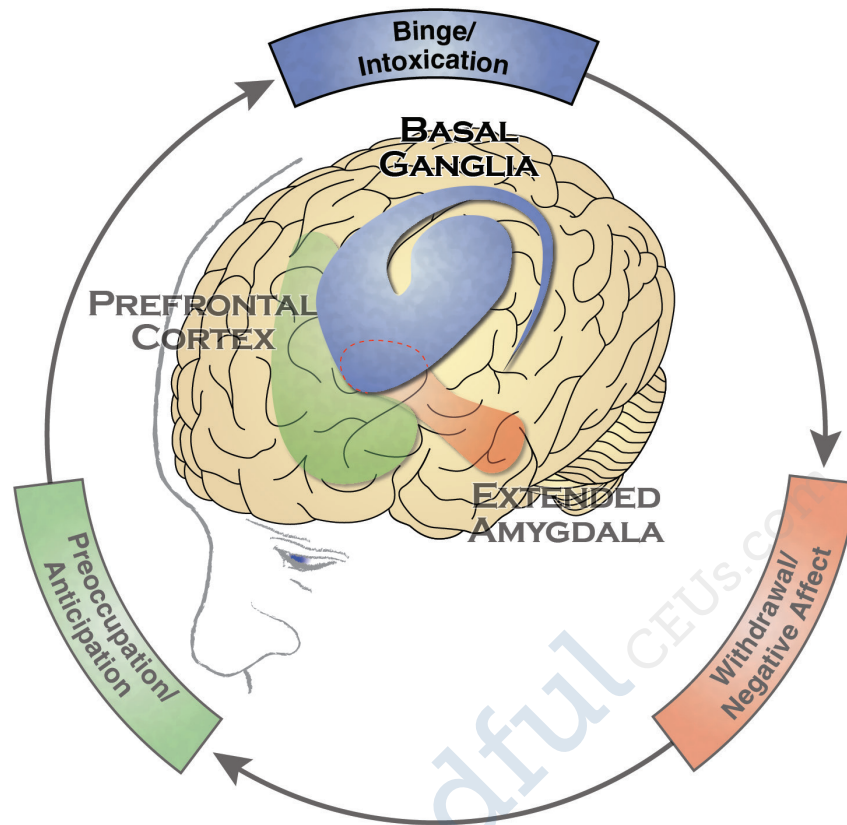
Impulsivity. An inability to resist urges, deficits in delaying gratification, and unreflective decision-making. It is a tendency to act without foresight or regard for consequences and to prioritize immediate rewards over long-term goals.¹

Positive reinforcement. The process by which presentation of a stimulus such as a drug increases the probability of a response like drug taking.

Negative reinforcement. The process by which removal of a stimulus such as negative feelings or emotions increases the probability of a response like drug taking.

Compulsivity. Repetitive behaviors in the face of adverse consequences, and repetitive behaviors that are inappropriate to a particular situation. People suffering from compulsions often recognize that the behaviors are harmful, but they nonetheless feel emotionally compelled to perform them. Doing so reduces tension, stress, or anxiety.¹

Figure 2.4: The Binge/Intoxication Stage and the Basal Ganglia



Addictive Substances “Hijack” Brain Reward Systems

All addictive substances produce feelings of pleasure. These “rewarding effects” positively reinforce their use and increase the likelihood of repeated use. The rewarding effects of substances involve activity in the nucleus accumbens, including activation of the brain’s dopamine and opioid signaling system. Many studies have shown that neurons that release dopamine are activated, either directly or indirectly, by all addictive substances, but particularly by stimulants such as cocaine, amphetamines, and nicotine (Figure 2.5).¹⁶ In addition, the brain’s opioid system, which includes naturally occurring opioid molecules (i.e., endorphins, enkephalins, and dynorphins) and three types of opioid receptors (i.e., mu, delta, and kappa), plays a key role in mediating the rewarding effects of other addictive substances, including opioids and alcohol. Activation of the opioid system by these substances stimulates the nucleus accumbens directly or indirectly through the dopamine system. Brain imaging studies in humans show activation of dopamine and opioid neurotransmitters during alcohol and other substance use (including nicotine).^{10,17} Other studies show that antagonists, or inhibitors, of dopamine and opioid receptors can block drug and alcohol seeking in both animals and humans.^{14,18,19}

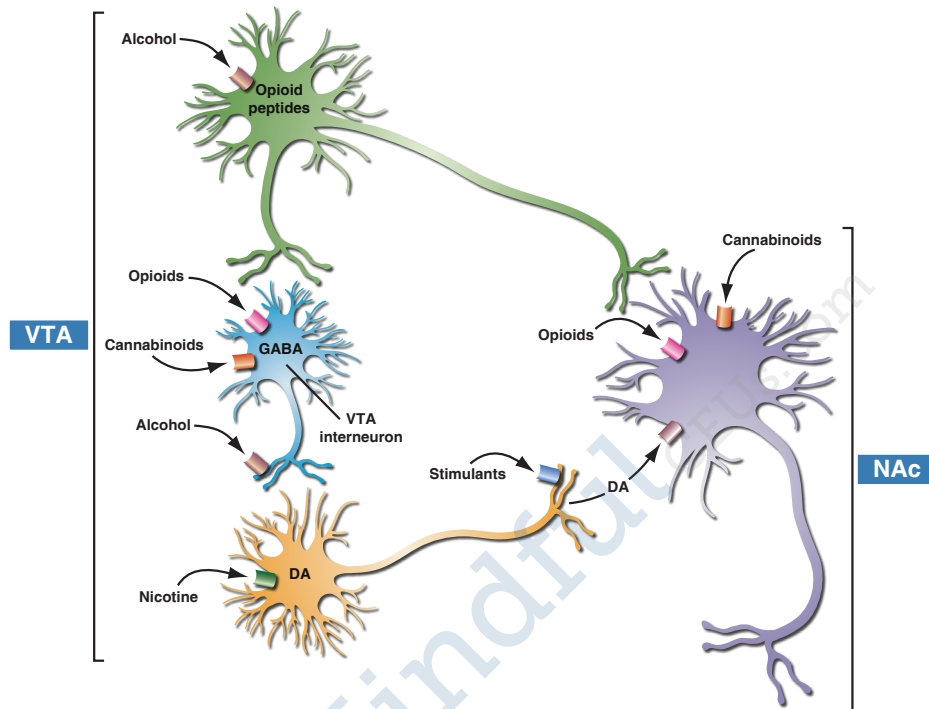


KEY TERMS

Antagonist. A chemical substance that binds to and blocks the activation of certain receptors on cells, preventing a biological response. Naloxone is an example of an opioid receptor antagonist.

Cannabinoids such as delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of marijuana, target the brain’s internal or endogenous cannabinoid system. This system also contributes to reward by affecting the function of dopamine neurons and the release of dopamine in the nucleus accumbens.

Figure 2.5: Actions of Addictive Substances on the Brain



Notes: Figure 2.5 is a simplified schematic of converging acute rewarding actions of addictive substances on the nucleus accumbens (NAc). Dopamine neurons that originate in the ventral tegmental area (VTA) project to the NAc. Opioid peptides act both in the VTA and NAc. Despite diverse initial actions, addictive substances produce some common effects on the VTA and NAc. Stimulants directly increase dopamine (DA) transmission in the NAc. Opioids, alcohol, and inhalants (e.g., the solvent toluene) do the same indirectly. Alcohol also activates the release of opioid peptides. Heroin and prescribed opioid pain relievers directly activate opioid peptide receptors. Nicotine activates dopamine neurons in the VTA. Cannabinoids may act in the VTA to activate dopamine neurons but also act on NAc neurons themselves.

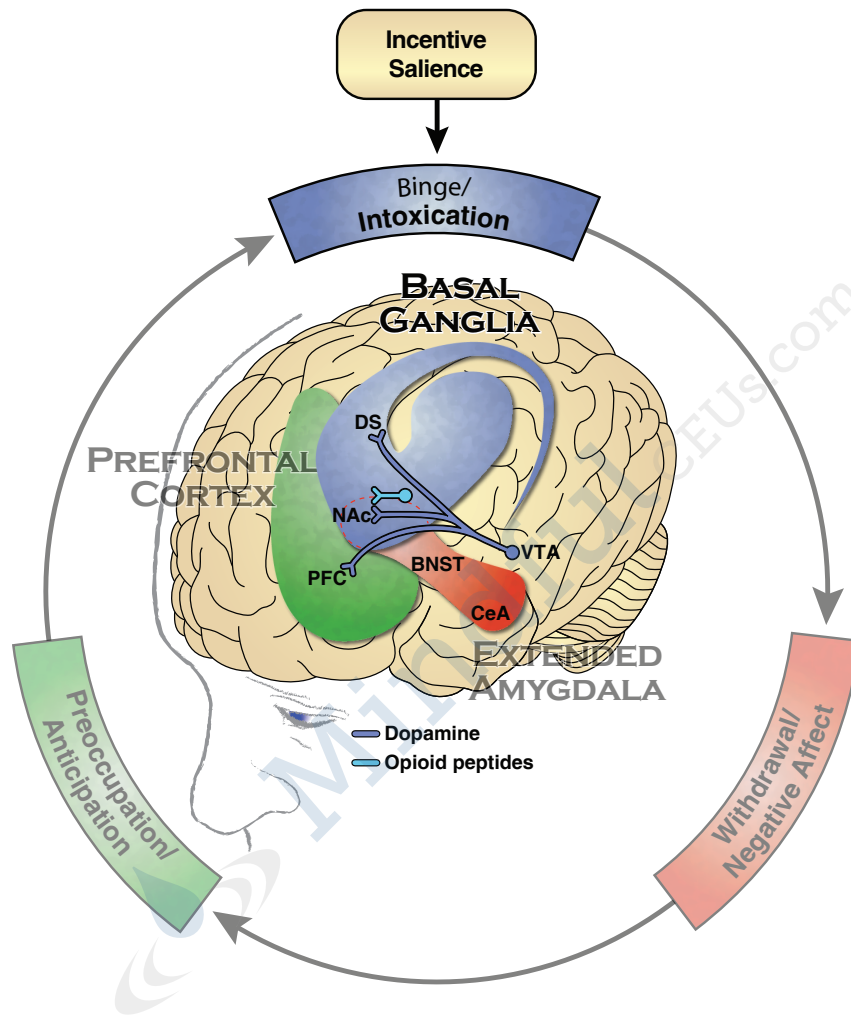
Source: Modified with permission from Nestler, (2005).¹⁶

Stimuli Associated with Addictive Substances Can Trigger Substance Use

Activation of the brain’s reward system by alcohol and drugs not only generates the pleasurable feelings associated with those substances, it also ultimately triggers changes in the way a person responds to stimuli associated with the use of those substances. A person learns to associate the stimuli present while using a substance—including people, places, drug paraphernalia, and even internal states, such as mood—with the substance’s rewarding effects. Over time, these stimuli can activate the dopamine system on their own and trigger powerful urges to take the substance. These “wanting” urges are called incentive salience and they can persist even after the rewarding effects of the substance have diminished. As a result, exposure to people, places, or things previously associated with substance use can serve as “triggers” or cues that promote substance seeking and taking, even in people who are in recovery.

Figure 2.6 shows the major neurotransmitter systems involved in the binge/intoxication stage of addiction. In this stage, the neurons in the basal ganglia contribute to the rewarding effects of addictive substances and to incentive salience through the release of dopamine and the brain's natural opioids.

Figure 2.6: Major Neurotransmitter Systems Implicated in the Neuroadaptations Associated with the Binge/Intoxication Stage of Addiction



Notes: Blue represents the basal ganglia involved in the Binge/Intoxication stage. Red represents the extended amygdala involved in the Negative Affect/Withdrawal stage. Green represents the prefrontal cortex involved in the Preoccupation/Anticipation stage.

Abbreviations: PFC - prefrontal cortex, DS - dorsal striatum, NAc - nucleus accumbens, BNST - bed nucleus of the stria terminalis, CeA - central nucleus of the amygdala, VTA - ventral tegmental area.

Source: Modified with permission from Koob & Volkow, (2010).¹⁴

Early studies in animals demonstrated how incentive salience works. For example, after researchers repeatedly gave an animal a stimulant drug (e.g., cocaine) along with a previously neutral stimulus, such as a light or a sound, they found that the neutral stimulus by itself caused the animal to engage in drug-seeking behavior, and it also resulted in dopamine release that had previously occurred only in response to the drug.²⁰ Even more compelling results were seen when scientists recorded the electrical activity of dopamine-transmitting neurons in animals that had been exposed multiple times to a neutral (non-

drug) stimulus followed by a drug. At first, the neurons responded only when they were exposed to the drug. However, over time, the neurons stopped firing in response to the drug and instead fired when they were exposed to the neutral stimulus associated with it. This means that the animals associated the stimulus with the substance and, in anticipation of getting the substance, their brains began releasing dopamine, resulting in a strong motivation to seek the drug.^{21,22} Imaging studies in humans have shown similar results. For example, dopamine is released in the brains of people addicted to cocaine when they are exposed to cues they have come to associate with cocaine.^{23,24} This effect occurs even though cocaine itself causes less dopamine to be released in these individuals compared to those who are not addicted to cocaine (an effect also seen with other substances).²⁵

Together, these studies indicate that stimuli associated with addictive drugs can, by themselves, produce drug-like effects on the brain and trigger drug use. These findings help to explain why individuals with substance use disorders who are trying to maintain abstinence are at increased risk of relapse if they continue to have contact with the people they previously used drugs with or the places where they used drugs.

Substances Stimulate Areas of the Brain Involved in Habit Formation

A second sub-region of the basal ganglia, the dorsal striatum, is involved in another critical component of the binge/intoxication stage: habit formation. The release of dopamine (along with activation of brain opioid systems) and release of glutamate (an excitatory neurotransmitter) can eventually trigger changes in the dorsal striatum.^{2,26} These changes strengthen substance-seeking and substance-taking habits as addiction progresses, ultimately contributing to compulsive use.

In Summary: The Binge/Intoxication Stage and the Basal Ganglia

The “reward circuitry” of the basal ganglia (i.e., the nucleus accumbens), along with dopamine and naturally occurring opioids, play a key role in the rewarding effects of alcohol and other substances and the ability of stimuli, or cues, associated with that substance use to trigger craving, substance seeking, and use.

As alcohol or substance use progresses, repeated activation of the “habit circuitry” of the basal ganglia (i.e., the dorsal striatum) contributes to the compulsive substance seeking and taking that are associated with addiction.

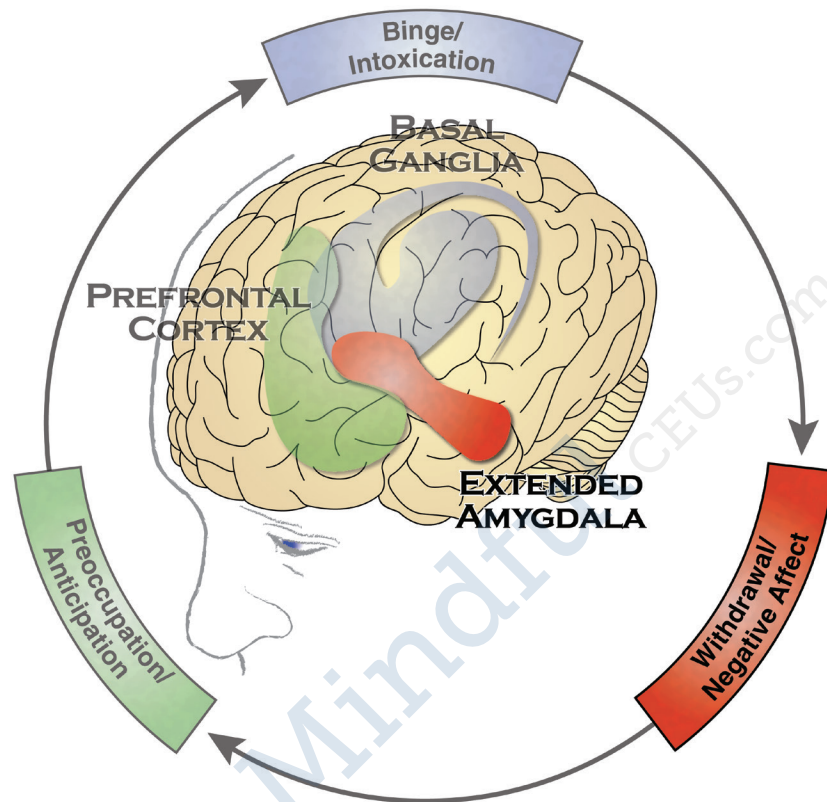
The involvement of these reward and habit neurocircuits helps explain the intense desire for the substance (craving) and the compulsive substance seeking that occurs when actively or previously addicted individuals are exposed to alcohol and/or drug cues in their surroundings.

Withdrawal/Negative Affect Stage: Extended Amygdala

The withdrawal/negative affect stage of addiction follows the binge/intoxication stage, and, in turn, sets up future rounds of binge/intoxication. During this stage, a person who has been using alcohol or drugs experiences withdrawal symptoms, which include negative emotions and, sometimes, symptoms of physical illness, when they stop taking the substance. Symptoms of withdrawal may occur with all

addictive substances, including marijuana, though they vary in intensity and duration depending on both the type of substance and the severity of use. The negative feelings associated with withdrawal are thought to come from two sources: diminished activation in the reward circuitry of the basal ganglia¹⁴ and activation of the brain's stress systems in the extended amygdala ([Figure 2.7](#)).

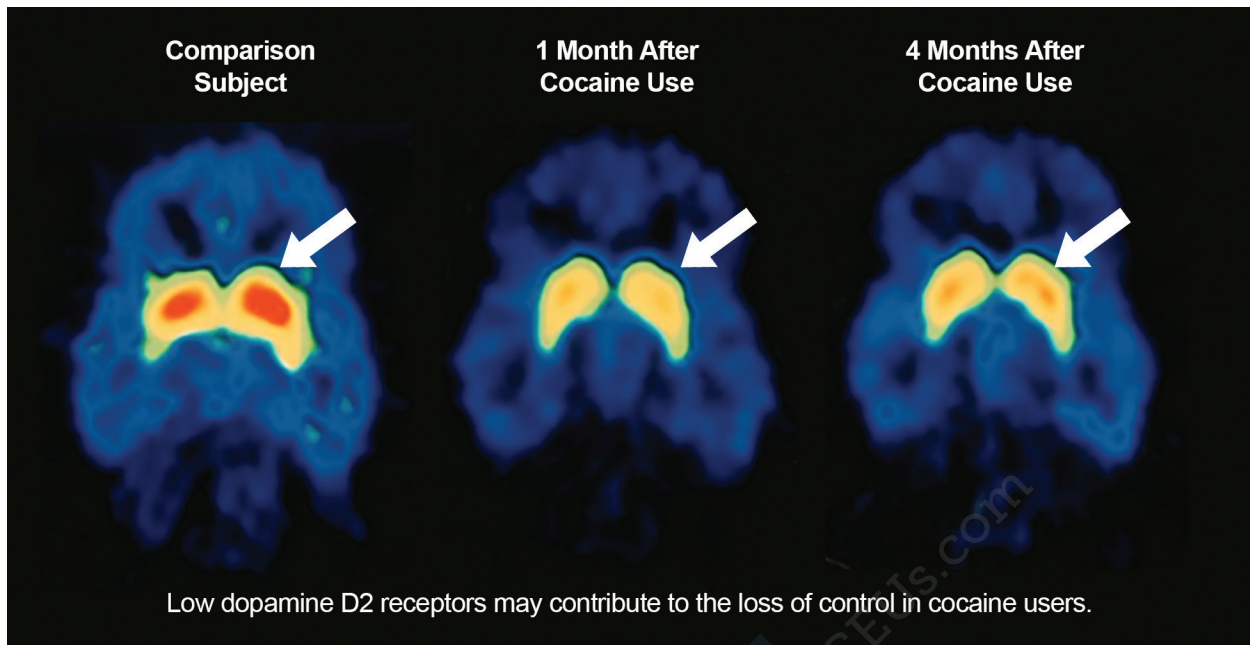
Figure 2.7: The Withdrawal/Negative Affect Stage and the Extended Amygdala



When used over the long-term, all substances of abuse cause dysfunction in the brain's dopamine reward system.²⁷ For example, brain imaging studies in humans with addiction have consistently shown long-lasting decreases in a particular type of dopamine receptor, the D2 receptor, compared with non-addicted individuals ([Figure 2.8](#)).^{25,28} Decreases in the activity of the dopamine system have been observed during withdrawal from stimulants, opioids, nicotine, and alcohol. Other studies also show that when an addicted person is given a stimulant, it causes a smaller release of dopamine than when the same dose is given to a person who is not addicted.

These findings suggest that people addicted to substances experience an overall reduction in the sensitivity of the brain's reward system (especially the brain circuits involving dopamine), both to addictive substances and also to natural reinforcers, such as food and sex. This is because natural reinforcers also depend upon the same reward system and circuits. This impairment explains why those who develop a substance use disorder often do not derive the same level of satisfaction or pleasure from once-pleasurable activities. This general loss of reward sensitivity may also account for the compulsive escalation of substance use as addicted individuals attempt to regain the pleasurable feelings the reward system once provided.¹⁵

Figure 2.8: Time-Related Decrease in Dopamine Released in the Brain of a Cocaine User



Notes: These fMRI images compare the brain of an individual with a history of cocaine use disorder (middle and right) to the brain of an individual without a history of cocaine use (left). The person who has had a cocaine use disorder has lower levels of the D2 dopamine receptor (depicted in red) in the striatum one month (middle) and four months (right) after stopping cocaine use compared to the non-user. The level of dopamine receptors in the brain of the cocaine user are higher at the 4-month mark (right), but have not returned to the levels observed in the non-user (left).

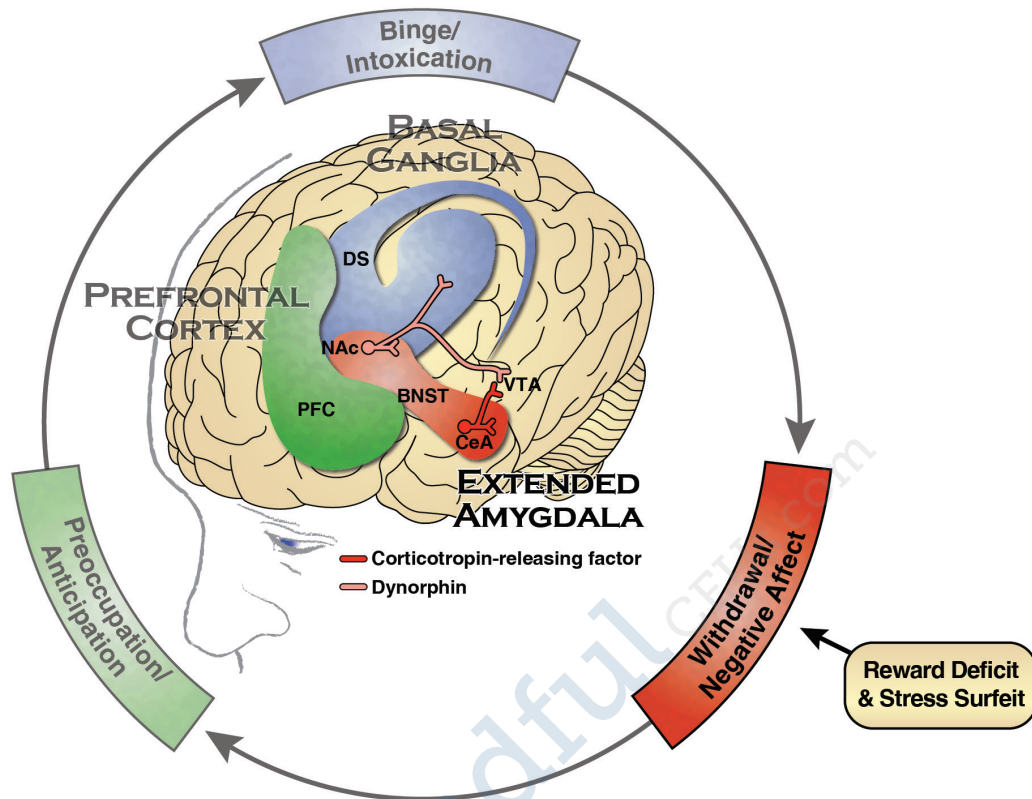
Source: Modified with permission from Volkow et al., (1993).²⁹

At the same time, a second process occurs during the withdrawal stage: activation of stress neurotransmitters in the extended amygdala. These stress neurotransmitters include corticotropin-releasing factor (CRF), norepinephrine, and dynorphin (Figure 2.9).³⁰

Studies suggest that these neurotransmitters play a key role in the negative feelings associated with withdrawal and in stress-triggered substance use. In animal and human studies, when researchers use special chemicals called antagonists to block activation of the stress neurotransmitter systems, it has the effect of reducing substance intake in response to withdrawal and stress. For example, blocking the activation of stress receptors in the brain reduced alcohol consumption in both alcohol-dependent rats and humans with an alcohol use disorder.³¹ Thus, it may be that an additional motivation for drug and alcohol seeking among individuals with substance use disorders is to suppress overactive brain stress systems that produce negative emotions or feelings. Recent research also suggests that neuroadaptations in the endogenous cannabinoid system within the extended amygdala contribute to increased stress reactivity and negative emotional states in addiction.³²

The desire to remove the negative feelings that accompany withdrawal can be a strong motivator of continued substance use. As noted previously, this motivation is strengthened through negative reinforcement, because taking the substance relieves the negative feelings associated with withdrawal, at least temporarily. Of course, this process is a vicious cycle: Taking drugs or alcohol to lessen the symptoms of withdrawal that occur during a period of abstinence actually causes those symptoms to be even worse the next time a person stops taking the substance, making it even harder to maintain abstinence.

Figure 2.9: Major Neurotransmitter Systems Implicated in the Neuroadaptations Associated with the Withdrawal/Negative Affect Stage of Addiction



Notes: Not shown is the neurotransmitter norepinephrine which is also activated in the extended amygdala during withdrawal.

Abbreviations: PFC - prefrontal cortex, DS - dorsal striatum, NAc - nucleus accumbens, BNST - bed nucleus of the stria terminalis, CeA - central nucleus of the amygdala, VTA - ventral tegmental area.

Source: Modified with permission from Koob & Volkow, (2010).¹⁴

In Summary: The Withdrawal/Negative Affect Stage and the Extended Amygdala

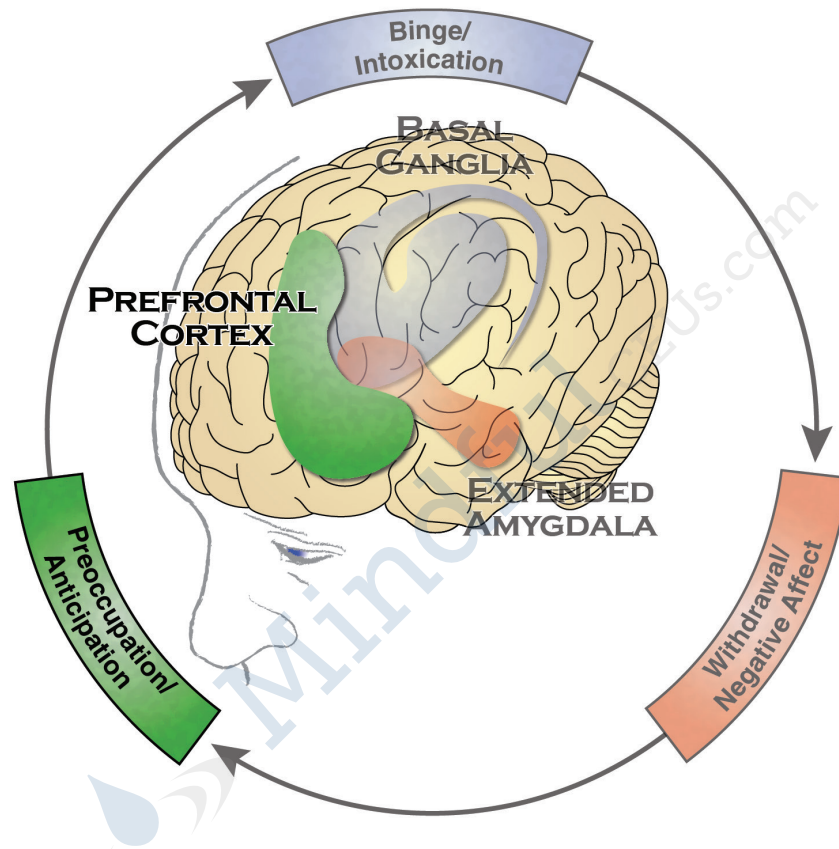
This stage of addiction involves a decrease in the function of the brain reward systems and an activation of stress neurotransmitters, such as CRF and dynorphin, in the extended amygdala. Together, these phenomena provide a powerful neurochemical basis for the negative emotional state associated with withdrawal. The drive to alleviate these negative feelings negatively reinforces alcohol or drug use and drives compulsive substance taking.

Preoccupation/Anticipation Stage: Prefrontal Cortex

The preoccupation/anticipation stage of the addiction cycle is the stage in which a person may begin to seek substances again after a period of abstinence. In people with severe substance use disorders, that period of abstinence may be quite short (hours). In this stage, an addicted person becomes preoccupied with using substances again. This is commonly called “craving.” Craving has been difficult to measure in human studies and often does not directly link with relapse.

This stage of addiction involves the brain's prefrontal cortex (Figure 2.10) the region that controls executive function: the ability to organize thoughts and activities, prioritize tasks, manage time, make decisions, and regulate one's own actions, emotions, and impulses. Executive function is essential for a person to make appropriate choices about whether or not to use a substance and to override often strong urges to use, especially when the person experiences triggers, such as stimuli associated with that substance (e.g., being at a party where alcohol is served or where people are smoking) or stressful experiences.

Figure 2.10: The Preoccupation/Anticipation Stage and the Prefrontal Cortex

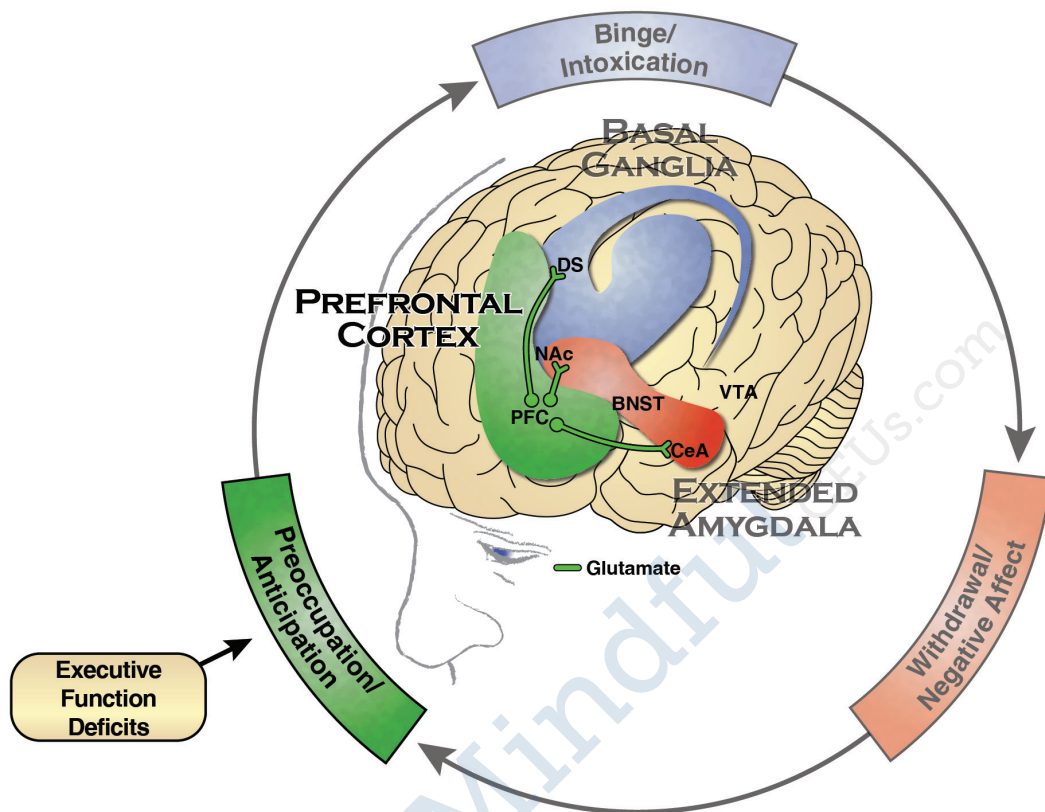


To help explain how the prefrontal cortex is involved in addiction, some scientists divide the functions of this brain region into a “Go system” and an opposing “Stop system.”³³ The Go system helps people make decisions, particularly those that require significant attention and those involved with planning. People also engage the Go system when they begin behaviors that help them achieve goals. Indeed, research shows that when substance-seeking behavior is triggered by substance-associated environmental cues (incentive salience), activity in the Go circuits of the prefrontal cortex increases dramatically. This increased activity stimulates the nucleus accumbens to release glutamate, the main excitatory neurotransmitter in the brain. This release, in turn, promotes incentive salience, which creates a powerful urge to use the substance in the presence of drug-associated cues.

The Go system also engages habit-response systems in the dorsal striatum, and it contributes to the impulsivity associated with substance seeking. Habitual responding can occur automatically and subconsciously, meaning a person may not even be aware that they are engaging in such behaviors. The

neurons in the Go circuits of the prefrontal cortex stimulate the habit systems of the dorsal striatum through connections that use glutamate (Figure 2.11).

Figure 2.11: Major Neurotransmitter Systems Implicated in the Neuroadaptations Associated with the Preoccupation/Anticipation Stage of Addiction



Abbreviations: PFC - prefrontal cortex, DS - dorsal striatum, NAc - nucleus accumbens, BNST - bed nucleus of the stria terminalis, CeA - central nucleus of the amygdala, VTA - ventral tegmental area.

Source: Modified with permission from Koob & Volkow, (2010).¹⁴

The Stop system inhibits the activity of the Go system. Especially relevant to its role in addiction, this system controls the dorsal striatum and the nucleus accumbens, the areas of the basal ganglia that are involved in the binge/intoxication stage of addiction. Specifically, the Stop system controls habit responses driven by the dorsal striatum, and scientists think that it plays a role in reducing the ability of substance-associated stimuli to trigger relapse—in other words, it inhibits incentive salience.³⁴

The Stop system also controls the brain's stress and emotional systems, and plays an important role in relapse triggered by stressful life events or circumstances. Stress-induced relapse is driven by activation of neurotransmitters such as CRF, dynorphin, and norepinephrine in the extended amygdala. As described above, these neurotransmitters are activated during prolonged abstinence during the withdrawal/negative affect stage of addiction. More recent work in animals also implicates disruptions in the brain's cannabinoid system, which also regulates the stress systems in the extended amygdala, in relapse. Studies show that lower activity in the Stop component of the prefrontal cortex is associated with increased activity of stress circuitry involving the extended amygdala, and this increased activity drives substance-taking behavior and relapse.³⁷

Brain imaging studies in people with addiction show disruptions in the function of both the Go and Stop circuits.³⁵⁻³⁷ For example, people with alcohol, cocaine, or opioid use disorders show impairments in executive function, including disruption of decision-making and behavioral inhibition. These executive function deficits parallel changes in the prefrontal cortex and suggest decreased activity in the Stop system and greater reactivity of the Go system in response to substance-related stimuli.

Indeed, a smaller volume of the prefrontal cortex in abstinent, previously addicted individuals predicts a shorter time to relapse.³⁸ Studies also show that diminished prefrontal cortex control over the extended amygdala is particularly prominent in humans with post-traumatic stress disorder (PTSD), a condition that is frequently accompanied by drug and alcohol use disorders.³⁹ These findings bolster support for the role of the prefrontal cortex-extended amygdala circuit in stress-induced relapse, and suggest that strengthening prefrontal cortex circuits could aid substance use disorder treatment.

In Summary: The Preoccupation/Anticipation Stage and the Prefrontal Cortex

This stage of the addiction cycle is characterized by a disruption of executive function caused by a compromised prefrontal cortex. The activity of the neurotransmitter glutamate is increased, which drives substance use habits associated with craving, and disrupts how dopamine influences the frontal cortex.² The over-activation of the Go system in the prefrontal cortex promotes habit-like substance seeking, and the under-activation of the Stop system of the prefrontal cortex promotes impulsive and compulsive substance seeking.

To recap, addiction involves a three-stage cycle—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—that worsens over time and involves dramatic changes in the brain reward, stress, and executive function systems. Progression through this cycle involves three major regions of the brain: the basal ganglia, the extended amygdala, and the prefrontal cortex, as well as multiple neurotransmitter systems (Figure 2.12). The power of addictive substances to produce positive feelings and relieve negative feelings fuels the development of compulsive use of substances. The combination of increased incentive salience (binge/intoxication stage), decreased reward sensitivity and increased stress sensitivity (withdrawal/negative affect stage), and compromised executive function (preoccupation/anticipation stage) provides an often overwhelming drive for substance seeking that can be unrelenting.

Different Classes of Substances Affect the Brain and Behavior in Different Ways

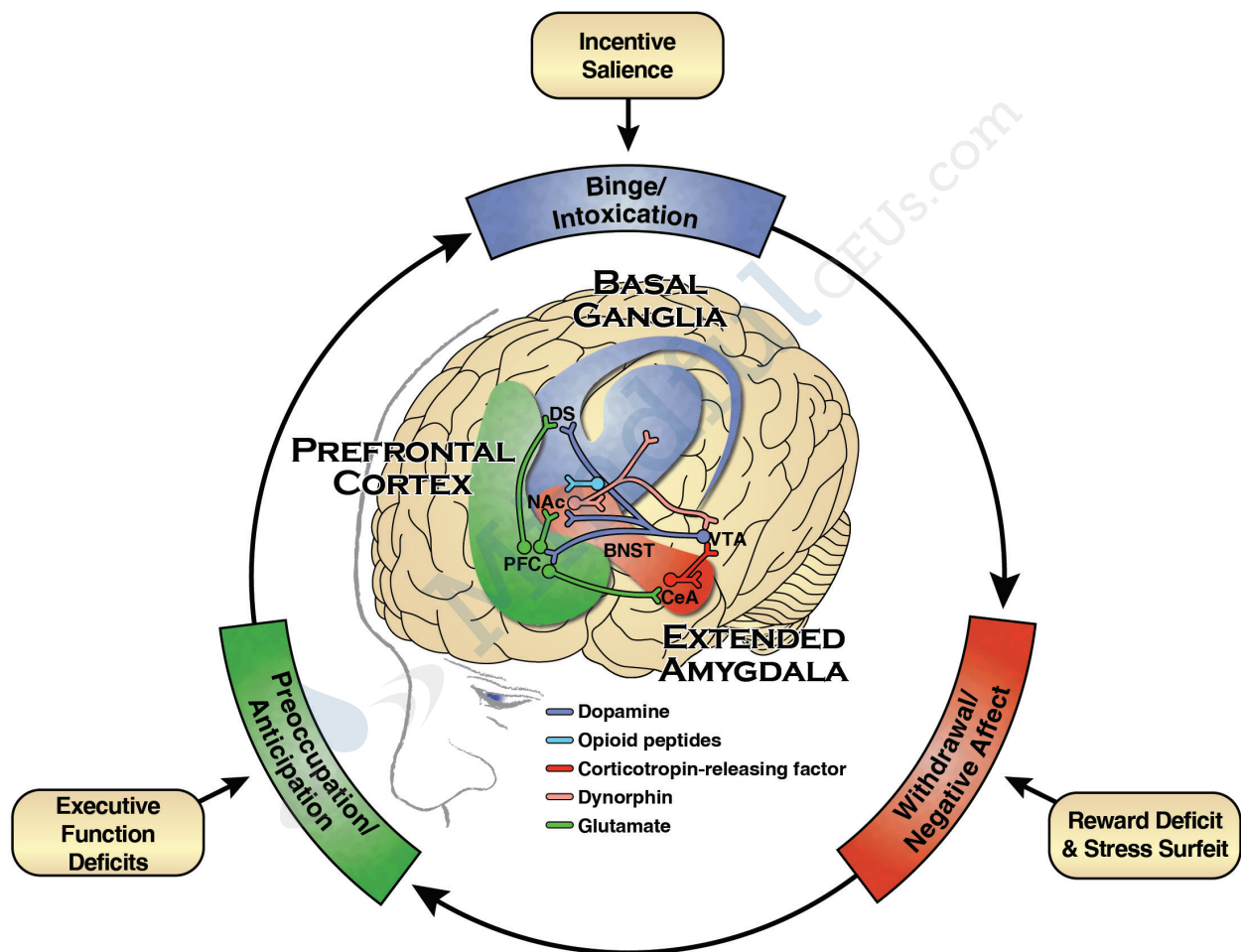
Although the three stages of addiction generally apply to all addictive substances, different substances affect the brain and behavior in different ways during each stage of the addiction cycle. Differences in the pharmacokinetics of various substances determine the duration of their effects on the body and partly account for the differences in their patterns of use. For example, nicotine has a short half-life, which means smokers need to smoke often to maintain the effect. In contrast, THC, the primary psychoactive compound in marijuana, has a much longer half-life. As a result, marijuana smokers do not typically smoke

as frequently as tobacco smokers.⁴⁰ Typical patterns of use are described below for the major classes of addictive substances. However, people often use these substances in combination.⁴¹ Additional research is needed to understand how using more than one substance affects the brain and the development and progression of addiction, as well as how use of one substance affects the use of others.

KEY TERMS

Pharmacokinetics. What the body does to a drug after it has been taken, including how rapidly the drug is absorbed, broken down, and processed by the body.

Figure 2.12: The Primary Brain Regions and Neurotransmitter Systems Involved in Each of the Three Stages of the Addiction Cycle



Opioids

Opioids attach to opioid receptors in the brain, which leads to a release of dopamine in the nucleus accumbens, causing euphoria (the high), drowsiness, and slowed breathing, as well as reduced pain signaling (which is why they are frequently prescribed as pain relievers). Opioid addiction typically involves a pattern of: (1) intense intoxication, (2) the development of tolerance, (3) escalation in use, and (4) withdrawal signs that include profound negative emotions and physical symptoms, such as

bodily discomfort, pain, sweating, and intestinal distress and, in the most severe cases, seizures. As use progresses, the opioid must be taken to avoid the severe negative effects that occur during withdrawal. With repeated exposure to opioids, stimuli associated with the pleasant effects of the substances (e.g., places, persons, moods, and paraphernalia) and with the negative mental and physical effects of withdrawal can trigger intense craving or preoccupation with use.

Alcohol

When alcohol is consumed it interacts with several neurotransmitter systems in the brain, including the inhibitory neurotransmitter GABA, glutamate, and others that produce euphoria as well as the sedating, motor impairing, and anxiety-reducing effects of alcohol intoxication. Alcohol addiction often involves a similar pattern as opioid addiction, often characterized by periods of binge or heavy drinking followed by withdrawal. As with opioids, addiction to alcohol is characterized by intense craving that is often driven by negative emotional states, positive emotional states, and stimuli that have been associated with drinking, as well as a severe emotional and physical withdrawal syndrome. Many people with severe alcohol use disorder engage in patterns of binge drinking followed by withdrawal for extended periods of time. Extreme patterns of use may evolve into an opioid-like use pattern in which alcohol must be available at all times to avoid the negative consequences of withdrawal.



KEY TERMS

Binge drinking. For men, drinking 5 or more standard alcoholic drinks, and for women, 4 or more standard alcoholic drinks on the same occasion on at least 1 day in the past 30 days.

Stimulants

Stimulants increase the amount of dopamine in the reward circuit (causing the euphoric high) either by directly stimulating the release of dopamine or by temporarily inhibiting the removal of dopamine from synapses, the gaps between neurons. These drugs also boost dopamine levels in brain regions responsible for attention and focus on tasks (which is why stimulants like methylphenidate [Ritalin[®]] or dextroamphetamine [Adderall[®]] are often prescribed for people with attention deficit hyperactivity disorder). Stimulants also cause the release of norepinephrine, a neurotransmitter that affects autonomic functions like heart rate, causing a user to feel energized.

Addiction to stimulants, such as cocaine and amphetamines (including methamphetamine), typically follows a pattern that emphasizes the binge/intoxication stage. A person will take the stimulant repeatedly during a concentrated period of time lasting for hours or days (these episodes are called binges). The binge is often followed by a crash, characterized by negative emotions, fatigue, and inactivity. Intense craving then follows, which is driven by environmental cues associated with the availability of the substance, as well as by a person's internal state, such as their emotions or mood.

Marijuana (Cannabis)

Like other drugs, marijuana (also called cannabis) leads to increased dopamine in the basal ganglia, producing the pleasurable high. It also interacts with a wide variety of other systems and circuits in the brain that contain receptors for the body's natural cannabinoid neurotransmitters. Effects can be different from user to user, but often include distortions in motor coordination and time perception. Cannabis addiction follows a pattern similar to opioids. This pattern involves a significant binge/

intoxication stage characterized by episodes of using the substance to the point of intoxication. Over time, individuals begin to use the substance throughout the day and show chronic intoxication during waking hours. Withdrawal is characterized by negative emotions, irritability, and sleep disturbances.⁴⁰ Although the craving associated with cannabis⁴² has been less studied than for other substances, it is most likely linked to both environmental and internal states, similar to those of other addictive substances.^{43,44}

Synthetic Drugs

Different classes of chemically synthesized (hence the term synthetic) drugs have been developed, each used in different ways and having different effects in the brain. Synthetic cathinones, more commonly known as “bath salts,” target the release of dopamine in a similar manner as the stimulant drugs described above. To a lesser extent, they also activate the serotonin neurotransmitter system, which can affect perception. Synthetic cannabinoids, sometimes referred to as “K2”, “Spice”, or “herbal incense,” somewhat mimic the effects of marijuana but are often much more powerful. Drugs such as MDMA (ecstasy) and lysergic acid diethylamide (LSD) also act on the serotonin neurotransmitter system to produce changes in perception. Fentanyl is a synthetic opioid medication that is used for severe pain management and is considerably more potent than heroin. Prescription fentanyl, as well as illicitly manufactured fentanyl and related synthetic opioids, are often mixed with heroin but are also increasingly used alone or sold on the street as counterfeit pills made to look like prescription opioids or sedatives.

Factors that Increase Risk for Substance Use, Misuse, and Addiction

Not all people use substances, and even among those who use them, not all are equally likely to become addicted. Many factors influence the development of substance use disorders, including developmental, environmental, social, and genetic factors, as well as co-occurring mental disorders. Other factors protect people from developing a substance use disorder or addiction. The relative influence of these risk and protective factors varies across individuals and the lifespan. The following sections discuss some of these factors.

Early Life Experiences

The experiences a person has early in childhood and in adolescence can set the stage for future substance use and, sometimes, escalation to a substance use disorder or addiction. Early life stressors can include physical, emotional, and sexual abuse; neglect; household instability (such as parental substance use and conflict, mental illness, or incarceration of household members);⁴⁵ and poverty.⁴⁶ Research suggests that the stress caused by these risk factors may act on the same stress circuits in the brain as addictive substances, which may explain why they increase addiction risk.⁴⁷

Adolescence is a critical period in the vulnerability to substance use and use disorders, because a hallmark of this developmental period is risk taking and experimentation, which for some young people includes trying alcohol, marijuana, or other drugs. In addition, the brain undergoes significant changes during this life stage, making it particularly vulnerable to substance exposure.⁴⁸ Importantly,



FOR MORE ON THIS TOPIC

See Chapter 1 - *Introduction and Overview* and Chapter 3 - *Prevention Programs and Policies*.

the frontal cortex—a region in the front part of the brain that includes the prefrontal cortex—does not fully develop until the early to mid-20s, and research shows that heavy drinking and drug use during adolescence affects development of this critical area of the brain.⁴⁹

About three quarters (74 percent) of 18- to 30-year-olds admitted to treatment programs began using substances at the age of 17 or younger.⁵⁰ Individuals who start using substances during adolescence often experience more chronic and intensive use, and they are at greater risk of developing a substance use disorder compared with those who begin use at an older age. In other words, the earlier the exposure, the greater the risk.⁵¹

Not all adolescents who experiment with alcohol, cigarettes, or other substances go on to develop a substance use disorder, but research suggests that those who do progress to more harmful use may have pre-existing differences in their brains. For example, a brain imaging study of adolescents revealed that the volume of the frontal cortex was smaller in youth who transitioned from no or minimal drinking to heavy drinking over the course of adolescence than it was in youth who did not drink during adolescence.⁴⁹ Additional research can shed light on how these differences contribute to the progression from use to a disorder, as well as how changes caused by substance use affect brain function and behavior and whether they can be reversed.

Genetic and Molecular Factors

Genetic factors are thought to account for 40 to 70 percent of individual differences in risk for addiction.^{52,53} Although multiple genes are likely involved in the development of addiction, only a few specific gene variants have been identified that either predispose to or protect against addiction. Some of these variants have been associated with the metabolism of alcohol and nicotine, while others involve receptors and other proteins associated with key neurotransmitters and molecules involved in all parts of the addiction cycle.⁵⁴ Genes involved in strengthening the connections between neurons and in forming drug memories have also been associated with addiction risk.^{55,56} Like other chronic health conditions, substance use disorders are influenced by the complex interplay between a person's genes and environment. Additional research on the mechanisms underlying gene by environment interactions is expected to provide insight into how substance use disorders develop and how they can be prevented and treated.

Use of Multiple Substances and Co-occurring Mental Health Conditions

Many individuals with a substance use disorder also have a mental disorder,^{57,58} and some have multiple substance use disorders. For example, according to the 2015 *National Survey on Drug Use and Health* (NSDUH), of the 20.8 million people aged 12 or older who had a substance use disorder during the past year, about 2.7 million (13 percent) had both an alcohol use and an illicit drug use disorder, and 41.2 percent also had a mental illness.⁵⁹ Particularly striking is the 3- to 4-fold higher rate of tobacco smoking among patients with schizophrenia and the high prevalence of co-existing alcohol use disorder in those meeting criteria for PTSD. It is estimated that 30-60 percent of patients seeking treatment for

alcohol use disorder meet criteria for PTSD,^{60,61} and approximately one third of individuals who have experienced PTSD have also experienced alcohol dependence at some point in their lives.⁶⁰

The reasons why substance use disorders and mental disorders often occur together are not clear, and establishing the relationships between these conditions is difficult. Still, three possible explanations deserve attention. One reason for the overlap may be that having a mental disorder increases vulnerability to substance use disorders because certain substances may, at least temporarily, be able to reduce mental disorder symptoms and thus are particularly negatively reinforcing in these individuals. Second, substance use disorders may increase vulnerability for mental disorders,⁶²⁻⁶⁴ meaning that the use of certain substances might trigger a mental disorder that otherwise would have not occurred. For example, research suggests that alcohol use increases risk for PTSD by altering the brain's ability to recover from traumatic experiences.^{65,66} Similarly, the use of marijuana, particularly marijuana with a high THC content, might contribute to schizophrenia in those who have specific genetic vulnerabilities.⁶⁷ Third, it is also possible that both substance use disorders and mental disorders are caused by shared, overlapping factors, such as particular genes, neurobiological deficits, and exposure to traumatic or stressful life experiences. As these possibilities are not mutually exclusive, the relationship between substance use disorders and mental disorders may result from a combination of these processes.

Regardless of which one might influence the development of the other, mental and substance use disorders have overlapping symptoms, making diagnosis and treatment planning particularly difficult. For example, people who use methamphetamine for a long time may experience paranoia, hallucinations, and delusions that may be mistaken for symptoms of schizophrenia. And, the psychological symptoms that accompany withdrawal, such as depression and anxiety, may be mistaken as simply part of withdrawal instead of an underlying mood disorder that requires independent treatment in its own right. Given the prevalence of co-occurring substance use and mental disorders, it is critical to continue to advance research on the genetic, neurobiological, and environmental factors that contribute to co-occurring disorders and to develop interventions to prevent and treat them.

Biological Factors Contributing to Population-based Differences in Substance Misuse and Substance Use Disorders

Differences Based on Sex

Some groups of people are also more vulnerable to substance misuse and substance use disorders. For example, men tend to drink more than women and they are at higher risk for alcohol use disorder, although the gender differences in alcohol use are declining.⁶⁸ Men are also more likely to have other substance use disorders.⁶⁹ However, clinical reports suggest that women who use cocaine, opioids, or alcohol progress from initial use to a disorder at a faster rate than do men (called "telescoping").⁷⁰⁻⁷² Compared with men, women also exhibit greater symptoms of withdrawal from some drugs, such as nicotine. They also report worse negative affects during withdrawal and have higher levels of the stress hormone cortisol.⁷³

Sex differences in reaction to addictive substances are not particular to humans. Female rats, in general, learn to self-administer drugs and alcohol more rapidly, escalate their drug taking more quickly, show greater symptoms of withdrawal, and are more likely to resume drug seeking in response to drugs, drug-related cues, or stressors. The one exception is that female rats show less withdrawal symptoms related to alcohol use.⁷⁴ Researchers are investigating the neurobiological bases for these differences.

Differences Based on Race and Ethnicity

Research on the neurobiological factors contributing to differential rates of substance use and substance use disorders in particular racial and ethnic groups is much more limited. A study using functional magnetic resonance imaging (fMRI) found that African American smokers showed greater activation of the prefrontal cortex upon exposure to smoking-related cues than did White smokers, an effect that may partly contribute to the lower smoking-cessation success rates observed among African Americans.⁷⁵

Alcohol research with racial and ethnic groups has shown that approximately 36 percent of East Asians carry a gene variant that alters the rate at which members of that racial group metabolize alcohol, causing a buildup of acetaldehyde, a toxic byproduct of alcohol metabolism that produces symptoms such as flushing, nausea, and rapid heartbeat. Although these effects may protect some individuals of East Asian descent from alcohol use disorder, those who drink despite the effects are at increased risk for esophageal⁷⁶ and head and neck cancers.⁷⁷ Another study found that even low levels of alcohol consumption by Japanese Americans may result in adverse effects on the brain, a finding that may be related to the differences in alcohol metabolism described above.⁷⁸ Additional research will help to clarify the interactions between race, ethnicity, and the neuroadaptations that underlie substance misuse and addiction. This work may inform the development of more precise preventive and treatment interventions.

Recommendations for Research

Decades of research demonstrate that chronic substance misuse leads to profound disruptions of brain circuits involved in the experience of pleasure or reward, habit formation, stress, and decision-making. This work has paved the way for the development of a variety of therapies that effectively help people reduce or abstain from alcohol and drug misuse and regain control over their lives. In spite of this progress, our understanding of how substance use affects the brain and behavior is far from complete. Four research areas are specifically emphasized in the text below.

Effects of Substance Use on Brain Circuits and Functions

Continued research is necessary to more thoroughly explain how substance use affects the brain at the molecular, cellular, and circuit levels. Such research has the potential to identify common neurobiological mechanisms underlying substance use disorders, as well as other related mental disorders. This research is expected to reveal new neurobiological targets, leading to new medications and non-pharmacological treatments—such as transcranial magnetic stimulation or vaccines—for the treatment of substance use disorders. A better understanding of the neurobiological mechanisms underlying substance use disorders could also help to inform behavioral interventions. Therefore, basic research that further elucidates the neurobiological framework of substance use disorders and

co-occurring mental disorders, as well as research leading to the development of new medications and other therapeutics to treat the underlying neurobiological mechanisms of substance use disorders should be accelerated.

As with other diseases, individuals vary in the development and progression of substance use disorders. Not only are some people more likely to use and misuse substances than are others and to progress from initial use to addiction differently, individuals also differ in their vulnerability to relapse and in how they respond to treatments. For example, some people with substance use disorders are particularly vulnerable to stress-induced relapse, but others may be more likely to resume substance use after being exposed to drug-related cues. Developing a thorough understanding of how neurobiological differences account for variation among individuals and groups will guide the development of more effective, personalized prevention and treatment interventions. Additionally, determining how neurobiological factors contribute to differences in substance misuse and addiction between women and men and among racial and ethnic groups is critical.

Continued advances in neuroscience research will further enhance our understanding of substance use disorders and accelerate the development of new interventions. Data gathered through the National Institutes of Health's Adolescent Brain Cognitive Development study, the largest long-term study of cognitive and brain development in children across the United States, is expected to yield unprecedented information about how substance use affects adolescent brain development. The Human Connectome Project and the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative are poised to spur an explosion of knowledge about the structure and function of brain circuits and how the brain affects behavior. Technologies that can alter the activity of dysfunctional circuits are being explored as possible treatments. Moreover, continued advances in genomics, along with President Obama's Precision Medicine Initiative, a national effort to better understand how individual variability in genes, environment, and lifestyle contribute to disease, are expected to bring us closer to developing individually-tailored preventive and treatment interventions for substance-related conditions.

Neurobiological Effects of Recovery

Little is known about the factors that facilitate or inhibit long-term recovery from substance use disorders or how the brain changes over the course of recovery. Developing a better understanding of the recovery process, and the neurobiological mechanisms that enable people to maintain changes in their substance use behavior and promote resilience to relapse, will inform the development of additional effective treatment and recovery support interventions. Therefore, an investigation of the neurobiological processes that underlie recovery and contribute to improvements in social, educational, and professional functioning is necessary.

Adolescence, Brain Change, and Vulnerability to Substance Use Disorders

Although young people are particularly vulnerable to the adverse effects of substance use, not all adolescents who experiment with alcohol or drugs go on to develop a substance use disorder. Prospective, longitudinal studies are needed to investigate whether pre-existing neurobiological factors contribute to adolescent substance use and the development of substance use disorders, how adolescent substance use affects brain structure and function, and whether the changes in brain structure and function that accompany chronic substance use can recover over time. Studies that follow groups of adolescents over time to learn about the developing human brain should be conducted. These studies should investigate how pre-existing neurobiological factors contribute to substance use, misuse, and addiction, and how adolescent substance use affects brain function and behavior.



KEY TERMS

Longitudinal study. A type of study in which data on a particular group of people are gathered repeatedly over a period of years or even decades.

Neurobiological Effects of Polysubstance Use and Emerging Drug Products

Patterns of alcohol and drug use change over time. New drugs or drug combinations, delivery systems, and routes of administration emerge, and with them new questions for public health. For example, concern is growing that increasing use of marijuana extracts with extremely high amounts of THC could lead to higher rates of addiction among marijuana users. Concerns also are emerging about how new products about which little is known, such as synthetic cannabinoids and synthetic cathinones, affect the brain. Additional research is needed to better understand how such products - as well as emerging addictive substances - affect brain function and behavior, and contribute to addiction.





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"This course was developed from the public domain document: Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health – U.S Department of Health and Human Services (2016)."