

Research Report

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Common Comorbidities with Substance Use Disorders Research Report

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Common Comorbidities with Substance Use Disorders

Research Report

Introduces a report that focuses on the topic of common physical and mental health comorbidities with substance use disorders, a research priority for NIDA.

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Introduction

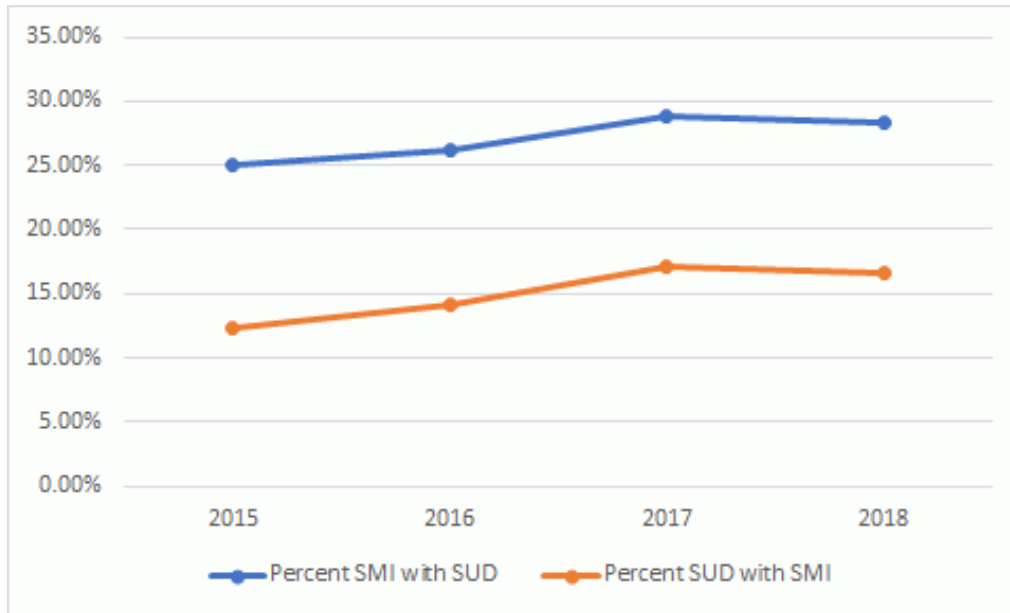
When two disorders or illnesses occur in the same person, simultaneously or sequentially, they are described as comorbid.¹ Comorbidity also implies that the illnesses interact, affecting the course and prognosis of both.^{1,2} This research report provides information on the state of the science in the comorbidity of substance use disorders with mental illness and physical health conditions

Part 1: The Connection Between Substance Use Disorders and Mental Illness

Many individuals who develop substance use disorders (SUD) are also diagnosed with mental disorders, and vice versa. Multiple national population surveys have found that about half of those who experience a mental illness during their lives will also experience a substance use disorder and vice versa.^{2,3} Although there are fewer studies on comorbidity among youth, research suggests that adolescents with substance use disorders also have high rates of co-occurring mental illness; over 60 percent of adolescents in community-based substance use disorder treatment programs also meet diagnostic criteria for another mental illness.⁴

Data show high rates of comorbid substance use disorders and anxiety disorders—which include generalized anxiety disorder, panic disorder, and post-traumatic stress disorder.^{5–9} Substance use disorders also co-occur at high prevalence with mental disorders, such as depression and bipolar disorder,^{6,9–11} attention-deficit hyperactivity disorder (ADHD),^{12,13} psychotic illness,^{14,15} borderline

personality disorder,¹⁶ and antisocial personality disorder.^{10,15} Patients with schizophrenia have higher rates of alcohol, tobacco, and drug use disorders than the general population.¹⁷ As Figure 1 shows, the overlap is especially pronounced with serious mental illness (SMI). Serious mental illness among people ages 18 and older is defined at the [federal level](#) as having, at any time during the past year, a diagnosable mental, behavior, or emotional disorder that causes serious functional impairment that substantially interferes with or limits one or more major life activities. Serious mental illnesses include major depression, schizophrenia, and bipolar disorder, and other mental disorders that cause serious impairment.¹⁸ Around 1 in 4 individuals with SMI also have an SUD.



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, Mental Health, Detailed Tables available at: <https://www.samhsa.gov/data/population-data-nsduh>

Data from a large nationally representative sample suggested that people with mental, personality, and substance use disorders were at increased risk for nonmedical use of prescription opioids.¹⁹ Research indicates that 43 percent of people in SUD treatment for nonmedical use of prescription painkillers have a diagnosis or symptoms of mental health disorders, particularly depression and anxiety.²⁰

Youth—A Vulnerable Time

Although drug use and addiction can happen at any time during a person's life, drug use typically starts in adolescence, a period when the first signs of mental illness commonly appear.

Comorbid disorders can also be seen among youth.²¹⁻²³ During the transition to young adulthood (age 18 to 25 years), people with comorbid disorders need coordinated support to help them navigate potentially stressful changes in education, work, and relationships.²¹

Drug Use and Mental Health Disorders in Childhood or Adolescence Increases Later Risk

The brain continues to develop through adolescence. Circuits that control executive functions such as decision making and impulse control are among the last to mature, which enhances vulnerability to drug use and the development of a substance use disorder.^{3,24} Early drug use is a strong risk factor for later development of substance use disorders,²⁴ and it may also be a risk factor for the later occurrence of other mental illnesses.^{25,26} However, this link is not necessarily causative and may reflect shared risk factors including genetic vulnerability, psychosocial experiences, and/or general environmental influences. For example, frequent marijuana use during adolescence can increase the risk of psychosis in adulthood, specifically in individuals who carry a particular gene variant.^{26,27}

It is also true that having a mental disorder in childhood or adolescence can increase the risk of later drug use and the development of a substance use disorder. Some research has found that mental illness may precede a substance use disorder, suggesting that better diagnosis of youth mental illness may help reduce comorbidity. One study found that adolescent-onset bipolar disorder confers a greater risk of subsequent substance use disorder compared to adult-onset bipolar disorder.²⁸ Similarly, other research suggests that youth develop internalizing disorders, including depression and anxiety, prior to developing substance use disorders.²⁹

Untreated Childhood ADHD Can Increase Later Risk of Drug Problems

Numerous studies have documented an increased risk for substance use disorders in youth with untreated ADHD,^{13,30} although some studies suggest that only those with comorbid conduct disorders have greater odds of later developing a substance use disorder.^{30,31} Given this linkage, it is important to determine whether effective treatment of ADHD could prevent subsequent drug

use and addiction. Treatment of childhood ADHD with stimulant medications such as methylphenidate or amphetamine reduces the impulsive behavior, fidgeting, and inability to concentrate that characterize ADHD.³²

That risk presents a challenge when treating children with ADHD, since effective treatment often involves prescribing stimulant medications with addictive potential. Although the research is not yet conclusive, many studies suggest that ADHD medications do not increase the risk of substance use disorder among children with this condition.^{31,32} It is important to combine stimulant medication for ADHD with appropriate family and child education and behavioral interventions, including counseling on the chronic nature of ADHD and risk for substance use disorder.^{13,32}

Why is there comorbidity between substance use disorders and mental illnesses?

The high prevalence of comorbidity between substance use disorders and other mental illnesses does not necessarily mean that one caused the other, even if one appeared first. Establishing causality or directionality is difficult for several reasons. For example, behavioral or emotional problems may not be severe enough for a diagnosis (called subclinical symptoms), but subclinical mental health issues may prompt drug use. Also, people's recollections of when drug use or addiction started may be imperfect, making it difficult to determine whether the substance use or mental health issues came first.

Three main pathways can contribute to the comorbidity between substance use disorders and mental illnesses:¹

1. Common risk factors can contribute to both mental illness and substance use and addiction.
2. Mental illness may contribute to substance use and addiction.
3. Substance use and addiction can contribute to the development of mental illness.

1. Common risk factors can contribute to both mental illness and substance use and addiction.

Both substance use disorders and other mental illnesses are caused by overlapping factors such as genetic and epigenetic vulnerabilities,^{27,33–35} issues with similar areas of the brain,^{2,3,36} and environmental influences such as early exposure to stress or trauma.^{3,27}

Genetic Vulnerabilities

It is estimated that 40–60 percent of an individual's vulnerability to substance use disorders is attributable to genetics.³⁷ An active area of comorbidity research involves the search for that might predispose individuals to develop both a substance use disorder and other mental illnesses, or to have a greater risk of a second disorder occurring after the first appears.^{27,33,34} Most of this vulnerability arises from complex interactions among multiple genes and genetic interactions with environmental influences.^{33,38} For example, frequent marijuana use during adolescence is associated with increased risk of psychosis in adulthood, specifically among individuals who carry a particular gene variant.^{25–27}

In some instances, a gene product may act directly, as when a protein influences how a person responds to a drug (e.g., whether the drug experience is pleasurable or not) or how long a drug remains in the body. Specific genetic factors have been identified that predispose an individual to alcohol dependence and cigarette smoking, and research is starting to uncover the link between genetic sequences and a higher risk of cocaine dependence, heavy opioid use, and cannabis craving and withdrawal.³⁷ But genes can also act indirectly by altering how an individual responds to stress³⁸ or by increasing the likelihood of risk-taking and novelty-seeking behaviors,³ which could influence the initiation of substance use as well as the development of substance use disorders and other mental illnesses. Research suggests that there are many genes that may contribute to the risk for both mental disorders and addiction, including those that influence the action of neurotransmitters—chemicals that carry messages from one neuron to another—that are affected by drugs and commonly dysregulated in mental illness, such as dopamine and serotonin.^{33,39}

Epigenetic Influences

Scientists are also beginning to understand the very powerful ways that genetic and environmental factors interact at the molecular level.^{40,41} Epigenetics refers to the study of changes in the regulation

of gene activity and expression that are not dependent on gene sequence; that is, changes that affect how genetic information is read and acted on by cells in the body. Environmental factors such as chronic stress, trauma, or drug exposure can induce stable changes in gene expression, which can alter functioning in neural circuits and ultimately impact behavior.⁴² For more information on epigenetics, see [Genetics and Epigenetics of Addiction DrugFacts](#).

Through epigenetic mechanisms, the environment can cause long-term genetic adaptations—influencing the pattern of genes that are active or silent in encoding proteins—without altering the DNA sequence. These modifications can sometimes even be passed down to the next generation.³⁵ There is also evidence that they can be reversed with interventions or environmental alteration.⁴¹

The epigenetic impact of environment is highly dependent on developmental stage.⁴² Studies suggest that environmental factors interact with genetic vulnerability during particular developmental periods to increase the risk for mental illnesses⁴² and addiction.³⁵ For example, animal studies indicate that a maternal diet high in fat during pregnancy can influence levels of key proteins involved in neurotransmission in the brain's reward pathway.⁴¹ Other animal research has shown that poor quality maternal care diminished the ability of offspring to respond to stress through epigenetic mechanisms.⁴¹ Researchers are using animal models to explore the epigenetic changes induced by chronic stress or drug administration, and how these changes contribute to depression- and addiction-related behaviors.⁴⁰ A better understanding of the biological mechanisms that underlie the genetic and biological interactions that contribute to the development of these disorders will inform the design of improved treatment strategies.^{40,42}

Brain Region Involvement

Many areas of the brain are affected by both substance use disorders and other mental illnesses. For example, the circuits in the brain that mediate reward, decision making, impulse control, and emotions may be affected by addictive substances and disrupted in substance use disorders, depression, schizophrenia, and other psychiatric disorders.^{2,3,34,43} In addition, multiple neurotransmitter systems have been implicated in both substance use disorders and other mental disorders including, but not limited to, dopamine,⁴⁴⁻⁴⁶ serotonin,^{47,48} glutamate,^{49,50} GABA,⁵¹ and norepinephrine.^{46,52,53}

Environmental Influences

Many environmental factors are associated with an increased risk for both substance use disorders and mental illness including chronic stress, trauma, and adverse childhood experiences, among others. Many of these factors are modifiable and; thus, prevention interventions will often result in reductions in both substance use disorders and mental illness, as discussed in the [Surgeon General's report](#) on alcohol, drugs, and health.

Stress

Stress is a known risk factor for a range of mental disorders and therefore provides one likely common neurobiological link between the disease processes of substance use disorders and mental disorders.^{3,38,54} Exposure to stressors is also a major risk factor for relapse to drug use after periods of recovery. Stress responses are mediated through the hypothalamic-pituitary-adrenal (HPA) axis, which in turn can influence brain circuits that control motivation. Higher levels of stress have been shown to reduce activity in the prefrontal cortex and increase responsivity in the striatum, which leads to decreased behavioral control and increased impulsivity.⁵⁵ Early life stress and chronic stress can cause long-term alterations in the HPA axis, which affects limbic brain circuits that are involved in motivation, learning, and adaptation, and are impaired in individuals with substance use disorders and other mental illnesses.^{2,3,34,43}

Importantly, dopamine pathways have been implicated in the way in which stress can increase vulnerability to substance use disorders. HPA axis hyperactivity has been shown to alter dopamine signaling, which may enhance the reinforcing properties of drugs.^{38,54,55} In turn, substance use causes changes to many neurotransmitter systems that are involved in responses to stress. These neurobiological changes are thought to underlie the link between stress and escalation of drug use as well as relapse. Treatments that target stress, such as mindfulness-based stress reduction, have been shown to be beneficial for reducing depression, anxiety, and substance use.⁵⁶

Trauma and Adverse Childhood Experiences

Physically or emotionally traumatized people are at much higher risk for drug use and SUDs.⁵⁷ and the co-occurrence of these disorders is associated with inferior treatment outcomes.⁵⁷ People with PTSD may use substances in an attempt to reduce their anxiety and to avoid dealing with trauma and its consequences.⁵⁸

The link between substance use disorder and PTSD is of particular concern for service members

returning from tours of duty in Iraq and Afghanistan. Between 2004 and 2010, approximately 16 percent of veterans had an untreated substance use disorder, and 8 percent needed treatment for serious psychological distress (SPD).⁵⁹ Data from a survey that used a contemporary, national sample of veterans estimated that the rate of lifetime PTSD was 8 percent, while approximately 5 percent reported current PTSD.⁶⁰ Approximately 1 in 5 veterans with PTSD also has a co-occurring substance use disorder.⁶¹

2. Mental illnesses can contribute to drug use and addiction.

Certain mental disorders are established risk factors for developing a substance use disorder.⁶² It is commonly hypothesized that individuals with severe, mild, or even subclinical mental disorders may use drugs as a form of self-medication.^{1,28} Although some drugs may temporarily reduce symptoms of a mental illness, they can also exacerbate symptoms, both acutely and in the long run. For example, evidence suggests that periods of cocaine use may worsen the symptoms of bipolar disorder and contribute to progression of this illness.⁶³

When an individual develops a mental illness, associated changes in brain activity may increase the vulnerability for problematic use of substances by enhancing their rewarding effects, reducing awareness of their negative effects, or alleviating the unpleasant symptoms of the mental disorder or the side effects of the medication used to treat it.¹ For example, neuroimaging suggests that ADHD is associated with neurobiological changes in brain circuits that are also associated with drug cravings, perhaps partially explaining why patients with substance use disorders report greater cravings when they have comorbid ADHD.⁶⁴⁻⁶⁶

3. Substance use and addiction can contribute to the development of mental illness.

Substance use can lead to changes in some of the same brain areas that are disrupted in other mental disorders, such as schizophrenia, anxiety, mood, or impulse-control disorders.^{2,36} Drug use that precedes the first symptoms of a mental illness may produce changes in brain structure and function that kindle an underlying predisposition to develop that mental illness.

The Comorbidity Between Mental Illness and Tobacco Use—Highlight on Schizophrenia

Based on nationally representative survey data from 2016, 30.5 percent of respondents who have a mental illness smoked cigarettes in the past month, which is about 66 percent higher than the rate among those with no mental illness. There is a strong association between mental illness, particularly depression and schizophrenia, and use of tobacco products.^{67–69} People with schizophrenia have the highest prevalence of smoking (70 to 80 percent)⁷⁰—with rates up to 5 times higher than the general population.⁶⁸

Smoking may reduce or help individuals cope with the symptoms of these illnesses, such as poor concentration, low mood, and stress.^{43,67,68} Such alleviation of symptoms may explain why people with mental illnesses are less likely to quit smoking compared with those in the general population.^{68,71,72} Unfortunately, high rates of smoking and difficulty quitting among people with schizophrenia may contribute to their greater prevalence of cardiovascular disease and shorter life expectancy.⁶⁸

Research on Schizophrenia and Nicotine

Research on how both nicotine and schizophrenia affect the brain has generated other possible explanations for the high rate of smoking among people with schizophrenia.⁴³ The presence of abnormalities in particular circuits of the brain may predispose individuals to schizophrenia and increase the rewarding effects of drugs like nicotine, and/or reduce an individual's ability to quit smoking.^{43,73} These mechanisms are consistent with the observation that both nicotine and the medication clozapine (which also acts at nicotinic acetylcholine receptors, among others) are effective in treating individuals with schizophrenia,^{17,74} and can serve as replacements for the nicotine obtained through cigarette smoking, thus making it easier to quit smoking.⁷⁴

The dorsal anterior cingulate cortex (dACC) is involved in decision-making and planning, focusing attention, and controlling impulses and emotions. Researchers have found that connections between this region and several other brain areas—including some involved in memory, emotion, and reward—are weaker among patients with schizophrenia compared with those without the disorder. This circuit was impaired among people with schizophrenia

regardless of whether they smoked or not, as well as among the close relatives of people with schizophrenia. Several of these neural circuits were also less active among individuals with severe nicotine use disorder, suggesting that this brain circuit is impaired in both schizophrenia and nicotine dependence.⁷³

A lower level of nicotinic acetylcholine receptors is a neurobiological hallmark of schizophrenia. These receptors, which are involved in cognition and memory,⁷⁵ are naturally activated by the neurotransmitter acetylcholine—but they can also be activated by nicotine. Researchers are working to develop medications that stimulate these specific receptors, which can counter the cognitive impairments associated with schizophrenia without the addictive potential of nicotine or the negative health consequences of smoking.⁷⁵ Understanding how and why patients with schizophrenia use nicotine may help inform the development of new treatments for both schizophrenia and nicotine dependence.

Although there is a great need for new treatments for both schizophrenia and nicotine dependence, people with these comorbid disorders can quit without worsening their mental health when they have appropriate support.^{67,76} For example, bupropion increases smoking abstinence rates in people with schizophrenia, with no apparent worsening of psychotic symptoms.^{77,78} Adding motivational incentives (rewarding patients for biologically verified abstinence) to bupropion medication may help prevent relapse during the initial phase of smoking cessation.⁷⁸ Varenicline may also improve smoking cessation rates in schizophrenia, but this medication may worsen psychiatric symptoms and requires additional research.^{78,79}

What are some approaches to diagnosis?

The high rate of comorbidity between drug use disorders and other mental illnesses highlights the need for an integrated approach to intervention that identifies and evaluates each disorder concurrently and provides treatment as appropriate for each patient's particular constellation of disorders.^{80,81} Enhanced understanding of the common genetic, neural, and environmental substrates of these disorders can lead to improved treatments for individuals with comorbidities and may help

diminish the social stigma that makes some patients reluctant to seek the treatment they need.

The diagnosis and treatment of comorbid substance use disorders and mental illness are complex, because it is often difficult to disentangle overlapping symptoms.^{2,80,81} Comprehensive assessment tools should be used to reduce the chance of a missed diagnosis.⁸¹ Patients who have both a drug use disorder and another mental illness often exhibit symptoms that are more persistent, severe, and resistant to treatment compared with patients who have either disorder alone.^{3,82}

Patients entering treatment for psychiatric illnesses should be screened for substance use disorders and vice versa. Accurate diagnosis is complicated, however, by the similarities between drug-related symptoms, such as withdrawal, and those of potentially comorbid mental disorders. Thus, when people who use drugs enter treatment, it may be necessary to observe them after a period of abstinence to distinguish between the effects of substance intoxication or withdrawal and the symptoms of comorbid mental disorders. This practice results in more accurate diagnoses and allows for better-targeted treatment.^{80,81}

Polysubstance Use and Comorbid Substance Use Disorders

Polysubstance use is common, and many people develop multiple comorbid substance use disorders ([Table 1](#)). For example, among people with a heroin use disorder over 66 percent are dependent on nicotine, nearly 25 percent have an alcohol use disorder, and over 20 percent have a cocaine use disorder. Among people with a cocaine use disorder nearly 60 percent have an alcohol use disorder, approximately 48 percent are dependent on nicotine, and over 21 percent have a marijuana use disorder. As with single-substance use disorders, the diagnosis and treatment of comorbid substance use disorders and mental illness are complex. The use of multiple substances can further complicate diagnosis and treatment.

Table 1: Comorbid Substance Use Disorders

Among individuals with:	Percentage of individuals who also have:					
	Alcohol Use Disorder	Nicotine Dependence	Marijuana Use Disorder	Cocaine Use Disorder	Prescription Opioid Use Disorder	Heroin Use Disorder
Alcohol Use Disorder	-	23.8	9.5	3.3	3.9	0.9
Nicotine Dependence	12.9	-	4.3	1.4	2.7	1.3
Marijuana Use Disorder	38.7	32.6	-	4.8	7.9	1.8
Cocaine Use Disorder	59.8	47.7	21.3	-	16.4	13.4
Prescription Opioid Use Disorder	35.2	45.4	17.6	8.2	-	11.2
Heroin Use Disorder	24.5	66.3	12.3	20.9	34.9	-

What are the treatments for comorbid substance use disorder and mental health conditions?

Integrated treatment for comorbid drug use disorder and mental illness has been found to be consistently superior compared with separate treatment of each diagnosis.^{3,81-83} Integrated treatment of co-occurring disorders often involves using cognitive behavioral therapy strategies to boost interpersonal and coping skills and using approaches that support motivation and functional recovery.⁸¹

Patients with comorbid disorders demonstrate poorer treatment adherence⁸⁴ and higher rates of treatment dropout^{3,82} than those without mental illness, which negatively affects outcomes.

Nevertheless, steady progress is being made through research on new and existing treatment options for comorbidity.^{74,81–83,85} In addition, research on implementation of appropriate screening and treatment within a variety of settings, including criminal justice systems, can increase access to appropriate treatment for comorbid disorders.⁸⁶

Treatment of comorbidity often involves collaboration between clinical providers and organizations that provide supportive services to address issues such as homelessness, physical health, vocational skills, and legal problems.⁸⁷ Communication is critical for supporting this integration of services. Strategies to facilitate effective communication may include co-location, shared treatment plans and records, and case review meetings.⁸⁷ Support and incentives for collaboration may be needed, as well as education for staff on co-occurring substance use and mental health disorders.

Treatment for Youth

As mentioned previously, the onset of mental illness and substance use disorders often occurs during adolescence, and people who develop problems earlier typically have a greater risk for severe problems as adults. Given the high prevalence of comorbid mental disorders and their adverse impact on SUD treatment outcomes, SUD programs for adolescents should screen for comorbid mental disorders and provide treatment as appropriate.^{21,23,88}

Research indicates that some mental, emotional, and behavioral problems among youth can be prevented or significantly mitigated by evidence-based prevention interventions.⁸⁹ These interventions can help reduce the impact of risk factors for substance use disorders and other mental illnesses, including parental unemployment, maternal depression, child abuse and neglect, poor parental supervision, deviant peers, deprivation, poor schools, trauma, limited health care, and unsafe and stressful environments. Implementation of policies, programs, and practices that decrease risk factors and increase resilience can help reduce both substance use disorders and other mental illnesses, potentially saving billions of dollars in associated costs related to health care and incarceration.⁸⁹

Other evidence-based interventions emphasize strengthening protective factors to enhance young people’s well-being and provide the tools to process emotions and avoid behaviors with negative consequences. Key protective factors include supportive family, school, and community environments.

In addition to the treatment options discussed in this research report, the following treatments have been shown to be effective for children and adolescents:

- **Multisystemic Therapy (MST).** MST targets key factors that are associated with serious antisocial behavior in children and adolescents with substance use disorders, such as attitudes, family, peer pressure, school and neighborhood culture.^{22,24}
- **Brief Strategic Family Therapy (BSFT).** BSFT targets family interactions that are thought to maintain or exacerbate adolescent substance use disorder and other co-occurring problem behaviors such as conduct problems, oppositional behavior, delinquency, associating with antisocial peers, aggressive and violent behavior, and risky sexual behaviors.⁹⁰
- **Multidimensional Family Therapy (MDFT).** MDFT, a comprehensive intervention for adolescents, focuses on multiple and interacting risk factors for substance use disorders and related comorbid conditions. This therapy addresses adolescents’ interpersonal and relationship issues, parental behaviors, and the family environment. Families receive assistance with navigating school and social service systems, as well as the juvenile justice system if needed. Treatment includes individual and family sessions.⁹¹

Medications

Effective medications exist for treating opioid, alcohol, and nicotine use disorders and for alleviating the symptoms of many other disorders.^{62,74,83} While most have not been well studied in comorbid populations, some medications may help treat multiple problems. For example, bupropion is approved for treating depression and nicotine dependence. For more information, see the table below.

Pharmacotherapies Used to Treat Alcohol, Nicotine, and Opioid Use Disorders

Medication	Use	Dosage Form	DEA Schedule*	Application
Buprenorphine-Naloxone	Opioid use disorder	<p>Sublingual or buccal film buprenorphine/naloxone 2mg/0.5mg, 4mg/1mg, 8mg/2mg, and 12mg/3mg</p> <p>Sublingual tablet: buprenorphine/naloxone 1.4mg/0.36mg, 2mg/0.5mg, 2.9/0.71mg, 5.7mg/1.4mg, 8mg/2mg, 8.6mg/2.1mg, 11.4mg/2.9mg</p> <p>Buccal film: buprenorphine/naloxone 2.1mg/0.3mg, 4.2mg/0.7mg, 6.3mg/1mg</p>	CIII	Used for detoxification and maintenance of abstinence for individuals aged 16 or older.

Buprenorphine Hydrochloride	Opioid use disorder	<p>Sublingual tablet: 2mg, 4mg, 8mg, and 12mg</p> <p>Probuphine® implants 80mgx4 implants for a total of 320mg</p>	CIII	<p>This formulation is indicated for treatment of opioid dependence and is preferred for induction. However, it is considered the preferred formulation for pregnant patients, patients with hepatic impairment, and patients with sensitivity to naloxone. It is also used for initiating treatment in patients transferring from methadone, in preference to products containing naloxone, because of the risk of precipitating withdrawal in these patients. For those already stable on low to moderate dose buprenorphine. The administration of the implant dosage form requires specific training and must be surgically.</p>
Methadone	Opioid use disorder	<p>Tablet: 5mg, 10mg</p> <p>Tablet for suspension: 40mg</p> <p>Oral concentrate: 10mg/mL</p> <p>Oral solution: 5mg/5mL, 10mg/5mL</p> <p>Injection: 10mg/mL</p>	CII	<p>Providers using this medication must be linked to a federally certified Opioid Treatment Program. Under federal regulations, it can be used in persons under age 18 at the discretion of an Opioid Treatment Program physician.</p>

Naltrexone	Opioid use disorder; alcohol use disorder	Tablets: 25mg, 50mg, and 100mg Extended-release injectable suspension: 380mg/vial	Not scheduled under the Controlled Substances Act	Provided by prescription; naltrexone blocks opioid receptors, reduces cravings, and diminishes the rewarding effects of alcohol and opioids. Extended-release injectable naltrexone is recommended to prevent relapse to opioids or alcohol. The prescriber need not be a physician, but must be licensed and authorized to prescribe by the state.
Acamprosate	Alcohol use disorder	Delayed-release tablet: 333mg	Not scheduled under the Controlled Substances Act	Provided by prescription; acamprosate is used in the maintenance of alcohol abstinence. The prescriber need not be a physician, but must be licensed and authorized to prescribe by the state.
Disulfiram	Alcohol use disorder	Tablet: 250mg, 500mg	Not scheduled under the Controlled Substances Act	When taken in combination with alcohol, disulfiram causes severe physical reactions, including nausea, flushing, and heart palpitations. The knowledge that such a reaction is likely if alcohol is consumed acts as a deterrent to drinking.

Nicotine Replacement Therapies	Nicotine use disorder	Transdermal patches: 7-22 mg/day Gum: 18-48 mg/day Lozenges: 40-80 mg/day Inhalers: Variable dosing Nasal spray: Up to 40 mg/day	Not scheduled under the Controlled Substances Act	Nicotine replacement therapy helps alleviate withdrawal symptoms in the short term, and patients with severe nicotine use disorder might benefit from more long-term use.
Bupropion HCl	Nicotine use disorder	Tablet: 150 mg/day for three days, then increase to 300 mg/day for 7-12 weeks	Not scheduled under the Controlled Substances Act	Bupropion HCl is an antidepressant that has also been shown to assist with nicotine cessation, although the mechanism of action is not understood.
Varenicline	Nicotine use disorder	Tablet: 0.5 mg/day for three days; 0.5 mg twice a day for days 4-7; then 1.0 mg twice a day through week 12	Not scheduled under the Controlled Substances Act	Varenicline helps reduce nicotine cravings.

Source: The [Surgeon General's report](#) and National Cancer Institute, [Cigarette Smoking: Health Risks and How to Quit](#)

Behavioral Therapies

Behavioral treatment (alone or in combination with medications) is a cornerstone to successful long-term outcomes for many individuals with drug use disorders or other mental illnesses.^{3,81–83,85} Several strategies have shown promise for treating specific comorbid conditions.

- **Cognitive Behavioral Therapy (CBT)**

CBT is designed to modify harmful beliefs and maladaptive behaviors and shows strong efficacy for individuals with substance use disorders. CBT is the most effective psychotherapy for children and adolescents with anxiety and mood disorders.^{22,24,88}

- **Dialectical Behavior Therapy (DBT)**

DBT is designed specifically to reduce self-harm behaviors including suicidal attempts, thoughts, or urges; cutting; and drug use. It is one of the few treatments effective for individuals who meet the criteria for borderline personality disorder.⁹²

■ ***Assertive Community Treatment (ACT)***

ACT programs integrate behavioral treatments for severe mental illnesses such as schizophrenia and co-occurring substance use disorders. ACT is differentiated from other approaches to case management through factors such as a smaller caseload size, team management, outreach emphasis, a highly individualized approach, and an assertive approach to maintaining contact with patients.⁹³

■ ***Therapeutic Communities (TCs)***

TCs are a common form of long-term residential treatment for substance use disorders. They focus on the “resocialization” of the individual, often using broad-based community programs as active components of treatment. TCs are appropriate for populations with a high prevalence of co-occurring disorders such as criminal justice-involved persons, individuals with vocational deficits, vulnerable or neglected youth, and homeless individuals.⁸⁶ In addition, some evidence suggests that TCs may be helpful for adolescents who have received treatment for substance use and addiction.⁹⁴

■ ***Contingency Management (CM) or Motivational Incentives (MI)***

CM/MI is used as an adjunct to treatment. Voucher or prize-based systems reward patients who practice healthy behaviors and reduce unhealthy behaviors, including smoking and drug use. Incentive-based treatments are effective for improving treatment compliance and reducing tobacco and other drug use, and can be integrated into behavioral health treatment programs for people with co-occurring disorders.⁹⁵

■ ***Exposure Therapy***

Exposure therapy is a behavioral treatment for some anxiety disorders (phobias and PTSD) that involves repeated exposure to a feared situation, object, traumatic event, or memory. This exposure can be real, visualized, or simulated, and is always contained in a controlled therapeutic environment. The goal is to desensitize patients to the triggering stimuli and help them develop coping mechanisms, eventually reducing or even eliminating symptoms. Several studies suggest that exposure therapy may be helpful for individuals with comorbid PTSD and cocaine use disorder, although retention in treatment is a challenge.⁵⁷

■ ***Integrated Group Therapy (IGT)***

IGT is a treatment developed specifically for patients with bipolar disorder and substance use disorder, designed to address both problems simultaneously.⁹⁶ This therapy is largely based on CBT principles and is usually an adjunct to medication. The IGT approach emphasizes helping

patients understand the relationship between the two disorders, as well as the link between thoughts and behaviors, and how they contribute to recovery and relapse.⁹⁶

- **Seeking Safety (SS)**

Seeking Safety is a present-focused therapy aimed at treating trauma-related problems (including PTSD) and substance use disorder simultaneously. Patients learn behavioral skills for coping with trauma/post-traumatic stress disorder and substance use disorder.⁹⁷

- **Mobile Medical Application**

In 2017, the Food and Drug Administration approved the first mobile medical application to help treat substance use disorders. The intention is for patients to use it with outpatient therapy to treat alcohol, cocaine, marijuana, and stimulant use disorders; it is not intended to treat opioid dependence. The device delivers CBT to patients to teach skills that aid in the treatment in substance use disorders and increase retention in outpatient therapy programs.⁹⁸

Part 2: Co-occurring Substance Use Disorder and Physical Comorbidities

People with substance use disorders also often experience comorbid chronic physical health conditions, including chronic pain,⁹⁹ cancer, and heart disease.¹⁰⁰ The use of various substances—including alcohol, heroin, prescription stimulants, methamphetamine, and cocaine—is independently associated with increased risk for cardiovascular and heart disease.¹⁰⁰

Chronic Pain

Chronic pain is a physical problem that has a complex relationship with substance use disorders, particularly opioid misuse and addiction.⁹⁹ An estimated 10 percent of chronic pain patients misuse prescription opioids.⁹⁹ Chronic pain and associated emotional distress are thought to dysregulate the brain's stress and reward circuitry, increasing the risk for opioid use disorder.⁹⁹ Opioid misuse and addiction are serious public health problems that led to more than 42,000 deaths in 2016 alone.¹⁰¹ High rates of opioid misuse and addiction among patients with chronic pain highlight the need for careful pre-treatment screening and education as well as ongoing monitoring for safety and effectiveness when opioid medications are used to treat pain.^{102,103}

Tobacco Use

One of the largest drivers of physical health comorbidities is cigarette smoking. It is linked to many major health conditions and remains the leading preventable cause of premature disease and death in the United States.¹⁰⁴ For example, the majority of lung cancer and approximately one-third of all cancer deaths are attributable to smoking.¹⁰⁴ Smoking is known to contribute to age-related macular degeneration, diabetes, colorectal cancer, liver cancer, adverse health outcomes in cancer patients and survivors, tuberculosis, erectile dysfunction, rheumatoid arthritis, inflammation, and impaired immune function.¹⁰⁴ Smoking is also an important comorbidity among people with other drug use disorders and contributes to their physical health problems. An estimated 77–93 percent of people in treatment for substance use disorders use tobacco.¹⁰⁰

Mental Illness

Physical illnesses not only affect the body and daily functioning, but they can also increase the risk for mental illnesses such as depression¹⁰⁵ and anxiety.¹⁰⁶ Depression has a negative impact on individuals with chronic physical conditions, reducing a person's quality of life and ability to manage their health.^{105,106} Comorbid mental illnesses are associated with greater functional impairments and mortality rates related to physical illnesses.¹⁰⁵ Older people with chronic physical illnesses or impairments may feel isolated and increase substance use.¹⁰⁰ Furthermore, as discussed in Part 1, mental illness may lead to substance use disorders and vice versa, thus, SUDs may play a role in linking mental illness and physical health.

Treatment Adherence

In addition to the direct effects, substance use disorders can have an indirect negative impact on the management of medical conditions. For example, people with substance use disorders are less likely to adhere with their treatment plans or to take medication regularly,^{107,108} which worsens the course of their illnesses. In addition, substance use can diminish the effectiveness of medications for physical conditions.^{100,109}

Infectious Disease Transmission

Substance use also increases the risk of infectious disease transmission, including HIV¹¹⁰ and the hepatitis C virus (HCV).¹¹¹ This increased risk is related to injection drug use and increased risky

sexual behaviors associated with drug use.^{110,111} For more information about the connection between substance use and HIV please go to Part 3 ("[The Connection between Substance Use Disorders and HIV](#)").

Implications for Health Care Delivery

Comorbid chronic physical and behavioral health conditions (mental and substance use disorders) are associated with greater functional impairment and increased health care costs. As with comorbid mental illness, integrated care is critical for addressing physical health comorbidities.¹¹² As discussed in Part 4 ("[Barriers to Comprehensive Treatment for Individuals with Co-Occurring Disorders](#)"), recent delivery system innovation models provide incentives to shift health care towards integrated care models. Integrated care offers greater opportunities for primary care providers, physician specialists, and behavioral health specialists to work together to reduce the impact of mental and physical health comorbidities on substance use disorder, and vice versa, to improve overall health outcomes.¹¹³

Part 3: The Connection between Substance Use Disorders and HIV

More than 1.2 million people in the United States are living with human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS).¹¹⁴ HIV is transmitted through contact with infected blood and bodily fluids. Such contact can occur through unprotected sex, through sharing needles or other drug injection equipment, through mother-to-child transmission during pregnancy or breastfeeding, and through infected blood transfusions and plasma products. While effective antiretroviral therapy (ART) is available, there is currently no cure for HIV/AIDS.^{115,116} However, the provision of ART reduces viral load—ultimately decreasing HIV transmission in the larger community.¹¹⁷

This national public health issue and the ongoing global HIV/AIDS pandemic are exacerbated by substance use, which serves as a powerful cofactor at every stage, including transmission, diagnosis, illness trajectories, and treatment. Since the beginning of the epidemic in the 1980s, drug use and HIV have been inextricably linked. Today, illicit drug use is an important driver of HIV across the globe.¹¹⁸

Intravenous drug use in particular continues to be a risk factor for transmission of the virus,^{118,119}

accounting for approximately 6 percent of HIV diagnoses in 2015.¹²⁰

In addition, drug use plays a more general role in the spread of HIV by increasing the likelihood of high-risk sex with infected partners.¹¹⁹ The intoxicating effects of many drugs can alter judgment and inhibition, and lead people to engage in impulsive and unsafe behaviors. Additionally, people who are addicted to drugs may engage in risky sexual behaviors to obtain drugs or money to buy them.¹¹⁹

Drug use and addiction can also hasten the progression of HIV and its consequences, especially in the brain. Clinical research indicates that drug use and addiction may increase viral load, accelerate disease progression, and worsen AIDS-related mortality even among patients who follow ART regimens.¹²¹ In addition, people with substance use disorders are less likely to take life-saving HIV medication regularly,¹⁰⁷ which worsens the course of their illness.

Although it is unclear whether HIV infection contributes to drug use and addiction in human patients,¹²¹ animal studies suggest that both types of brain cells—neurons and glia—can be infected by HIV, causing neurobiological disruptions to brain circuits that are effected by drug use and addiction.¹²²

Drugs can make it easier for HIV to enter the brain and trigger an immune response and the release of neurotoxins, which can cause chronic neuroinflammation.¹²³ HIV-induced inflammation in the brain underlies the neurocognitive disorders, also called NeuroHIV, that are a complication of HIV infection.¹²⁴

Around 50 percent of individuals with HIV and AIDS suffer from HIV-related neurocognitive disorders.¹²⁵ NeuroHIV is challenging to diagnose and treat, since other factors—such as aging, drug use, addiction, and psychiatric illnesses—are common and can produce similar cognitive symptoms.¹²⁶

There is an ongoing need for new therapeutic approaches to the neurological complications of HIV, as clinical trials of neuroprotective or anti-inflammatory medications have been unsuccessful.¹²⁶

Because people with HIV are living longer due to effective treatments, the influence of the virus on the aging brain and neurocognition is a growing concern. Around half of all HIV-infected persons are 50 years old or over.¹²⁷ Neuroimaging research conducted prior to effective treatment or on untreated individuals suggests that HIV accelerates aging of the brain. Comorbid substance use disorder may exacerbate neurological aging among people with HIV.¹²⁷

Testing for and treating HIV in criminal justice settings benefits both the health of inmates and overall public health. People with HIV infection are overrepresented in prisons; in 2010, there were 20,093

inmates with HIV/AIDS in state and federal prisons.¹²⁸ Most incarcerated individuals with HIV acquired it in the community prior to incarceration.¹²⁹ Individuals with HIV often begin treatment while incarcerated, but they experience a disruption of care when they return to the community, in addition to facing challenges coping with substance use and mental health problems.¹³⁰ Therefore it is particularly important to link people who have HIV and a history of substance use to community HIV services, substance abuse treatment, mental health services, and other wrap around services in their community to reduce recidivism, improve their health, reduce the spread of the infection to others, and prevent relapse to substance abuse.¹²⁹⁻¹³¹

Why is HIV screening important?

The risk of HIV transmission is lower when people who are infected with HIV receive ART to suppress their viral load. Despite CDC's recommendations and efforts to increase HIV testing.¹³² One survey found that only about 19 percent of people aged 15 to 44 were tested for HIV during the past year.¹³³ This means that people who may have HIV are unaware of their status and, thus, are not receiving ART, which increases the transmission rate nation-wide.

Because HIV, drug use, and addiction are inextricably linked, one strategy for reducing incidence is to implement HIV testing at SUD treatment facilities.¹³⁴ An analysis of nationally representative data from privately funded SUD treatment programs found that most programs provided education and prevention services. While the proportion of programs offering on-site HIV testing and the percentage of patients who received testing increased in recent years,¹³⁴ fewer than one-third of programs offered on-site testing. In those programs, fewer than one-third of patients received testing.¹³⁴

NIDA is collaborating with the Substance Abuse and Mental Health Services Administration (SAMHSA) and others to expand rapid HIV testing to drug treatment facilities to better identify HIV infections and engage patients more efficiently in comprehensive treatment for both substance use disorder and HIV infection. Many health insurance providers cover HIV testing without a co-pay or deductible.¹³⁵ To find a local HIV testing center visit: <https://www.cdc.gov/hiv/>.

What are some methods for HIV prevention and treatment for individuals with substance use disorders?

Research indicates that SUD treatment,¹³⁶ sterile syringe programs,¹³⁷ community-based outreach, testing, and linkage to comprehensive care for HIV and other infections^{138–140} are the most effective ways to reduce transmission among individuals who use drugs. Because these individuals often face barriers to testing, treatment, and adhering to ART, unique supports are needed for prevention and treatment within this population.¹⁰⁷

Pre-exposure prophylaxis (PrEP)

PrEP is an important component of HIV prevention. In this approach, people who are at significant risk but not infected with HIV take a daily oral dose of medication to prevent them from contracting the virus.¹⁴¹ The World Health Organization recommends PrEP as one component of prevention for individuals at high risk for HIV.¹⁴² As with all medications, adherence is critical to effectiveness.^{143,144} There have been some promising results of PrEP among people who inject drugs, with one clinical trial finding that it decreased the risk of HIV infection by as much as 84 percent for those who were highly adherent, but only about 50 percent overall.¹⁴⁵ More research is needed on optimizing PrEP adherence and the best ways to integrate it into SUD treatment.¹⁴⁶ Despite research indicating that PrEP is generally safe and effective for those who are at significant risk of HIV infection,¹⁰⁷ strategies to increase access to PrEP among injection drug users should be explored.^{143,144}

The Seek, Test, Treat, and Retain (STTR) Model of Care

People continue to be infected by HIV through unsafe contact with others who are either unaware that they have the virus or have inadequately suppressed their viral load.¹⁴⁸ The STTR model of care is specifically designed to address these two drivers of new HIV infections, particularly considering the well-documented delays in testing and treatment experienced by individuals with substance use disorders.¹⁴⁹ This approach involves reaching out to high-risk, hard-to-reach drug-using populations who have not recently been tested for HIV (seeking); engaging them in HIV testing (testing); initiating, monitoring, and maintaining ART for those testing positive (treating); and retaining patients in care (retaining).

Incorporating rapid on-site HIV testing into SUD treatment is an important component of efforts to

identify those who are infected, initiate care earlier, and reduce transmission.¹⁵⁰ However, treatment programs may not have sufficient resources to provide HIV testing. Reducing barriers by providing start-up costs and staff training on how to support individuals who test positive, and addressing staffing needs are crucial to establishing and maintaining rapid on-site HIV testing in SUD treatment facilities.¹⁵⁰ Researchers estimate that testing people who inject drugs for HIV every 6 months is cost effective, compared with annual testing, at \$133,200 in incremental costs per quality-adjusted life year gained.¹⁵¹

ART has improved the survival of people with HIV, including those who inject drugs, so that they now tend to live as long as those who are not infected with the virus.¹⁵² Most patients, regardless of injection drug use history, can achieve viral suppression with ART,¹⁵³ which can significantly reduce transmission of HIV to others.¹³⁸ This approach, called Treatment as Prevention, is a crucial part of efforts to reduce the spread of the virus and a key component of the STTR strategy. The Treatment as Prevention approach relies on identifying undiagnosed individuals, linking them to treatment with ART, and retaining them in care.¹³⁸ Retention in treatment is key to achieving full viral suppression (i.e., virus is below detectable levels) and preventing transmission of HIV. CDC estimates that 49 percent of people with HIV in the United States had full viral suppression in 2014.¹⁵⁴ Data from 2011 showed that among people whose viral load was not suppressed, 20 percent had never been diagnosed with HIV, 66 percent were diagnosed but not engaged in medical care for HIV, 4 percent were engaged in HIV medical care but not prescribed ART, and 10 percent were prescribed ART but had not achieved viral suppression.¹⁵⁵

Substance Use Disorder Treatment

Studies find that behavioral treatments such as cognitive behavioral therapy and motivational interviewing not only reduce drug use but also improve adherence to ART regimens¹⁵⁶ and medications for HCV.¹⁵⁷ Among men who have sex with men (MSM), SUD treatment is associated with reduced drug use and risky sexual behavior, and those with HIV report improvements in viral load.¹⁵⁸ Addiction pharmacotherapies also reduce the risk for HIV. Pooled results from multiple studies indicate that methadone or buprenorphine treatment for opioid use disorder is associated with a 54 percent reduction in risk of HIV infection among people who inject drugs.¹³⁶ HIV-infected people who inject drugs are more likely to initiate ART when engaged in methadone treatment.¹⁵⁹ Because people who inject drugs also have a relatively high prevalence of mental illness, research suggests that fully integrated addiction, psychiatric, and HIV care might increase the likelihood of ART

adherence and improve health outcomes.^{160,161}

How can we achieve an AIDS-free generation?

Although more research is needed, the scientific and medical communities continue to develop and disseminate effective HIV prevention and treatment approaches. Three key principles underlie NIDA's strategy: (1) substance use disorder and HIV are linked in ways that extend beyond injection drug use; (2) substance use disorder and HIV remain intertwined epidemics in the United States and around the world—therefore, SUD treatment *is* HIV prevention; and (3) the STTR approach, especially when implemented in high-risk populations or settings, can decrease viral load and HIV incidence at a population level, improving outcomes for all. Implementing these evidence-based strategies will bring the United States closer to the goal of an "AIDS-free generation."

Part 4: Barriers to Comprehensive Treatment for Individuals with Co-Occurring Disorders

Although evidence indicates the need for comprehensive and integrated therapy to address comorbidity,^{3,22,82,83} research shows that only about 18 percent of SUD treatment programs and 9 percent of mental health treatment organizations have the capacity to serve dually diagnosed patients.¹⁶²

Provision of such treatment can be problematic for several reasons:

- In the United States, SUD treatment is often siloed from the general health care system.^{23,163} Primary care physicians are most often the front line of treatment for mental disorders. The specialty mental health treatment system typically addresses only severe mental illness, while drug treatment is typically provided by a separate SUD treatment system. Typically, none of these systems have sufficiently broad expertise to address the full range of problems presented by dually diagnosed patients.
- A lingering bias remains in some SUD treatment centers against using any medications, including those necessary to treat serious mental illnesses including depression, although this is slowly changing.¹⁶⁴ Additionally, many SUD treatment programs do not employ clinicians who can prescribe, dispense, and monitor medications.¹⁶²

- Many individuals who would benefit from treatment are in the criminal justice system. It is estimated that about 45 percent of individuals in state and local prisons and jails have a mental health problem comorbid with substance use or addiction.¹⁶⁵ However, adequate treatment services for both drug use disorders and other mental illnesses are often not available within these settings. Treatment of comorbid disorders can reduce not only medical comorbidities, but also negative social outcomes by mitigating against a return to criminal behavior and re-incarceration.¹⁶⁶

While these barriers loom large, changes to the U.S. health care system can help improve care for people with comorbidities.¹⁶⁷ The Mental Health Parity and Addiction Equity Act of 2008 (also known as the Parity Act) and the Patient Protection and Affordable Care Act of 2010 (also known as the Affordable Care Act or ACA) have increased the number of people with insurance that covers addiction and mental health treatment. The Parity Act mandates that health care plans that cover behavioral health treatments do so to the same extent as treatments for physical health conditions.¹⁶⁸ The ACA requires that addiction and mental health treatment be covered as [one of the ten Essential Benefit categories](#). With healthcare reform's other provisions to increase the quality of care, clinicians now have greater support and incentives to implement evidence-based practices^{23,169} and to collaborate in teams that provide integrated care for physical and mental disorders.^{23,163,168,169}

Where can I get more scientific information on comorbid substance use disorder, mental illness, and medical conditions?

To learn more about substance use disorders and other mental illnesses, or to order materials on these topics free of charge in English or Spanish, visit the NIDA website at www.drugabuse.gov or contact the *DrugPubs* Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

NIDA's website includes:

- Information on drugs of use and misuse and related health consequences
- NIDA publications, news, and events

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

NIDA websites and webpages

- [Comorbidity](#)
- [Comorbidity: Substance Use Disorders and Other Mental Illnesses DrugFacts](#)
- teens.drugabuse.gov
- researchstudies.drugabuse.gov
- irp.drugabuse.gov

For physician information

- NIDAMED: drugabuse.gov/nidamed

Other websites

Information on mental illnesses, substance use, and substance use disorder is also available through these other websites:

- [National Institute of Mental Health \(NIMH\)](#)
 - [Substance Use and Mental Health](#)
 - [HIV/AIDS and Mental Health](#)
- [National Institute on Alcohol Abuse and Alcoholism \(NIAAA\)](#)
 - [Other Psychiatric Disorders](#)

- [Other Substance Abuse](#)
- [Substance Abuse and Mental Health Services Administration \(SAMHSA\)](#)
 - [Common Comorbidities](#)
 - [Co-occurring Disorders](#)
 - [Publications and Resources](#)
- [Centers for Disease Control and Prevention—Coping With a Disaster or Traumatic Event \(CDC\)](#)
 - [HIV/AIDS](#)
- [HIV.gov](#)
- [Office of HIV/AIDS and Infectious Disease Policy \(OHAIDP\)](#)

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