National Institute on Drug Abuse
Advancing Addiction Science

Research Report
Revised April 2020

Common Comorbidities with Substance Use Disorders Research Report

Table of Contents

Common Comorbidities with Substance Use Disorders Research Report

Introduction

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

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

What are some approaches to diagnosis?

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

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

Part 3: The Connection between Substance Use Disorders and HIV

Why is HIV screening important?

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

How can we achieve an AIDS-free generation?

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

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

References

Common Comorbidities with Substance Use Disorders Research Report

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

Introduction

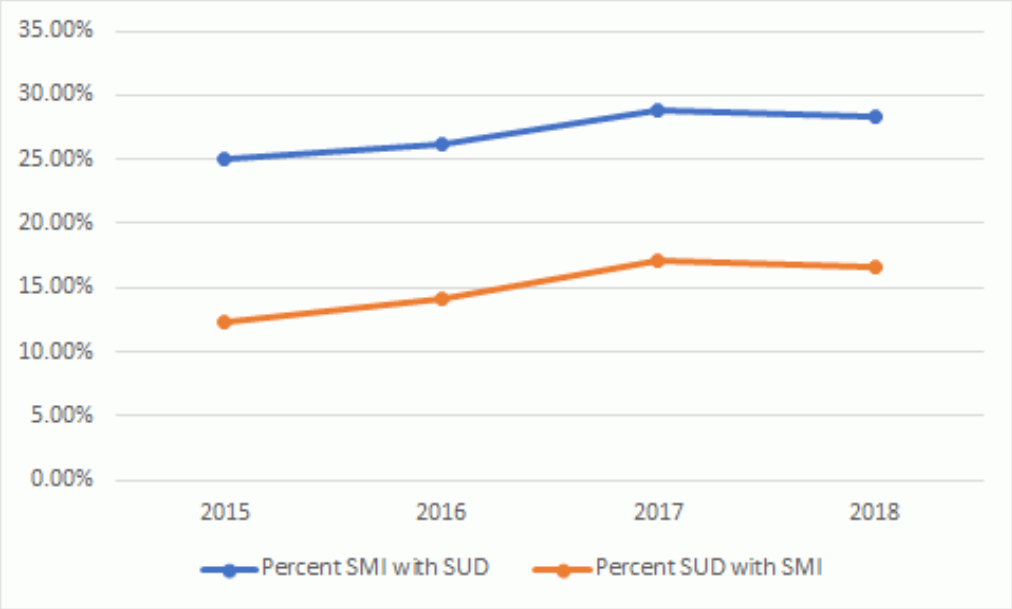
When two disorders or illnesses occur in the same person, simultaneously or sequentially, they are described as comorbid.[1] Comorbidity also implies that the illnesses interact, affecting the course and prognosis of both.[1,2] This research report provides information on the state of the science in 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 stress[38] 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 illnesses[42] 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	-
Source: NSDUH 2014.						

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 adherence[84] 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	Sublingual or buccal film buprenorphine/naloxone 2mg/0.5mg, 4mg/1mg, 8mg/2mg, and 12mg/3mg 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 Buccal film: buprenorphine/naloxone 2.1mg/0.3mg, 4.2mg/0.7mg, 6.3mg/1mg	CIII	Used for detoxification and maintenance of abstinence for individuals aged 16 or older.

Buprenorphine Hydrochloride	Opioid use disorder	Sublingual tablet: 2mg, 4mg, 8mg, and 12mg Probuphine® implants 80mgx4 implants for a total of 320mg	CIII	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.
Methadone	Opioid use disorder	Tablet: 5mg, 10mg Tablet for suspension: 40mg Oral concentrate: 10mg/mL Oral solution: 5mg/5mL, 10mg/5mL Injection: 10mg/mL	CII	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.

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 depression[105] 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 HIV[110] 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[133] found that only about 19 percent of people aged 15 to 44 were tested for HIV during the past year. 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.[143,14]

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 regimens[156] 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?

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
- researchstudies.drugabuse.gov
- irp.drugabuse.gov

For physician information

- NIDAMED: nida.nih.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-occuring 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)

References

1. Santucci K. Psychiatric disease and drug abuse. *Curr Opin Pediatr*. 2012;24(2):233-237. doi:10.1097/MOP.0b013e3283504fbf.
2. Ross S, Peselow E. Co-occurring psychotic and addictive disorders: neurobiology and diagnosis. *Clin Neuropharmacol*. 2012;35(5):235-243. doi:10.1097/WNF.0b013e318261e193.
3. Kelly TM, Daley DC. Integrated Treatment of Substance Use and Psychiatric Disorders. *Soc Work Public Health*. 2013;28(0):388-406. doi:10.1080/19371918.2013.774673.
4. Hser YI, Grella CE, Hubbard RL, et al. An evaluation of drug treatments for adolescents in 4 US cities. *Arch Gen Psychiatry*. 2001;58(7):689-695.
5. Magidson JF, Liu S-M, Lejuez CW, Blanco C. Comparison of the Course of Substance Use Disorders among Individuals With and Without Generalized Anxiety Disorder in a Nationally Representative Sample. *J Psychiatr Res*. 2012;46(5):659-666. doi:10.1016/j.jpsychires.2012.02.011.
6. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2006;67(2):247-257.
7. Brady KT, Haynes LF, Hartwell KJ, Killeen TK. Substance use disorders and anxiety: a treatment challenge for social workers. *Soc Work Public Health*. 2013;28(3-4):407-423. doi:10.1080/19371918.2013.774675.
8. Wolitzky-Taylor K, Operskalski JT, Ries R, Craske MG, Roy-Byrne P. Understanding and treating comorbid anxiety disorders in substance users: review and future directions. *J Addict Med*. 2011;5(4):233-247. doi:10.1097/ADM.0b013e31823276d7.
9. Torrens M, Gilchrist G, Domingo-Salvany A, psyCoBarcelona Group. Psychiatric comorbidity in illicit drug users: substance-induced versus independent disorders. *Drug Alcohol Depend*. 2011;113(2-3):147-156. doi:10.1016/j.drugalcdep.2010.07.013.
10. Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2007;64(5):566-576. doi:10.1001/archpsyc.64.5.566.
11. Pettinati HM, O'Brien CP, Dundon WD. Current Status of Co-Occurring Mood and Substance Use Disorders: A New Therapeutic Target. *Am J Psychiatry*. 2013;170(1):23-30. doi:10.1176/appi.ajp.2012.12010112.

12. De Alwis D, Lynskey MT, Reiersen AM, Agrawal A. Attention-deficit/hyperactivity disorder subtypes and substance use and use disorders in NESARC. *Addict Behav*. 2014;39(8):1278-1285. doi:10.1016/j.addbeh.2014.04.003.

13. Harstad E, Levy S, Abuse C on S. Attention-Deficit/Hyperactivity Disorder and Substance Abuse. *Pediatrics*. 2014;134(1):e293-e301. doi:10.1542/peds.2014-0992.

14. Hartz SM, Pato CN, Medeiros H, et al. Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry*. 2014;71(3):248-254. doi:10.1001/jamapsychiatry.2013.3726.

15. Flórez-Salamanca L, Secades-Villa R, Budney AJ, García-Rodríguez O, Wang S, Blanco C. Probability and predictors of cannabis use disorders relapse: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2013;132(0):127-133. doi:10.1016/j.drugalcdep.2013.01.013.

16. Pennay A, Cameron J, Reichert T, et al. A systematic review of interventions for co-occurring substance use disorder and borderline personality disorder. *J Subst Abuse Treat*. 2011;41(4):363-373. doi:10.1016/j.jsat.2011.05.004.

17. Lubman DI, King JA, Castle DJ. Treating comorbid substance use disorders in schizophrenia. *Int Rev Psychiatry Abingdon Engl*. 2010;22(2):191-201. doi:10.3109/09540261003689958.

18. Substance Abuse and Mental Health Services Administration (SAHMSA). Mental and Substance Use Disorders. https://www.samhsa.gov/disorders. Published June 20, 2014. Accessed February 21, 2018.

19. Katz C, El-Gabalawy R, Keyes KM, Martins SS, Sareen J. Risk factors for incident nonmedical prescription opioid use and abuse and dependence: results from a longitudinal nationally representative sample. *Drug Alcohol Depend*. 2013;132(1-2):107-113. doi:10.1016/j.drugalcdep.2013.01.010.

20. Goldner EM, Lusted A, Roerecke M, Rehm J, Fischer B. Prevalence of Axis-1 psychiatric (with focus on depression and anxiety) disorder and symptomatology among non-medical prescription opioid users in substance use treatment: systematic review and meta-analyses. *Addict Behav*. 2014;39(3):520-531. doi:10.1016/j.addbeh.2013.11.022.

21. Sheidow AJ, McCart M, Zajac K, Davis M. Prevalence and impact of substance use among emerging adults with serious mental health conditions. *Psychiatr Rehabil J*. 2012;35(3):235-243. doi:10.2975/35.3.2012.235.243.

22. Bukstein OG, Horner MS. Management of the adolescent with substance use disorders and comorbid psychopathology. *Child Adolesc Psychiatr Clin N Am*. 2010;19(3):609-623. doi:10.1016/j.chc.2010.03.011.

23. Sterling S, Weisner C, Hinman A, Parthasarathy S. Access to Treatment for Adolescents With Substance Use and Co-Occurring Disorders: Challenges and Opportunities. *J Am Acad Child Adolesc Psychiatry*. 2010;49(7):637-726. doi:10.1016/j.jaac.2010.03.019.

24. Winters KC, Tanner-Smith EE, Bresani E, Meyers K. Current advances in the treatment of adolescent drug use. *Adolesc Health Med Ther*. 2014;5:199-210. doi:10.2147/AHMT.S48053.

25. Barkus E, Murray RM. Substance use in adolescence and psychosis: clarifying the relationship. *Annu Rev Clin Psychol*. 2010;6:365-389. doi:10.1146/annurev.clinpsy.121208.131220.

26. Parakh P, Basu D. Cannabis and psychosis: have we found the missing links? *Asian J Psychiatry*. 2013;6(4):281-287. doi:10.1016/j.ajp.2013.03.012.

27. Pelayo-Terán JM, Suárez-Pinilla P, Chadi N, Crespo-Facorro B. Gene-environment interactions underlying the effect of cannabis in first episode psychosis. *Curr Pharm Des*. 2012;18(32):5024-5035.

28. Goldstein BI, Bukstein OG. Comorbid substance use disorders among youth with bipolar disorder: opportunities for early identification and prevention. *J Clin Psychiatry*. 2010;71(3):348-358. doi:10.4088/JCP.09r05222gry.

29. O'Neil KA, Conner BT, Kendall PC. Internalizing disorders and substance use disorders in youth: comorbidity, risk, temporal order, and implications for intervention. *Clin Psychol Rev*. 2011;31(1):104-112. doi:10.1016/j.cpr.2010.08.002.

30. Wilens TE, Martelon M, Joshi G, et al. Does ADHD predict substance-use disorders? A 10-year follow-up study of young adults with ADHD. *J Am Acad Child Adolesc Psychiatry*. 2011;50(6):543-553. doi:10.1016/j.jaac.2011.01.021.

31. Zulauf CA, Sprich SE, Safren SA, Wilens TE. The complicated relationship between attention deficit/hyperactivity disorder and substance use disorders. *Curr Psychiatry Rep*. 2014;16(3):436. doi:10.1007/s11920-013-0436-6.

32. Nelson A, Galon P. Exploring the relationship among ADHD, stimulants, and substance abuse. *J Child Adolesc Psychiatr Nurs Off Publ Assoc Child Adolesc Psychiatr Nurses Inc*. 2012;25(3):113-118. doi:10.1111/j.1744-6171.2012.00322.x.

33. Cerdá M, Sagdeo A, Johnson J, Galea S. Genetic and environmental influences on psychiatric comorbidity: a systematic review. *J Affect Disord*. 2010;126(1-2):14-38. doi:10.1016/j.jad.2009.11.006.

34. Tsuang MT, Francis T, Minor K, Thomas A, Stone WS. Genetics of smoking and depression. *Hum Genet*. 2012;131(6):905-915. doi:10.1007/s00439-012-1170-6.

35. Nestler EJ. Epigenetic mechanisms of drug addiction. *Neuropharmacology*. 2014;76 Pt B:259-268. doi:10.1016/j.neuropharm.2013.04.004.

36. Fontenelle LF, Oostermeijer S, Harrison BJ, Pantelis C, Yücel M. Obsessive-compulsive disorder, impulse control disorders and drug addiction: common features and potential treatments. *Drugs*. 2011;71(7):827-840. doi:10.2165/11591790-000000000-00000.

37. Wang J-C, Kapoor M, Goate AM. The genetics of substance dependence. *Annu Rev Genomics Hum Genet*. 2012;13:241-261. doi:10.1146/annurev-genom-090711-163844.

38. Enoch M-A. The influence of gene-environment interactions on the development of alcoholism and drug dependence. *Curr Psychiatry Rep*. 2012;14(2):150-158. doi:10.1007/s11920-011-0252-9.

39. Hartz SM, Bierut LJ. Genetics of addictions. *Psychiatr Clin North Am*. 2010;33(1):107-124. doi:10.1016/j.psc.2009.10.003.

40. Mahgoub M, Monteggia LM. Epigenetics and psychiatry. *Neurother J Am Soc Exp Neurother*. 2013;10(4):734-741. doi:10.1007/s13311-013-0213-6.

41. Guintivano J, Kaminsky ZA. Role of epigenetic factors in the development of mental illness throughout life. *Neurosci Res*. 2016;102:56-66. doi:10.1016/j.neures.2014.08.003.

42. Peña CJ, Bagot RC, Labonté B, Nestler EJ. Epigenetic signaling in psychiatric disorders. *J Mol Biol* . 2014;426(20):3389-3412. doi:10.1016/j.jmb.2014.03.016.

43. Wing VC, Wass CE, Soh DW, George TP. A review of neurobiological vulnerability factors and treatment implications for comorbid tobacco dependence in schizophrenia. *Ann N Y Acad Sci*. 2012;1248:89-106. doi:10.1111/j.1749-6632.2011.06261.x.

44. Howes OD, Fusar-Poli P, Bloomfield M, Selvaraj S, McGuire P. From the prodrome to chronic schizophrenia: the neurobiology underlying psychotic symptoms and cognitive impairments. *Curr Pharm Des*. 2012;18(4):459-465.

45. Volkow ND, Fowler JS, Wang G-J, Swanson JM, Telang F. Dopamine in Drug Abuse and Addiction: Results of Imaging Studies and Treatment Implications. *Arch Neurol*. 2007;64(11):1575-1579. doi:10.1001/archneur.64.11.1575.

46. Xing B, Li Y-C, Gao W-J. Norepinephrine versus Dopamine and their Interaction in Modulating Synaptic Function in the Prefrontal Cortex. *Brain Res*. 2016;1641(Pt B):217-233. doi:10.1016/j.brainres.2016.01.005.

47. Marazziti D. Understanding the role of serotonin in psychiatric diseases. *F1000Research*. 2017;6. doi:10.12688/f1000research.10094.1.

48. Müller CP, Homberg JR. The role of serotonin in drug use and addiction. *Behav Brain Res*. 2015;277:146-192. doi:10.1016/j.bbr.2014.04.007.

49. Tsapakis EM, Travis MJ. Glutamate and psychiatric disorders. *Adv Psychiatr Treat*. 2002;8(3):189-197. doi:10.1192/apt.8.3.189.

50. Tzschentke TM, Schmidt WJ. Glutamatergic mechanisms in addiction. *Mol Psychiatry*. 2003;8(4):373-382. doi:10.1038/sj.mp.4001269.

51. Kumar K, Sharma S, Kumar P, Deshmukh R. Therapeutic potential of GABAB receptor ligands in drug addiction, anxiety, depression and other CNS disorders. *Pharmacol Biochem Behav*. 2013;110:174-184. doi:10.1016/j.pbb.2013.07.003.

52. Aston-Jones G, Kalivas PW. Brain norepinephrine rediscovered in addiction research. *Biol Psychiatry*. 2008;63(11):1005-1006. doi:10.1016/j.biopsych.2008.03.016.

53. Langer SZ. ?2-Adrenoceptors in the treatment of major neuropsychiatric disorders. *Trends Pharmacol Sci*. 2015;36(4):196-202. doi:10.1016/j.tips.2015.02.006.

54. Norman SB, Myers US, Wilkins KC, et al. Review of biological mechanisms and pharmacological treatments of comorbid PTSD and substance use disorder. *Neuropharmacology*. 2012;62(2):542-551. doi:10.1016/j.neuropharm.2011.04.032.

55. Sinha R. Chronic Stress, Drug Use, and Vulnerability to Addiction. *Ann N Y Acad Sci*. 2008;1141:105-130. doi:10.1196/annals.1441.030.

56. Brewer JA, Bowen S, Smith JT, Marlatt GA, Potenza MN. Mindfulness-Based Treatments for Co-Occurring Depression and Substance Use Disorders: What Can We Learn from the Brain? *Addict Abingdon Engl*. 2010;105(10):1698-1706. doi:10.1111/j.1360-0443.2009.02890.x.

57. Berenz EC, Coffey SF. Treatment of Co-occurring Posttraumatic Stress Disorder and Substance Use Disorders. *Curr Psychiatry Rep*. 2012;14(5):469-477. doi:10.1007/s11920-012-0300-0.

58. Boden MT, Kimerling R, Kulkarni M, Bonn-Miller MO, Weaver C, Trafton J. Coping among military veterans with PTSD in substance use disorder treatment. *J Subst Abuse Treat*. 2014;47(2):160-167. doi:10.1016/j.jsat.2014.03.006.

59. Golub A, Vazan P, Bennett AS, Liberty HJ. Unmet need for treatment of substance use disorders and serious psychological distress among veterans: a nationwide analysis using the NSDUH. *Mil Med*. 2013;178(1):107-114.

60. Wisco BE, Marx BP, Wolf EJ, Miller MW, Southwick SM, Pietrzak RH. Posttraumatic stress disorder in the US veteran population: results from the National Health and Resilience in Veterans Study. *J Clin Psychiatry*. 2014;75(12):1338-1346. doi:10.4088/JCP.14m09328.

61. VA Health Care, National Center for PTSD. *Understanding PTSD and Substance Abuse*. National Center for Posttraumatic Stress Disorder; 2011.

62. Baigent M. Managing patients with dual diagnosis in psychiatric practice. *Curr Opin Psychiatry*. 2012;25(3):201-205. doi:10.1097/YCO.0b013e3283523d3d.

63. Post RM, Kalivas P. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. *Br J Psychiatry J Ment Sci*. 2013;202(3):172-176. doi:10.1192/bjp.bp.112.116855.

64. Pérez de Los Cobos J, Siñol N, Puerta C, Cantillano V, López Zurita C, Trujols J. Features and prevalence of patients with probable adult attention deficit hyperactivity disorder who request treatment for cocaine use disorders. *Psychiatry Res*. 2011;185(1-2):205-210. doi:10.1016/j.psychres.2009.03.019.

65. Berlin I, Hu M-C, Covey LS, Winhusen T. Attention-deficit/hyperactivity disorder (ADHD) symptoms, craving to smoke, and tobacco withdrawal symptoms in adult smokers with ADHD. *Drug Alcohol Depend*. 2012;124(3):268-273. doi:10.1016/j.drugalcdep.2012.01.019.

66. Seitz A, Wapp M, Burren Y, Stutz S, Schläfli K, Moggi F. Association between craving and attention deficit/hyperactivity disorder symptoms among patients with alcohol use disorders. *Am J Addict*. 2013;22(3):292-296. doi:10.1111/j.1521-0391.2012.12000.x.

67. Aubin H-J, Rollema H, Svensson TH, Winterer G. Smoking, quitting, and psychiatric disease: a review. *Neurosci Biobehav Rev*. 2012;36(1):271-284. doi:10.1016/j.neubiorev.2011.06.007.

68. Minichino A, Bersani FS, Calò WK, et al. Smoking behaviour and mental health disorders--mutual influences and implications for therapy. *Int J Environ Res Public Health*. 2013;10(10):4790-4811. doi:10.3390/ijerph10104790.

69. Center for Behavioral Health Statistics and Quality. *Results from the 2016 National Survey on Drug Use and Health: Detailed Tables*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2017.

70. Winterer G. Why do patients with schizophrenia smoke? *Curr Opin Psychiatry*. 2010;23(2):112-119. doi:10.1097/YCO.0b013e3283366643.

71. Donald S, Chartrand H, Bolton JM. The relationship between nicotine cessation and mental disorders in a nationally representative sample. *J Psychiatr Res*. 2013;47(11):1673-1679. doi:10.1016/j.jpsychires.2013.05.011.

72. Mackowick KM, Lynch M-J, Weinberger AH, George TP. Treatment of tobacco dependence in people with mental health and addictive disorders. *Curr Psychiatry Rep*. 2012;14(5):478-485.

doi:10.1007/s11920-012-0299-2.

73. Moran LV, Sampath H, Kochunov P, Hong LE. Brain circuits that link schizophrenia to high risk of cigarette smoking. *Schizophr Bull*. 2013;39(6):1373-1381. doi:10.1093/schbul/sbs149.

74. Murthy P, Chand P. Treatment of dual diagnosis disorders. *Curr Opin Psychiatry*. 2012;25(3):194-200. doi:10.1097/YCO.0b013e328351a3e0.

75. Dineley KT, Pandya AA, Yakel JL. Nicotinic ACh receptors as therapeutic targets in CNS disorders. *Trends Pharmacol Sci*. 2015;36(2):96-108. doi:10.1016/j.tips.2014.12.002.

76. Ragg M, Gordon R, Ahmed T, Allan J. The impact of smoking cessation on schizophrenia and major depression. *Australas Psychiatry Bull R Aust N Z Coll Psychiatr*. 2013;21(3):238-245. doi:10.1177/1039856213486213.

77. Tsoi DT, Porwal M, Webster AC. Efficacy and safety of bupropion for smoking cessation and reduction in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry J Ment Sci*. 2010;196(5):346-353. doi:10.1192/bjp.bp.109.066019.

78. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database Syst Rev*. 2013;(2):CD007253. doi:10.1002/14651858.CD007253.pub3.

79. Cerimele JM, Durango A. Does varenicline worsen psychiatric symptoms in patients with schizophrenia or schizoaffective disorder? A review of published studies. *J Clin Psychiatry*. 2012;73(8):e1039-1047. doi:10.4088/JCP.11r07410.

80. Morojele NK, Saban A, Seedat S. Clinical presentations and diagnostic issues in dual diagnosis disorders. *Curr Opin Psychiatry*. 2012;25(3):181-186. doi:10.1097/YCO.0b013e328351a429.

81. Mueser KT, Gingerich S. Treatment of co-occurring psychotic and substance use disorders. *Soc Work Public Health*. 2013;28(3-4):424-439. doi:10.1080/19371918.2013.774676.

82. Torrens M, Rossi PC, Martinez-Riera R, Martinez-Sanvisens D, Bulbena A. Psychiatric co-morbidity and substance use disorders: treatment in parallel systems or in one integrated system? *Subst Use Misuse*. 2012;47(8-9):1005-1014. doi:10.3109/10826084.2012.663296.

83. Kelly TM, Daley DC, Douaihy AB. Treatment of substance abusing patients with comorbid psychiatric disorders. *Addict Behav*. 2012;37(1):11-24. doi:10.1016/j.addbeh.2011.09.010.

84. DeMarce JM, Lash SJ, Stephens RS, Grambow SC, Burden JL. Promoting continuing care adherence among substance abusers with co-occurring psychiatric disorders following residential treatment. *Addict Behav*. 2008;33(9):1104-1112. doi:10.1016/j.addbeh.2008.02.008.

85. Hunt GE, Siegfried N, Morley K, Sitharthan T, Cleary M. Psychosocial Interventions for People With Both Severe Mental Illness and Substance Misuse. *Schizophr Bull*. 2014;40(1):18-20. doi:10.1093/schbul/sbt160.

86. Sacks S, Sacks J. Research on the effectiveness of the modified therapeutic community for persons with co-occurring substance use and mental disorders. *Ther Communities*. 2010;31:176-211.

87. Lee SJ, Crowther E, Keating C, Kulkarni J. What is needed to deliver collaborative care to address comorbidity more effectively for adults with a severe mental illness? *Aust N Z J Psychiatry*. 2013;47(4):333-346. doi:10.1177/0004867412463975.

88. Macgowan MJ, Engle B. Evidence for optimism: behavior therapies and motivational interviewing in adolescent substance abuse treatment. *Child Adolesc Psychiatr Clin N Am*. 2010;19(3):527-545. doi:10.1016/j.chc.2010.03.006.

89. National Research Council (US) and Institute of Medicine (US) Committee on the Prevention of Mental Disorders and Substance Abuse Among Children, Youth, and Young Adults: Research Advances and Promising Interventions. *Preventing Mental, Emotional, and Behavioral Disorders Among Young People: Progress and Possibilities*. (O'Connell ME, Boat T, Warner KE, eds.). Washington (DC): National Academies Press (US); 2009. http://www.ncbi.nlm.nih.gov/books/NBK32775/. Accessed August 22, 2017..

90. Szapocznik J, Zarate M, Duff J, Muir J. Brief strategic family therapy: engaging drug using/problem behavior adolescents and their families in treatment. *Soc Work Public Health*. 2013;28(3-4):206-223. doi:10.1080/19371918.2013.774666.

91. Rowe CL. Multidimensional family therapy: addressing co-occurring substance abuse and other problems among adolescents with comprehensive family-based treatment. *Child Adolesc Psychiatr Clin N Am*. 2010;19(3):563-576. doi:10.1016/j.chc.2010.03.008.

92. Axelrod SR, Perepletchikova F, Holtzman K, Sinha R. Emotion regulation and substance use frequency in women with substance dependence and borderline personality disorder receiving dialectical behavior therapy. *Am J Drug Alcohol Abuse*. 2011;37(1):37-42. doi:10.3109/00952990.2010.535582.

93. Fries HP, Rosen MI. The efficacy of assertive community treatment to treat substance use. *J Am Psychiatr Nurses Assoc*. 2011;17(1):45-50. doi:10.1177/1078390310393509.

94. Jainchill N, Hawke J, Messina M. Post-Treatment Outcomes Among Adjudicated Adolescent Males and Females in Modified Therapeutic Community Treatment. *Subst Use Misuse*. 2005;40(7):975-996. doi:10.1081/JA-200058857.

95. Tidey JW. Using incentives to reduce substance use and other health risk behaviors among people with serious mental illness. *Prev Med*. 2012;55 Suppl:S54-60. doi:10.1016/j.ypmed.2011.11.010.

96. Farren CK, Hill KP, Weiss RD. Bipolar disorder and alcohol use disorder: a review. *Curr Psychiatry Rep*. 2012;14(6):659-666. doi:10.1007/s11920-012-0320-9.

97. Najavits LM, Hien D. Helping vulnerable populations: a comprehensive review of the treatment outcome literature on substance use disorder and PTSD. *J Clin Psychol*. 2013;69(5):433-479. doi:10.1002/jclp.21980.

98. FDA permits marketing of mobile medical application for substance use disorder [FDA News Release]. *Food and Drug Administration (FDA)*. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm576087.htm. Published September 14, 2017. Accessed February 8, 2018.

99. Garland EL, Froeliger B, Zeidan F, Partin K, Howard MO. The Downward Spiral of Chronic Pain, Prescription Opioid Misuse, and Addiction: Cognitive, Affective, and Neuropsychopharmacologic Pathways. *Neurosci Biobehav Rev*. 2013;37(10 0 2):2597-2607. doi:10.1016/j.neubiorev.2013.08.006.

100. Schulte MT, Hser Y-I. Substance Use and Associated Health Conditions throughout the Lifespan. *Public Health Rev*. 2014;35(2).

101. Centers for Disease Control and Prevention (CDC). *Data Brief 294. Drug Overdose Deaths in the United States, 1999–2016*. National Center for Health Statistics https://www.cdc.gov/nchs/data/databriefs/db294_table.pdf#page=4.

102. Berland D, Rodgers P. Rational use of opioids for management of chronic nonterminal pain. *Am Fam Physician*. 2012;86(3):252-258.

103. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician*. 2012;15(3 Suppl):ES67-92.

104. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

105. Kang H-J, Kim S-Y, Bae K-Y, et al. Comorbidity of Depression with Physical Disorders: Research and Clinical Implications. *Chonnam Med J*. 2015;51(1):8-18. doi:10.4068/cmj.2015.51.1.8.

106. DeJean D, Giacomini M, Vanstone M, Brundisini F. Patient experiences of depression and anxiety with chronic disease: a systematic review and qualitative meta-synthesis. *Ont Health Technol*

Assess Ser. 2013;13(16):1-33.

107. Campbell ANC, Tross S, Caslyn DA. Substance Use Disorders and HIV/AIDS Prevention and Treatment Intervention: Research and Practice Considerations. *Soc Work Public Health*. 2013;28(0):333-348. doi:10.1080/19371918.2013.774665.

108. Magura S, Rosenblum A, Fong C. Factors associated with medication adherence among psychiatric outpatients at substance abuse risk. *Open Addict J*. 2011;4:58-64. doi:10.2174/1874941001104010058.

109. Bidell MR, McLaughlin M, Faragon J, Morse C, Patel N. Desirable Characteristics of Hepatitis C Treatment Regimens: A Review of What We Have and What We Need. *Infect Dis Ther*. 2016;5(3):299-312. doi:10.1007/s40121-016-0118-x.

110. El-Bassel N, Shaw SA, Dasgupta A, Strathdee SA. Drug use as a driver of HIV risks: re-emerging and emerging issues. *Curr Opin HIV AIDS*. 2014;9(2):150-155. doi:10.1097/COH.0000000000000035.

111. Klevens RM, Hu DJ, Jiles R, Holmberg SD. Evolving epidemiology of hepatitis C virus in the United States. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2012;55 Suppl 1:S3-9. doi:10.1093/cid/cis393.

112. Young JQ, Kline-Simon AH, Mordecai DJ, Weisner C. Prevalence of behavioral health disorders and associated chronic disease burden in a commercially insured health system: findings of a case-control study. *Gen Hosp Psychiatry*. 2015;37(2):101-108. doi:10.1016/j.genhosppsych.2014.12.005.

113. Shim RS, Koplan C, Langheim FJP, et al. Health care reform and integrated care: a golden opportunity for preventive psychiatry. *Psychiatr Serv Wash DC*. 2012;63(12):1231-1233. doi:10.1176/appi.ps.201200072.

114. Centers for Disease Control and Prevention (CDC). *HIV in the United States: At A Glance*.; 2017. https://www.cdc.gov/hiv/statistics/overview/ataglance.html. Accessed February 8, 2018.

115. Archin NM, Margolis DM. Emerging strategies to deplete the HIV reservoir. *Curr Opin Infect Dis*. 2014;27(1):29-35. doi:10.1097/QCO.0000000000000026.

116. Barton KM, Burch BD, Soriano-Sarabia N, Margolis DM. Prospects for treatment of latent HIV. *Clin Pharmacol Ther*. 2013;93(1):46-56. doi:10.1038/clpt.2012.202.

117. Montaner JSG, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet Lond Engl*. 2010;376(9740):532-539. doi:10.1016/S0140-6736(10)60936-1.

118. Degenhardt L, Whiteford HA, Ferrari AJ, et al. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet Lond Engl*. 2013;382(9904):1564-1574. doi:10.1016/S0140-6736(13)61530-5.

119. Volkow ND, Baler RD, Normand JL. The unrealized potential of addiction science in curbing the HIV epidemic. *Curr HIV Res*. 2011;9(6):393-395.

120. Centers for Disease Control and Prevention (CDC). *HIV and Injection Drug Use*.; 2017. https://www.cdc.gov/hiv/risk/idu.html. Accessed February 8, 2018.

121. Dash S, Balasubramaniam M, Villalta F, Dash C, Pandhare J. Impact of cocaine abuse on HIV pathogenesis. *Front Microbiol*. 2015;6. doi:10.3389/fmicb.2015.01111.

122. Hauser KF, Knapp PE. Interactions of HIV and drugs of abuse: the importance of glia, neural progenitors, and host genetic factors. *Int Rev Neurobiol*. 2014;118:231-313. doi:10.1016/B978-0-12-801284-0.00009-9.

123. Dahal S, Chitti SVP, Nair MPN, Saxena SK. Interactive effects of cocaine on HIV infection: implication in HIV-associated neurocognitive disorder and neuroAIDS. *Front Microbiol*. 2015;6:931. doi:10.3389/fmicb.2015.00931.

124. Chang SL, Connaghan KP, Wei Y, Li MD. NeuroHIV and use of addictive substances. *Int Rev Neurobiol*. 2014;118:403-440. doi:10.1016/B978-0-12-801284-0.00013-0.

125. Nasi M, Pinti M, De Biasi S, et al. Aging with HIV infection: a journey to the center of inflammAIDS, immunosenescence and neuroHIV. *Immunol Lett*. 2014;162(1 Pt B):329-333. doi:10.1016/j.imlet.2014.06.012.

126. Alfahad TB, Nath A. Update on HIV-associated neurocognitive disorders. *Curr Neurol Neurosci Rep*. 2013;13(10):387. doi:10.1007/s11910-013-0387-7.

127. Holt JL, Kraft-Terry SD, Chang L. Neuroimaging studies of the aging HIV-1-infected brain. *J Neurovirol*. 2012;18(4):291-302. doi:10.1007/s13365-012-0114-1.

128. Laura M. Maruschak. *HIV in Prisons, 2001-2010*. U.S. Department of Justice; 2012. https://www.bjs.gov/content/pub/pdf/hivp10.pdf.

129. Beckwith CG, Zaller ND, Fu JJ, Montague BT, Rich JD. Opportunities to diagnose, treat, and prevent HIV in the criminal justice system. *J Acquir Immune Defic Syndr 1999*. 2010;55 Suppl 1:S49-55. doi:10.1097/QAI.0b013e3181f9c0f7.

130. Montague BT, Rosen DL, Solomon L, et al. Tracking linkage to HIV care for former prisoners. *Virulence*. 2012;3(3):319-324. doi:10.4161/viru.20432.

131. Iroh PA, Mayo H, Nijhawan AE. The HIV Care Cascade Before, During, and After Incarceration: A Systematic Review and Data Synthesis. *Am J Public Health*. 2015;105(7):e5-16. doi:10.2105/AJPH.2015.302635.

132. National Center for Health Statistics. *Early Release of Selected Estimates Based on Data from The National Health Interview Survey*. Atlanta, GA: Centers for Disease Control and Prevention; 2015. https://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201506_10.pdf.

133. Copen CE, Chandra A, Febo-Vazquez I. HIV Testing in the Past Year Among the U.S. Household Population Aged 15-44: 2011-2013. *NCHS Data Brief*. 2015;(202):1-8.

134. Aletraris L, Roman PM. Provision of onsite HIV Services in Substance Use Disorder Treatment Programs: A Longitudinal Analysis. *J Subst Abuse Treat*. 2015;57:1-8. doi:10.1016/j.jsat.2015.04.005.

135. The White House. *National HIV/AIDS Strategy for the United States: Updated to 2020*.; 2015. https://www.hiv.gov/federal-response/national-hiv-aids-strategy/overview.

136. MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *BMJ*. 2012;345:e5945.

137. Friedman SR, Downing MJ, Smyrnov P, et al. Socially-integrated transdisciplinary HIV prevention. *AIDS Behav*. 2014;18(10):1821-1834. doi:10.1007/s10461-013-0643-5.

138. Hull MW, Wu Z, Montaner JSG. Optimizing the engagement of care cascade: a critical step to maximize the impact of HIV treatment as prevention. *Curr Opin HIV AIDS*. 2012;7(6):579-586. doi:10.1097/COH.0b013e3283590617.

139. Maina G, Mill J, Chaw-Kant J, Caine V. A systematic review of best practices in HIV care. *J HIVAIDS Soc Serv*. 2016;15(1):114-126.

140. Montaner JSG. Treatment as prevention: toward an AIDS-free generation. *Top Antivir Med*. 2013;21(3):110-114.

141. Castel AD, Magnus M, Greenberg AE. Pre-exposure prophylaxis for human immunodeficiency virus: the past, present, and future. *Infect Dis Clin North Am*. 2014;28(4):563-583. doi:10.1016/j.idc.2014.08.001.

142. World Health Organization. *Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*. World Health Organization; 2015. https://www.ncbi.nlm.nih.gov/books/NBK327115/.

143. Baeten J, Grant R. Use of Antiretrovirals for HIV Prevention: What Do We Know and What Don't We Know? *Curr HIV/AIDS Rep*. 2013;10(2):142-151. doi:10.1007/s11904-013-0157-9.

144. Blumenthal J, Haubrich R. Pre-exposure Prophylaxis (PrEP) for HIV Infection: How Antiretroviral Pharmacology helps to Monitor and Improve Adherence. *Expert Opin Pharmacother*. 2013;14(13):1777-1785. doi:10.1517/14656566.2013.812072.

145. Martin M, Vanichseni S, Suntharasamai P, et al. The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs. *AIDS Lond Engl*. 2015;29(7):819-824. doi:10.1097/QAD.0000000000000613.

146. Escudero DJ, Lurie MN, Kerr T, Howe CJ, Marshall BDL. HIV pre-exposure prophylaxis for people who inject drugs: a review of current results and an agenda for future research. *J Int AIDS Soc*. 2014;17:18899.

147. Burns DN, Grossman C, Turpin J, Elharrar V, Veronese F. Role of oral pre-exposure prophylaxis (PrEP) in current and future HIV prevention strategies. *Curr HIV/AIDS Rep*. 2014;11(4):393-403. doi:10.1007/s11904-014-0234-8.

148. Gwadz M, Cleland CM, Hagan H, et al. Strategies to uncover undiagnosed HIV infection among heterosexuals at high risk and link them to HIV care with high retention: a “seek, test, treat, and retain” study. *BMC Public Health*. 2015;15:481. doi:10.1186/s12889-015-1816-0.

149. Meyer JP, Althoff AL, Altice FL. Optimizing care for HIV-infected people who use drugs: evidence-based approaches to overcoming healthcare disparities. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2013;57(9):1309-1317. doi:10.1093/cid/cit427.

150. Hood KB, Robertson AA, Baird-Thomas C. Implementing solutions to barriers to on-site HIV testing in substance abuse treatment: a tale of three facilities. *Eval Program Plann*. 2015;49:1-9. doi:10.1016/j.evalprogplan.2014.11.001.

151. Hutchinson AB, Farnham PG, Sansom SL, Yaylali E, Mermin JH. Cost-Effectiveness of Frequent HIV Testing of High-Risk Populations in the United States. *J Acquir Immune Defic Syndr 1999*. 2016;71(3):323-330. doi:10.1097/QAI.0000000000000838.

152. Muga R, Langohr K, Tor J, et al. Survival of HIV-infected injection drug users (IDUs) in the highly active antiretroviral therapy era, relative to sex- and age-specific survival of HIV-uninfected IDUs. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007;45(3):370-376. doi:10.1086/519385.

153. Lima VD, Nosyk B, Wood E, et al. Assessing the effectiveness of antiretroviral regimens in cohort studies involving Hiv-positive injection drug users. *Aids*. 2012;26(12):1491-1500. doi:10.1097/QAD.0b013e3283550b68.

154. Centers for Disease Control and Prevention (CDC). More people with HIV have the virus under control [press release]. *NCHHSTP Newsroom*. https://www.cdc.gov/nchhstp/newsroom/2017/2017-HIV-Continuum-Press-Release.html. Published July 27, 2017. Accessed February 8, 2018.

155. Bradley H, Hall HI, Wolitski RJ, et al. *Vital Signs: HIV Diagnosis, Care, and Treatment Among Persons Living with HIV — United States, 2011*. Centers for Disease Control and Prevention (CDC); 2014. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6347a5.htm#fig2. Accessed February 8, 2018.

156. Durvasula R, Miller TR. Substance abuse treatment in persons with HIV/AIDS: challenges in managing triple diagnosis. *Behav Med Wash DC*. 2014;40(2):43-52. doi:10.1080/08964289.2013.866540.

157. Dimova RB, Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, Talal AH. Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2013;56(6):806-816. doi:10.1093/cid/cis1007.

158. Carrico AW, Flentje A, Gruber VA, et al. Community-Based Harm Reduction Substance Abuse Treatment with Methamphetamine-Using Men Who Have Sex with Men. *J Urban Health*. 2014;91(3):555-567. doi:10.1007/s11524-014-9870-y.

159. Joseph B, Wood E, Hayashi K, et al. Factors associated with initiation of antiretroviral therapy among HIV-positive people who use injection drugs in a Canadian setting. *AIDS Lond Engl*. 2016;30(6):925-932. doi:10.1097/QAD.0000000000000989.

160. Buckingham E, Schrage E, Cournos F. Why the Treatment of Mental Disorders Is an Important Component of HIV Prevention among People Who Inject Drugs. *Adv Prev Med*. 2013;2013:690386. doi:10.1155/2013/690386.

161. Kamarulzaman A, Altice FL. The Challenges in Managing HIV in People Who Use Drugs. *Curr Opin Infect Dis*. 2015;28(1):10-16. doi:10.1097/QCO.0000000000000125.

162. McGovern MP, Lambert-Harris C, Gotham HJ, Claus RE, Xie H. Dual diagnosis capability in mental health and addiction treatment services: An assessment of programs across multiple state systems. *Adm Policy Ment Health*. 2014;41(2):205-214. doi:10.1007/s10488-012-0449-1.

163. Croft B, Parish SL. Care Integration in the Patient Protection and Affordable Care Act: Implications for Behavioral Health. *Adm Policy Ment Health*. 2013;40(4). doi:10.1007/s10488-012-0405-0.

164. Perfas FB, Spross S. Why the concept-based therapeutic community can no longer be called drug-free. *J Psychoactive Drugs*. 2007;39(1):69-79. doi:10.1080/02791072.2007.10399866.

165. James DJ, Glaze LE. *Mental Health Problems of Prison and Jail Inmates*.; 2006.

166. Baillargeon J, Penn JV, Knight K, Harzke AJ, Baillargeon G, Becker EA. Risk of reincarceration among prisoners with co-occurring severe mental illness and substance use disorders. *Adm Policy Ment Health*. 2010;37(4):367-374. doi:10.1007/s10488-009-0252-9.

167. Pating DR, Miller MM, Goplerud E, Martin J, Ziedonis DM. New systems of care for substance use disorders: treatment, finance, and technology under health care reform. *Psychiatr Clin North Am*. 2012;35(2):327-356. doi:10.1016/j.psc.2012.03.004.

168. Mechanic D. Seizing opportunities under the Affordable Care Act for transforming the mental and behavioral health system. *Health Aff Proj Hope*. 2012;31(2):376-382. doi:10.1377/hlthaff.2011.0623.

169. Druss BG, Mauer BJ. Health care reform and care at the behavioral health—primary care interface. *Psychiatr Serv Wash DC*. 2010;61(11):1087-1092. doi:10.1176/ps.2010.61.11.1087.