



Co-occurring Disorders

5

Aaron Meyer, Gabriela G. Mejia, and Hilary M. Gould

Introduction

Co-occurring disorders, concurrent substance use and mental illness, often have synergistic effects that place an individual at increased risk of occupational, legal, and health hazards. These disorders affect those at the highest echelons of wealth and the most destitute. Addressing co-occurring disorders requires a multifaceted approach involving psychotherapy, support groups, and psychopharmacology. In this chapter, cultural aspects of co-occurring disorders are explored, including the role of public policy, healthcare organizations, and the legal system in combatting (and at times, perpetuating) the scourge of moralistic beliefs that have isolated this population from evidence-based interventions.

Substance use disorders are common in the United States and contribute to a large percentage of hospitalizations and mortality. There are about 20 million people with substance use disorders in the USA [1]. In 2010, 0.8% of global disability-adjusted life years were related to illicit substance use disorders [2]. Explanations for these rates are attributed to cardiovascular, digestive, respiratory, and endocrine diseases, cancers, suicide, overdoses, and injuries. In fact, of all hospitalized adult patients, 20% have a substance use disorder. These patients are three times more likely to leave the hospital against medical advice [3]. Consequences of leaving against medical advice are severe, with studies suggesting a doubling of 30-day mortality [4]. For patients with opioid use disorders, methadone induction has shown to reduce frequency of patients leaving against medical advice [3].

Mental health diagnoses often predate or co-occur with substance use disorders. In the USA in 2019, nearly half (49.2%) of patients with a substance use disorder were also diagnosed with a mental illness [1]. Concurrent diagnoses are especially common among patients with serious mental illness; patients with

A. Meyer (✉) · G. G. Mejia · H. M. Gould
Department of Psychiatry, University of California San Diego, San Diego, CA, USA
e-mail: aameyer@health.ucsd.edu; gmejia@health.ucsd.edu; hgould@health.ucsd.edu

schizophrenia have a 50% risk of developing a substance use disorder [5]. Disturbingly, a co-occurring disorder significantly increases the risk of psychiatric hospitalization, treatment nonadherence, and homelessness. Along with marketing, peer influence, and genetic predisposition, iatrogenic perpetuation of substance use disorders is a relevant issue. In a prospective analysis of 203 patients with co-occurring severe mental illness and substance use disorders, 43% were prescribed benzodiazepines. This group was twice as likely to abuse benzodiazepines than those who were not prescribed benzodiazepines [6]. The current opioid epidemic has been fueled in part by pharmaceutical advertising and physician prescribing.

Substance use disorders cost an estimated \$700 billion a year, mostly related to lost productivity [7, 8]. Despite this high cost, there are significant structural barriers associated with care delivery. As Massachusetts' health expansion demonstrated, adding substance use disorder treatment to insurance coverage does not necessarily lead to increased utilization or care [9]. Lack of utilization is likely multifactorial and certainly not solely due to the insurer. Individuals decline to engage in treatment for a myriad of reasons including denial, fear of adverse impact on employment, and time constraints [9]. Unfortunately, the Mental Health Parity and Addiction Equity Act in 2008 does not require insurers to provide substance use disorder treatment. Instead, this law exclusively applied to businesses with 50 or more employees who were already providing insurance coverage for mental health and substance use treatment [10]. In 2014, the Affordable Care Act (ACA) required insurers to cover treatment for mental health and substance use disorders [10]. Even so, in 2017 17% of workers were exempt from these essential health benefit additions due to enrollment in older "grandfathered" plans [10]. Patients continue to face increased barriers utilizing substance use disorder treatment compared to other medical care. In one study of 11,732 privately insured participants, an underlying issue they identified was decreased individual awareness regarding whether their plan covered substance use disorder treatment [10]. Another study cites 24% of privately insured individuals did not receive treatment because of insurance difficulties, such as coverage or affordability. However, in the same study, 97% did not perceive a need for treatment which highlights the need of outreach initiatives to advertise the benefit and accessibility of substance use disorder treatment [9]. In recent years, mental health spending and coverage have been expanded, but substance use coverage has not followed suit. Private insurance, Medicare, and Medicaid total mental health share coverage increased from 44% (1986) to 68% (2014), while the share of spending for substance use disorder treatment abysmally went from 45% (1986) to 46% (2014) [11]. Between 1986 and 2014, mental health treatment shifted primarily from governments to insurance companies; yet, substance use disorder treatment continues to be financed primarily from government entities [11].

Currently, treatments authorized by insurance companies are not always aligned with best practices. Prior authorization requirements and nonquantitative limits on treatment and lifetime treatment limitations begs the question of whether there is true parity between physical and mental healthcare. Individuals with substance use disorders are often excluded from transplantation, acute care facilities, and outpatient parenteral antibiotic treatment [12]. A study through Health Resources and

Services Administration demonstrated that stigma was one of the most cited reasons for not participating in substance use treatment. Methadone treatment is often perceived as degrading and humiliating. Patients with co-occurring disorders are less likely to engage in treatment and are at increased risk for suicide [13]. Individuals are twice as likely to utilize services for mental health treatment rather than for management of a substance use disorder [14].

Background

Historical Significance

Humans have been abusing substances since the earliest historical records. Throughout history, there has been a spectrum of beliefs regarding the etiology of substance use disorders. In this chapter, four main substances are discussed: alcohol, opioids, stimulants, and tobacco. Although not covered in depth in this chapter, benzodiazepines, cannabis, inhalants, steroids, and other substances contribute to morbidity and mortality. Substances are rarely used in isolation and interactions can lead to unintended effects.

Alcohol

Alcohol has been consumed for at least the past 10,000 years. Some original inceptions include beer, without hops, and mead, an elixir made from honey. Christianity helped popularize wine through connecting its consumption with Jesus' last supper. Beneficial health effects of alcohol in treating snake bites have been cited by Cato the Elder. British physicians have considered alcohol's role in curing venereal disease [15]. There has also been a focus on alcohol's negative effects. For instance, slaves were banned from alcohol consumption due to perceived increased likelihood of upending social order. The English legal system began regulating alehouses in the fifteenth century. Alcohol increasingly became more accessible to working-class people during the Industrial Revolution, notably, with 25% of London households producing gin. As consumption of alcohol increased in the nineteenth century, a counter focus on the negative effects of alcohol arose through the "temperance movement." Physicians referred to alcohol as "a disease of the will." Homes for inebriates and asylums were established to treat alcohol use disorder during the Prohibition era.

Before Prohibition, there were no systematic efforts to quantify alcohol use [16]. In the USA, 1889 marked the founding of the Sociology Group, which investigated social problems. In 1893 they began addressing problems associated with alcohol consumption and rebranded to the Committee of Fifty [17]. Members of the Committee of Fifty were mainly upper-class business and financial elites. They drafted a volume titled *The Liquor Problem: A Summary of Investigations Conducted by the Committee of Fifty, 1893–1903*, which formed basis for further restrictions on alcohol use [16]. Congress passed Wartime Prohibition in 1917, and National Prohibition was passed in January 1920 (18th Amendment), until it was overturned

in 1933 (21st Amendment) [16]. Despite doubling of enforcement budget between 1921 and 1930, efforts to curtail alcohol consumption were largely unsuccessful due to illegal manufacturing and trade. Additionally, there was increased support for alcohol consumption during Prohibition attributed to the romanticized thrill of danger. John Rockefeller and others founded the Research Council on Problems of Alcohol in 1937, in part to consider ramifications of repeal [18]. According to this group, “an alcoholic should be regarded as a sick person, just as one who is suffering from tuberculosis, cancer, heart disease, or other serious chronic disorder” [18].

Alcohol consumption, abuse, hospitalizations, and deaths have increased in the past two decades. A study examining alcohol-related deaths from US mortality data from the National Center for Health Statistics found that 2.6% of all deaths in 2017 involved alcohol [19]. Those at highest risk were men, middle-aged adults, and American Indians or Alaska Natives. Rate increases were highest among non-Hispanic white women, which is consistent with data on opioid use and other substance disorders.

Opioids

Opioid use disorder was originally considered a medical problem in the late 1800s. The Society for Promoting Legislation for Control and Cure of Habitual Drunkards (established in 1876) helped link substance dependence with medical treatment. Increasing use among lower socioeconomic groups in England led to concerns about “deviance” and increasingly punitive policies in the early 1900s [20]. The International Opium Convention of 1912 limited use of opiates and cocaine to medical use [21]. The Harrison Narcotic Act of 1914 required medical professionals to register with the Department of the Treasury and maintain prescribing records. In 1956, medical use of heroin was withdrawn in the USA (via the US Narcotic Drug Control Act), but any physician could still prescribe heroin to patients with opioid use disorder until 1968. Medication-assisted treatment emerged in the 1970s. Shifts in drug policy occurred in the 1980s, with the emergence of HIV/AIDS, leading to more favorable views of oral opioids such as methadone. In the 1990s, a number of pharmaceutical companies, physicians, and pain organizations began advocating for more aggressive use of opioids for chronic and nonmalignant pain conditions. During this time, opioid prescribing began to exponentially increase which led to dependence and growth in illegal marketplaces. Subsequently, other countries such as Australia and Switzerland renewed interest in heroin prescribing with the hopes of increasing access and interest in treatment and rehabilitation programs. A Geneva study investigated 46 patients randomized to receive heroin or methadone; at 6 months, the heroin group demonstrated reductions in illicit heroin use and legal infractions [22].

Concerningly, first-time heroin users have doubled to 169,000 between 2006 and 2013 [23]. Opioid use disorder is associated with significant cost, \$51.2 billion in the USA related to productivity losses, drug costs, incarceration, and treatment for hepatitis C [23]. Overdose deaths have tripled since 2002 [23]. Harm reduction efforts, such as needle exchange programs, were banned due to concerns of facilitating substance use [24]. In 2015, Congress partially repealed this ban allowing federal funding for all aspects of needle exchange programs except clean needles [24].

Significant attention has been paid to geographical variance of overdose trends. Upper Appalachia is notorious for its high overdose fatality rates [25]. Native Americans are at the highest overdose risk and have the highest opioid overdose death rate, 8.4 deaths per 100,000 people [26]. Additionally, shifts in employment opportunities with decreased manufacturing and mining opportunities are associated with an increased overdose risk, particularly individuals without a college degree raised in a single-parent family. Sadly, for every 1% increase in unemployment, opioid fatalities increase by 3.6% [27]. In the 2010s, the increased heroin overdoses in urban areas were related to increased availability from drug trafficking organizations in Mexico and synthetic drug production from China. Soon after in 2013, the USA witnessed an exponential increase in fentanyl production and the overwhelming effects on overdose deaths [28]. By 2019, half of the drug overdose deaths in the USA involved synthetic opioids as they are both deliberately and inadvertently paired with other drugs [29]. These synthetics are significantly more potent than morphine (pure carfentanil is 10,000 times), and they continue to drive and expand the opioid epidemic [27].

Stimulants

Stimulant use via chewing coca leaves dates back 8,000 years ago in northern Peru. Throughout colonization, use was primarily endemic to South America because the coca leaf lost potency quickly. The active alkaloid, cocaine, was first isolated by German chemist, Friedrich Gaedcke, in 1855. By the 1880s, the medical community began recommending cocaine for treatment of depression and local anesthesia for ophthalmological procedures. Sigmund Freud touted it as miracle drug and partnered with pharmaceutical companies for sponsorship. Coca leaves were used in the soft drink Coca-Cola from 1886 to 1903. After several years, social and medical concerns surfaced, and the Harrison Act in 1914 banned all distribution of coca products (and opiates as described above).

Synthetic stimulants including amphetamine and methamphetamine were isolated in 1887 and 1919, respectively. By the 1950s and 1960s, methamphetamine was widely prescribed for obesity and depression [30]. In the early 1970s, Nixon declared a “war on drugs” to combat the sharp rise in cocaine abuse. The Controlled Substances Act of 1971 also led to a decline in prescribed amphetamines. The Reagan administration expanded these policies with emergence of the “Just Say No” movement, implementation of drug prevention programs in schools and signing the Anti-Drug Abuse Act in 1986. This law established mandatory prison penalties for specific drug offenses and led to a massive surge in incarcerations. By the 1990s there was a resurgence of methamphetamine popularity, originally isolated to “meth labs” in California but later spreading nationwide.

Current estimates for stimulant misuse are on the rise with 5.5 million Americans using cocaine and 1.9 million using methamphetamine in 2018 [31]. In some parts of the country, stimulant use exceeds opioid use. Amphetamine-related hospital costs reached 2.17 billion in 2015 [32]. Overdoses involving psychostimulants have increased in the past two decades, in part due to synthetic opioids being mixed into stimulants often without user awareness. In 2018, greater than 50% of psychostimulant-related overdose deaths involved opioids [28].

Tobacco

Archaeological evidence reveals tobacco use many millennia ago in ancient indigenous communities in Mesoamerica and South America. Tobacco was a heavily traded commodity and use increased nearly exponentially from the 1800s to mid-1960s, especially with the invention of cigarettes [33]. Since the identification of harmful health consequences and publication of the Surgeon General's report in 1964, rates in the USA have declined. Statewide campaigns, such as the California Tobacco Control Program, have been instrumental in decreasing tobacco use via policy measures (e.g., taxes, reducing secondhand smoke, regulation of tobacco industry, providing cessation services) targeted to create social norm and cultural changes.

Currently, tobacco use has remained relatively stable, in part due to increased consumption of e-cigarettes and related products. It continues to remain the most common substance use disorder and leading source of preventable disease, disability, and death in the USA [34]. In 2019, 14.0% of adults (34.1 million) smoked cigarettes. More than 480,000 deaths every year are attributed to cigarette smoking, and data suggests that 16 million Americans live with a smoking-related disease [34]. Annual costs are approximately \$300 billion, including direct medical care and lost productivity due to premature death and secondhand smoke [34]. Importantly, tobacco use disorders remain undertreated, even among individuals attending substance use programs. Less than half (47%) of all substance use treatment facilities offer tobacco cessation services with only one-quarter offering nicotine replacement therapy [35]. Moreover, while tobacco use rates are declining nationally, subgroup rates are disproportionate. Individuals who smoke menthol cigarettes, live in rural environments, have low socioeconomic status, identify as LGBTQ, and/or have serious mental illness are more likely to have continued use [34].

Cultural Considerations

Cultural factors are important to consider when discussing co-occurring disorders. Defining the terms "culture," "ethnicity," and "race" is necessary to facilitate dialogue. Cultural factors may either stigmatize or protect certain groups of people within larger systems of law enforcement, legal, and healthcare services.

Culture is the characteristics and knowledge of a particular group of people, which may involve ethnic and racial characteristics [36]. It is dynamic and changes over time. It can also involve age, class, and power dynamics. Culture can be used to distance or reinforce stigma. For instance, whiteness has been defined as a hegemonic system of domination to maintain power and influence in mainstream society. Core principles of whiteness are that it is invisible, socially constructed, and grants unearned privileges to members of the culture it represents [37].

White privilege is seemingly a worldwide phenomenon, with roots stemming from European colonialism. In the field of psychiatry, DSM diagnostic categories

and criteria are presumed “culture-free” despite originating from Europe and Northern America [36]. Reinforcing the dominant invisibility, highlighting specific “culture-bound” disorders, shields whiteness from a similar psychopathological focus. European and North American psychiatrists have presumptively assumed authority to ascribe diagnoses to not only North American and European culture but other cultures as well. Along with highlighting cultural “otherness,” cultural richness has been further subjugated by a reductionist appeal to neurobiology. Culture in medical settings often distances the clinician from the patient (e.g., cultural differences may be viewed as an impediment to shared understanding) [36]. Poor attention to the importance of culturally competent care in psychiatry often leads to lower utilization of outpatient mental health services [36].

Racialization of substance use disorders has been repeatedly utilized throughout time and regions. Examples in the USA include the use of phrases such as “cocaine-crazed Negroes” and “Chinese opium dens,” despite the reality that narcotic use was highest among whites. The 1986 Anti-Drug Abuse Act enforced similar sentencing for possession of crack cocaine (perceived as a Black drug) at 1/100th the amount of powder cocaine (perceived as a white drug). This led to targeting of communities of color with increased spending on incarceration in these neighborhoods. Similarly within healthcare systems, buprenorphine was marketed to general medicine clinics as an option for “stable,” “suburban” populations (implicitly linked to whiteness). Contrastingly, methadone clinics are often located in minority neighborhoods despite a stated preference for buprenorphine [8]. While individuals in developed countries and wealthier environments are more likely to use substances, people who are socially and economically disadvantaged are more likely to develop substance use disorders [38]. The intersection of public policy, healthcare organizations, and the legal system impact the context in which patients receive care.

Vignette

Malachi is a 46-year-old homeless male with opioid use disorder admitted to hospital medicine for management of bacteremia. This is not his first hospitalization at this hospital as he has been admitted previously for the treatment of cellulitis to both lower extremities. His bed was positioned in the emergency department (ED) hallway where he avoided eye contact with people he did not know. While in the ED, his nurses complained of difficulty obtaining intravenous line access. He endured loud sighs as ultrasound-guided placement of his intravenous line was finally successful. Malachi declined his dinner that evening (two half-slices of white bread with deli turkey) due to nausea from opiate withdrawal. His attempts to obtain treatment for withdrawal symptoms were unsuccessful, and he suffered the humiliation of defecating in his bed due to diarrhea. Despite his protests, his bedsheets were not changed for 3 hours. The ED nurse informed him that he would be admitted.

After he showered and changed into ill-fitting hospital-donated clothes, he decided to go outside and smoke a cigarette. Upon returning, he was sternly reminded by the unit clerk, “next time, you better sign out.” He replied that he was unaware of the unit expectations and would remember to sign out next time. Two hours later, he wanted to smoke another cigarette. The binder to sign out was nowhere to be found and attempts to locate it were unsuccessful. A hospital staff member informed him that he was allowed to smoke a cigarette. Upon return, he found two security officers and a medicine intern in his room. They asked about his whereabouts and suspiciously questioned his time off the unit. The young male intern informed him that he will need a urine drug screen. Malachi was then presented with a behavioral contract. He was enraged when he read “I will be discharged if I leave the unit” and “I am to remain on the unit at all times.”

Malachi angrily crumpled up the piece of paper and tossed it at the intern. Immediately turning bright red, the intern sputtered, “the hospital is not a place for drug users. It’s a place for people who want to get better.” The security officers then proceeded to demand access to his personal belongings and confiscated two lighters from his backpack. They quickly followed the intern out of the room, making eye contact with Malachi saying, “we have our eyes on you.” Malachi went to bed feeling angry and upset that he was accused but also increasingly uncomfortable and ashamed about his craving for heroin.

The next morning, Malachi awoke to the sound of a large cylindrical structure being wheeled into his room by hospital staff. He was informed that this was a “video-monitoring unit” to discourage “funny business.” This device would provide 24/7 surveillance, essentially leaving him devoid of privacy. Due to ongoing opiate withdrawal, Malachi had to make several trips to the bathroom. At each use, hospital staff made a point to knock loudly on his bathroom door, often saying “everything all right in there?” He did not know why the nurses would wake him up in the middle of the night by jostling the arm with his intravenous line.

On Hospital Day 3, Malachi had made up his mind to leave the hospital. His withdrawal symptoms had escalated considerably. He was too uncomfortable to discuss his rationale with the physician and did not know what the intern meant when he said, “you don’t have the capacity to leave.” He soon found out, however, when the same two security guards firmly instructed him to lay back down on the bed. Arguing that he has “had it with this hospital,” he was aggressively situated in bed while physical restraints were applied to both wrists and ankles. Crying out loudly “get me out of here,” he eventually fell asleep after intramuscular medications were administered.

Although his bacterial infection was clearing, the physician informed him that there were no accepting inpatient rehabilitation facilities because of his drug history and insurance coverage. Malachi pleaded with the intern to come back daily to the ED, but the intern scoffed “you think we would let you out of here with an IV? Give me a break.” That night, Malachi left the hospital. His absence was noticed 3 hours later. He was not there to hear the nurse complain, “shit, he left with his IV.”

Discussion

Patients like Malachi present difficult challenges to healthcare systems, both in terms of treatment and policy recommendations. Multifactorial etiologies (medical, psychiatric, substance) combined with multidisciplinary involvement (physician, nurse, clinical care partner, hospital security, hospital administration) and systemic factors (fee for service versus value-based payments, available outpatient treatment options) require a comprehensive, coordinated approach that is challenging to organize and influence.

Malachi has chronic bacteremia that has not been successfully treated despite numerous hospitalizations and ED visits. His irritable impulsivity is likely related to opioid withdrawal but could be a sign of an underlying psychiatric disorder, such as bipolar disorder. Verbalizing a desire to leave against medical advice will prompt considerations of capacity. Determining a patient's understanding of the rationale for hospitalization and risks/benefits of leaving against medical advice is necessary. Patients must be able to articulate a greater understanding of their current condition and risks of discharging against medical advice in accordance with the severity of their condition. There are several tools available to assist clinicians in these decisions.

Recognizing nonspecific behavioral manifestations of substance use disorders should lead to consultation with an inpatient psychiatrist for diagnostic clarification and treatment recommendations. Prompt consideration of medication-assisted treatment to decrease the discomfort of withdrawal will help decrease the likelihood of patients leaving against medical advice. Physicians and staff developing an awareness of organizational stigma surrounding substance use disorder and the impact on the medical care available to these individuals, for both related and unrelated issues, is critical for equitable care delivery. Examples include outpatient parenteral antibiotic therapy guidelines excluding patients with intravenous substance use disorders, behavioral agreements that restrictively confine patients to their hospital room, and lack of substance use navigators within hospital settings. All these practices are common problem areas that isolate patients with substance use disorders from medical care. Reducing stigma among healthcare providers is challenging in environments that lack resources to address the problem. Rather than retreating to cynicism, civic engagement with local behavioral health leaders may help reduce the sense of helplessness and futility many healthcare workers face when treating patients presenting to emergency departments. Advocating for increased resources, such as substance use navigators who can assist patients engage with a complex, Rube Goldbergian, health system may be useful.

In Malachi's case, several modifications are required to provide optimal clinical care. First and foremost, treating patients with respect should be the default, not diagnosis dependent. Demeaning comments reinforce stigma and isolate the patient from beneficent care. His substance use and withdrawal symptoms should have been more thoroughly assessed. This would have increased the opportunity for his provider to offer nicotine replacement therapy or medication to manage

discomfort associated with opiate withdrawal. A consult to psychiatry may have been useful to help clarify psychiatric history and diagnoses, manage his substance use while in the hospital, and offer recommendations for his behavioral disturbances. To prevent the miscommunications that occurred, upon admittance, the hospital staff should have provided Malachi with clear instructions and expectations regarding leaving his room. Several members of the team including the medicine intern, nurse, and security guard should have been more mindful of their biases and language. Malachi's decision to leave against medical advice perpetuated the pattern of untreated medical, psychiatric, and substance use problems.

Culturally Competent Care in Co-occurring Disorders

To provide culturally competent care for patients with co-occurring disorders, mental healthcare providers must recognize the role of the environment they are seeking care in, obtain personal and familial history, assess for social risk factors, and identify personal values and motivations. Examination of specific populations demonstrates the need for targeted and adapted interventions. Communication should be effective, attending to native language and nuanced interactions. Awareness of personal and systemic limitations, gaps, and biases should be recognized, and steps should be taken to reduce misunderstandings and barriers to care.

Social Risk Factors

Isolation

Social identity and social supports impact the development of substance use disorders, particularly during formative adolescent years. Nearly all adults who go on to develop substance use disorders begin using during adolescence. For those that develop a substance use disorders in adolescence, nearly 60% also have a concurrent mental illness [39]. Using substances may be associated with an increased or decreased number of social support sources, which are perceived as an "identity gain" or "identity loss," respectively [40]. Social connection is vital for humans, and poor social support and isolation are risk factors for developing both mental health and substance use disorders. Attending to the social network and potential loss of social connections during recovery is an important part of the treatment process and sustaining change.

Isolation can be grouped into three subtypes: (1) being unliked (not receiving social ties), (2) disengaged (not sending ties to others), and (3) outside-oriented (having out-of-network ties) [41]. Individuals with fewer social supports and more isolative behaviors are at greater risk for adverse health outcomes, including antisocial acts, mood disturbances, and suicide [42]. Laboratory research has also demonstrated the deleterious effects of depriving rats from social engagement, including increased cocaine abuse [43]. While social isolation and rejection can increase risk

of using substances, many also turn to substances to ameliorate feelings of loneliness [44] which perpetuates the disorder.

Stigma

Given the importance of social supports, community, and connection, it is not surprising that stigma, or marked disapproval of an individual, is associated with less access and utilization of care and worse mental health outcomes [45]. Substance use disorders are one of the most stigmatized health conditions in the world. They are often understood as extrinsic, environmental problems rather than biological or genetic ones. Therefore, if an individual is unable to control their substance use, the individual is to blame. Additionally, there is a moral aspect that further reinforces stigma, which is closely linked with the emotion of shame. Individuals with substance use disorders are often thought to be “weak and incompetent, more responsible for their disorder, and less pitiable and worthy of help” [45]. Similar stigmatizing language is also used against individuals with mental illness; use of the terms “maniac,” “lunatic,” and “psycho” perpetuate beliefs that individuals with mental illness are violent. Individuals with both substance use and psychiatric diagnoses are likely to be subject to more stigma than either one alone.

Stigma can affect an individual in three different ways: (1) experienced stigma, including acts of discrimination; (2) perceived stigma, how one believes society views them; and (3) self-stigma, or internalization of public perception [7]. Stigma related to substance use disorders is related to social stereotypes, internalization of these stereotypes, and reinforcement through societal shaming behaviors. Use of the term “addict” is often linked to a moral judgment or internalization as a “bad person” [7].

Unfortunately, physicians are also exposed to a system of blame, shame, and stigma for substance use disorders. Studies have documented that physicians may view individuals with substance use disorders as having lower importance and more likely to commit violence and manipulate others [7]. Surprisingly, these views do not always change with more training and education. In a study of psychiatry residents, negative attitudes toward patients with substance use disorder increased throughout training. Addiction psychiatrists and community psychiatrists had more negative attitudes toward patients with a co-occurring mental health and substance use disorder than patients with either diagnosis alone [7]. Negative beliefs about patients with substance use disorders are partly related to the perception that this population places an undue burden on our healthcare system. Additionally, despite understanding that substance use disorders create reward circuitry dysfunction, moralistic oversimplification attitudes (e.g., “this guy should just shape up”) remain prevalent among healthcare workers. There is also a bias in hospital settings toward primarily interacting with individuals who have severe untreated substance use disorders rather than treating individuals who are in recovery. Unfortunately, trainee exposure to the “hidden curriculum” may foster negative attitudes rather than positive mentorship that contextualizes substance use disorders within a medical framework indicating a need for larger systemic change. Notably, physicians experience substance use disorder rates similar to the general population, but the formal

treatment they are offered through physician health programs is thought to be attributed to their significantly smaller relapse rate from the general population.

Addressing public stigma can alleviate the severity of self-stigma. One way to address public stigma is through decriminalization, as laws are seen as a codification of social norms []. The swinging pendulum from criminal to medical interventions for substance use disorders can be viewed across time as described above in the “Historical Significance” section. Additionally, treatment for substance use disorders typically includes both psychoeducation and support groups for patients and family members that can help connect them to a supportive social group, overcome shame and blamed based thinking, and realize they are not alone.

Special Populations

Pregnancy, Postpartum, and Motherhood

From 1999 to 2015, prescription opioid fatalities increased by 471% for women compared to 218% for men [46]. Similar increases in misuse and mortality for women have been observed in alcohol and other substances [19]. Despite the growing rates of substance abuse concerns in women, they are less likely to receive treatment. It is hypothesized that this is related to increased stigma, higher burden of caregiving responsibilities, and treatment approaches that have been designed based on research conducted primarily on male populations. Substance use in the context of pregnancy and motherhood may be particularly challenging. The postpartum period is a critical time where many mothers may start using substances again after pausing during pregnancy and is associated with postpartum depression. The American College of Obstetricians and Gynecologists assert that women with an opioid use disorder should not face criminal or civil penalties including loss of custody [47]. Loss of custody is associated with substance relapse and increased risk for depression. Fear of child separation is one reason women opt to avoid substance use disorder treatment. Black and Latinx women with opioid use disorders are more likely than white women with opioid use disorders to be incarcerated and separated from their children. Twenty-three states classify substance use in pregnancy as child abuse, and three states classify substance use as grounds for civil commitment.

Women with substance use disorders have higher rates of mental health diagnoses than men, which may be attributed to a combination of adverse childhood experiences, lifetime trauma, and low self-esteem []. The Substance Use and Mental Health Services Administration (SAMHSA) notes that “trauma is an almost universal experience” for women with co-occurring disorders [48]. Whereas men with substance use disorders are more likely to exhibit externalizing behaviors (e.g., aggression), women are more likely to internalize (e.g., self-criticism). These externalizing behaviors decrease with age in men, but internalizing behaviors increase with age in women.

Physical and Cognitive Disabilities

Individuals with disabilities are at higher risk for developing co-occurring mental illness and substance use disorders. They are also less likely to engage in treatment [49] and are more likely to be heavy users compared to individuals without disabilities [50]. Disabilities may be physical (e.g., deaf and hard of hearing) and/or cognitive (e.g., traumatic brain injury). Increased risk for developing substance use disorders appears to be related to social isolation, limited access to services, poor health literacy, unemployment, and level of disability acceptance [51]. Treatment services are critical. One study found that suicidal behavior is increased in deaf individuals with co-occurring disorders compared to deaf individuals with a mental health diagnosis alone [49]. While access to care remains challenging, efforts to increase access via environmental modifications (e.g., wheelchair ramps) and resource materials (e.g., Braille, sign language interpretation) are being made in support programs.

Incarcerated Populations

Incarcerated populations face significant challenges and limited resources. These limitations, coupled with a multitude of factors, place them at increased risk for both substance use disorders and mental illness [52]. Prisoners reported increased use of cannabis (40%), cocaine (21.4%), methamphetamine (12.2%), and heroin (8.2%) compared to the general population. Symptoms of mental illness are also significantly higher, specifically mania (43.2% versus 2%), depression (23.5% versus 7%), and psychosis (15.4% versus 3%). Forty-one percent of incarcerated individuals have a co-occurring disorder. Incarceration alone increases the risk for suicide attempt (2.3% versus 0.4%) and completion compared to the general population [53]. Mood disorders in an incarcerated person increase the individual's suicide risk to 13%. Placement in maximum security settings increase the risk of suicide attempts [54].

Rates of co-occurring serious mental illness and substance use disorders are high in incarcerated populations (4–6x in jail, 3–4x in prison compared to national averages) [54]. Elevated rates of substance use disorders are related to federal and state drug policies (in 2015, >50% of federal prison population were related to drug offenses), homelessness, and higher rates of criminal behaviors [55]. An increased focus on community services (e.g., drug courts, mental health courts, assertive community treatment programs) for incarcerated individuals with co-occurring disorders has led to decreased rates of incarceration.

Treatment of substance use disorders in jail and prison settings is often rudimentary and limited, with only 11% of individuals receiving any treatment at all [7]. Perceived social support for prisoners was negatively correlated with number of substance use disorders [7]. In 2015, the US population was 13% Black, but the US prison population was 38% Black [7]. Evidence suggests that the general public assigns greater blame to Black individuals with substance use disorders than their white counterparts [7]. White inmates are also more likely than Black inmates to receive substance use treatment [7].

Additionally, there is inadequate access to medication-assisted treatments. If these treatments are provided, inmates are typically charged extra for this service. As of August 2018, only Rhode Island provides all three forms (methadone, buprenorphine, naltrexone) of medication-assisted treatment, and 28 states do not prescribe any form of medication-assisted treatment [7]. Paltry medication formularies often lead to psychiatric decompensation due to reduced access to nonformulary medications and challenges related to restrictions on dosage and use. Logistical factors such as clinicians having a Drug Enforcement Administration waiver may also affect access to pharmacological treatments. Medication cessation can lead to behavioral dysregulation and increased risk for placement in administrative segregation (solitary confinement) [54]. Lack of reentry programs can lead to further destabilization.

Military Service Members and Veterans

Active duty and veteran service members suffer from higher than average prevalence rates of both mental health disorders and substance use disorders, which places them at increased risk of developing co-occurring disorders. Higher rates of substance abuse, particularly alcohol misuse, are observed in those that have deployed [55, 56]. This is likely due to a combination of factors including the culture, setting, and experiences, such as exposure to combat. Prescriptions for pain medications also increased exponentially in the early 2000s among military physicians [56], increasing concerns for opioid use disorders. Service members are likely to have co-occurring substance and mental health disorders, such as posttraumatic stress disorder, depression, and anxiety. Those with co-occurring disorders are at increased risk for suicide. The suicide rate for service members exceeded suicides in the general population, and more than 1,100 military members died by suicide between 2005 and 2009 [55]. Efforts have been made to address these growing concerns including reducing access to alcohol on military sites and reinforcing underage laws, reducing stigma to accessing treatment, and offering more confidential and intensive services to treat substance use and co-occurring disorders [56].

Indigenous Populations

Indigenous populations have a high prevalence of substance use and co-occurring disorders. Historically, American Indians and Alaska Natives have had the highest rates of alcohol, marijuana, cocaine, hallucinogen, and methamphetamine use disorders [1, 57]. Rates for psychosocial stressors, adverse childhood experiences, and poverty are also elevated. Substance use disorders in this population affect not only individuals and families but communities on a larger scale. In addition to increased risk due to disparities in social determinants of health, these populations often have limited access to treatment across rural and urban settings. Access to treatment is challenging due to transportation issues, limited insurance coverage, low socioeconomic status, stigma, and shortage of treatment programs (particularly interventions that have culturally informed adaptations) [57]. Encouragingly, access to medication-assisted treatments continues to increase every year and the expansion of telemedicine services is likely to benefit rural populations [1].

Treatment for Co-occurring Disorders

Traditionally, treatments for substance use disorders were sequestered from general and mental health care services. Services provided were also limited, often reduced to urgent or emergency care rather than treatment and recovery services. The benefits of treating substance and mental health disorders concurrently are evident. Integrated treatment approaches including psychosocial interventions, case management (e.g., housing, finances, education/vocation), peer supports (e.g., 12-step groups, recovery support specialists), and family services (e.g., psychoeducation, support groups) are recommended. These approaches are not just beneficial for patient outcomes but also valuable for larger systems of care, such as reducing unnecessary expensive hospital visits. Table 5.1 outlines unique and shared treatment approaches across alcohol, opioid, stimulant, and tobacco use disorders. Despite information about the effectiveness of comprehensive and integrated treatments, the majority of patients with co-occurring disorders receive treatment for only one disorder or no treatment at all [1]. Additional work is needed to inform public policy, address stigma, and shift the perspective of substance use disorders as a social or criminal problem rather than a public health need.

Alcohol

Six percent of all deaths globally and 3% of deaths in the USA are related to alcohol use [18, 19]. Prolonged cessation from alcohol abuse without support is successful for 20% of population suffering from alcohol use disorder [18]. However, only 8.3% of 15 million adults struggling with alcohol use disorder received treatment in 2015 [58]. Twelve-step programs started with Alcoholics Anonymous (AA), founded in 1934 after the repeal of Prohibition [18]. Importantly, while other groups were focused on societal problems associated with alcohol use, AA focused on the individual's consumption of alcohol. AA chose to avoid other aspects of alcohol use disorder, such as underlying etiology (genetic, societal, medical, personal). The group emphasized the need for spirituality conversion as central to recovery. Members of AA found solace in descriptions of alcohol as an "allergy" and "obsession," advocating abstinence in order for individuals to address spiritual maladies. Central to AA is "identity diffusion," where individuals listen to personal stories from other members, allowing them to connect to shared experiences in the group [59]. After completion of residential treatment, rates of abstinence double with participation in AA compared to no participation [60]. Similarly, increased participation in AA is associated with increased periods of sobriety [60]. A Cochrane review demonstrated equal levels of effectiveness of 12-step programs compared to other interventions such as self-help groups [61].

For individuals who require more intensive structure than recovery meetings, residential treatment is often sought. Residential treatment is a 24-hour nonhospital level of care setting with intensive substance abuse programming. People with co-occurring disorders often are treated in residential facilities because of their more

Table 5.1 Treatment recommendations for substance use and co-occurring disorders

	Pharmacotherapy/ medication- assisted treatment	Other treatments	Experimental treatments requiring more research
Alcohol	Disulfiram Naltrexone Injectable naltrexone Acamprosate	Modified therapeutic communities (inpatient, residential, or recovery treatment) Peer supports (e.g., 12-step programs, recovery support specialists) Motivational interviewing and enhancement Behavioral couples therapy	Transcranial magnetic stimulation Buprenorphine Varenicline Intranasal oxytocin Gabapentin Prazosin Topiramate Buspirone
Opioids	Methadone Buprenorphine Naltrexone	Needle exchange programs Modified therapeutic communities Peer supports Motivational interviewing and enhancement	Ketamine Heroin-assisted treatment Transcranial magnetic stimulation Buspirone
Stimulants	N/A	Contingency management therapy Community reinforcement approach Modified therapeutic communities Peer supports Motivational interviewing and enhancement	Dexamphetamine Methylphenidate Topiramate Disulfiram Buprenorphine Naltrexone Bupropion N-acetylcysteine Mirtazapine Valproic acid Transcranial magnetic stimulation Cognitive behavioral therapy
Tobacco	Nicotine replacement therapy Bupropion Varenicline	Motivational interviewing and enhancement Telephone support and quit lines Cognitive-behavioral therapy and mindfulness interventions	Nortriptyline N-acetylcysteine Transcranial magnetic stimulation

complex treatment needs, and evidence suggests that residential treatment settings are effective in reducing substance use and promoting higher quality of life. As untreated depression or posttraumatic stress disorder hastens alcohol craving and relapse, integrated residential care settings are important for those with co-occurring disorders [63]. Notably, duration of residential treatment differs by country; Swiss residential treatment duration is about five times (122 days) that of the USA (25 days) [64]. Although depressive symptoms at admission to residential treatment were associated with alcohol use at 1 year after residential treatment discharge, improvements in depressive scores were not associated with subsequent alcohol use at 1 year [64]. Co-management, including pharmacologically, for alcohol use disorder and major depression leads to decreased relapse rates and increased sobriety [65].

Unfortunately, prescription rates for treatment of alcohol use disorders are woefully low; from 2002 to 2007, one study indicated that only 9% of individuals received one of the four medications (i.e., disulfiram, naltrexone, injectable naltrexone, acamprosate) the Federal Drug Administration (FDA) has approved for alcohol use disorder [58]. Medications that have been used to treat other substance use disorders may also aid the treatment of alcohol use disorder. Specifically, high doses of buprenorphine has shown decreased alcohol consumption, theoretically by blocking reward circuitry [62]. Similarly, varenicline decreased the number of heavy drinking days [62]. Decreasing glutamate through topiramate has also demonstrated a concomitant decrease in stress-related alcohol consumption [62]. Tracking serum glutamate levels are of importance as individuals with higher serum glutamate levels were more likely to respond to acamprosate (returning to normal serum glutamate levels) than those with lower baseline glutamate levels. Intranasal oxytocin is associated with decreased alcohol cravings, likely through stress-mediated pathways [62]. Data suggests that gabapentin is efficacious in reducing withdrawal symptoms and increasing duration of sobriety [65].

In addition to psychosocial and pharmacologic treatments, neuromodulation is a potential avenue to address alcohol use disorder. Due to compulsive behavior associated with alcohol use and positive results using transcranial magnetic stimulation (TMS) in patients with obsessive-compulsive disorder, TMS has also been posited as a possible treatment for alcohol use disorder [66]. By targeting dorsolateral prefrontal cortex and medial prefrontal cortex, investigators hope to disrupt pathways implicated in alcohol abuse [67]. In early studies, repetitive transcranial magnetic stimulation directed to dorsolateral prefrontal cortex and medial prefrontal cortex resulted in decreased alcohol craving compared to placebo [67]. Similar results have been demonstrated with transcranial direct current stimulation [67]. This has implications for future indications of transcranial magnetic stimulation.

Opioids

Rates of opioid misuse rose exponentially in the past few decades, resulting in high disability, infectious disease burden, and overdose deaths. First line recommended and FDA-approved treatment is medication-assisted treatment including buprenorphine, methadone, and extended-release naltrexone. Pharmacotherapy should be combined with behavioral counseling. Studies have demonstrated support for decreased opioid-related deaths and infectious disease transmission, increased engagement in treatment and functioning, and improved neonatal outcomes once medication-assisted therapies have been introduced [47, 68, 69]. However, access to these treatments remains sparse with nearly all US states having insufficient treatment options. On average, only 11% of patients with opioid use disorder receive medication-assisted treatment [70].

In addition to currently approved medications, researchers are investigating alternative methods of treating opioid use disorder. One potential option is ketamine [71]. In one promising study, abstinence rates were 85% at 1 month and 24% at

1 year for high-dose ketamine (2 mg/kg) versus 6% for low-dose ketamine (0.2 mg/kg). This study was limited by lack of a placebo group [72]. Noninvasive brain stimulation including TMS, transcranial direct current stimulation, and auricular vagus nerve stimulation may have therapeutic benefits as an augmentation strategy, particularly during withdrawal and cravings [73]. Research is still preliminary and ongoing studies with larger samples, placebo groups, and generalizable findings are needed.

Supervised injectable heroin treatment was started during the 1990s. This intervention is used when first-line options (methadone, buprenorphine, residential treatment) are unsuccessful. Patients inject about 200 mg of heroin with direct supervision [21]. Introduction of supervised injection sites has led to a decrease in illicit heroin use along with use of cocaine and alcohol. Social functioning including housing, drug-free contacts, employment, and incarceration rates have improved [21]. Patients are prohibited from leaving the site with any heroin. Negative connotations associated with substance use disorders have infected public policy and hospital practices. While heroin-assisted treatment is utilized in some European countries, its use is banned in the USA.

Six countries (i.e., Canada, Germany, Spain, Switzerland, the Netherlands and the UK) have studied heroin-assisted treatment (HAT) to determine if this option is superior to the standard of care, especially when other options have failed. The most common reasons for prescribing heroin among English psychiatrists was continued illicit heroin use by injection, methadone refusal, crime reduction (e.g., purchasing heroin through sex work), and previous treatment failure [21]. In Germany, HAT led to health system net savings of ~\$6,000 per patient per year compared to a net cost of ~\$2,000 per patient per year with methadone maintenance. Also, HAT programs maintained higher retention rates [21]. Broadening treatment required legislative changes to Germany's federal narcotics control law. Similarly, a multicenter study in the Netherlands demonstrated therapeutic benefit (i.e., physical health, mental health, and social functioning) of HAT compared to methadone [21]. Political opposition has proven the rate-limiting step in many of these countries [75].

Stimulants

Methamphetamine intoxication is associated with psychosis. Its effects can be explained by dopamine binding and sympathetic stimulation by monoamine release. Frequent, prolonged methamphetamine use can lead to mood disturbances, impulsivity, and cognitive deficits [76]. Depression and anxiety are common comorbidities among patients with methamphetamine use. Over half of the women in one study reported a history of sexual assault [77]. In a study of 16 patients with methamphetamine use disorder, 53% experienced psychiatric disorders (i.e., unipolar depression, attention-deficit/hyperactivity disorder, substance-induced psychosis) [77]. It is unknown whether cognitive deficits related to methamphetamine

use are completely reversible; however, attentional problems improve with sustained sobriety [76]. Patients who inject methamphetamine, versus inhale, demonstrated an increased risk for suicidal ideation and attempts as well as violent behavior [77].

The global market for stimulants is expanding. Use of cocaine and methamphetamine has been increasing for the past decade, reaching a high in 2018 of 19 million cocaine users (primarily in North America/Western Europe) and 27 million amphetamine users (primarily in Southeast Asia) [38]. Seizures from amphetamine use quadrupled between 2009 and 2018 [38]. Treatment for stimulant use disorder is particularly challenging as no medications have FDA approval or demonstrated consistent efficacy. Psychosocial interventions, such as contingency management, have demonstrated support in reducing stimulant use and improving functioning and treatment engagement. Additionally, there is some evidence that prescription psychostimulants may promote sustained drug abstinence. Trials with dexamphetamine have demonstrated prolonged methamphetamine cessation and decreased craving [78]. Once daily dosing was used with maximum dose of 110 mg/day. Buprenorphine showed greater decrease in craving compared to methadone [79], and naltrexone may be helpful regarding cravings in laboratory and clinical studies [80]. Bupropion and N-acetylcysteine are helpful at reducing methamphetamine withdrawal symptoms. Research findings for modafinil are mixed and limited. One study supported adding mirtazapine to cognitive behavioral therapy/motivational interviewing to decrease methamphetamine use [81]. Ongoing research is needed, and individuals with stimulant use disorders are considerably undertreated.

Tobacco

Smoking is the leading cause of preventable disease, disability, and death in the USA [34]. Although many smokers express interest in quitting smoking or smokeless tobacco, much fewer are successful in doing so. On average, individuals undergo 30 quit attempts before successful discontinuation [82]. First-line treatment for smoking cessation includes a combination of medication (bupropion and varenicline) and nicotine replacement therapy (NRT; transdermal, lozenges, gum). Combining short- and long-acting NRT can be more effective than using one form only. Patients may also benefit from additional counseling via quit hotlines, phone apps, individual, and/or group therapies. Strategies that have demonstrated efficacy include setting a quit date, recognizing behavioral and environmental triggers, and having identified reasons for quitting. Similar to other substance use disorders, early studies indicate TMS may be helpful on craving and intake [83].

Individuals with schizophrenia have the highest rates of tobacco use (70–80%) compared to those with other mental health diagnoses [5]. Data suggests that

treatment with first-generation antipsychotics may worsen substance use disorders, particularly tobacco use disorders [5]. Increased tobacco use is attributed to extrapyramidal side effects associated with first-generation antipsychotics. Smoking cessation interventions may be more effective with atypical antipsychotics, but larger studies are necessary to support these studies with small sample sizes [5]. Additional research is needed to inform best practice prescribing patterns in psychotic patients with a known tobacco use disorder.

Conclusion

Co-occurring disorders are common but undertreated due to a combination of factors related to addiction and systemic barriers to care including stigma, discrimination, limited resources, and lack of access to appropriate treatments. Even among healthcare professionals, negative attitudes toward individuals with a substance use disorder are extremely prevalent. Although increased training is not always effective at reducing stigma, hospitals are encouraged to utilize substance use navigators to better guide treatment and advocate for patients. Evidence-based treatments are underutilized, especially in custodial and hospital settings. Inadequate recognition and treatment of co-occurring disorders often have deleterious consequences. Efforts to address substance use disorders as diagnoses, rather than moral failings, will improve patient care.

Summary of High-Yield Points

- Mental health diagnoses often predate or co-occur with substance use disorders.
- Individuals with co-occurring disorders are at increased risk for suicide, poor treatment adherence, and homelessness.
- Social isolation is a common risk factor for developing a substance use disorder.
- Patients are more likely to have their mental health diagnosis treated than their substance use disorder.
- Clinician attitudes toward patients with co-occurring disorders affect utilization of healthcare services.
- Even when substance use disorder treatment is covered by insurance providers, patients face increased barriers and are often unaware that this resource is available to them.
- In addition to 12-step programs and FDA-approved medications, transcranial magnetic stimulation has been posited as possible treatment for alcohol use disorder and other substance use disorders.
- Treatment for stimulant use disorder is particularly challenging as no medications have FDA approval or demonstrated consistent efficacy.
- Heroin-assisted treatment is utilized in other countries for patients who are difficult to engage with medication-assisted treatment or fail to respond to the standard of care.

References

1. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. Key substance use and mental health indicators in the United States: results from the 2019 National Survey on Drug Use and Health. 2019.
2. Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, Freedman G, Burstein R, Johns N, Engell RE, Flaxman A. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382(9904):1564–74.
3. Ti L, Ti L. Leaving the hospital against medical advice among people who use illicit drugs: a systematic review. *Am J Public Health*. 2015;105(12):2587.
4. Tan SY, Feng JY, Joyce C, Fisher J, Mostaghimi A. Association of hospital discharge against medical advice with readmission and in-hospital mortality. *JAMA Netw Open*. 2020;3(6):e206009.
5. Green AI, Drake RE, Brunette MF, Noordsy DL. Schizophrenia and co-occurring substance use disorder. *Am J Psychiatry*. 2007;164(3):402–8. <https://doi.org/10.1176/ajp.2007.164.3.402>. PMID: 17329463
6. Brunette MF, Noordsy DL, Xie H, Drake RE. Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. *Psychiatr Serv*. 2003;54(10):1395–401. <https://doi.org/10.1176/appi.ps.54.10.1395>. PMID: 14557527
7. Avery JD, Avery JJ, editors. *The stigma of addiction: an essential guide*. Springer; 2019.
8. National Institute on Drug Abuse. *Trends & Statistics*. 2017.
9. Ali MM, Teich JL, Mutter R. The role of perceived need and health insurance in substance use treatment: implications for the Affordable Care Act. *J Subst Abuse Treat*. 2015;54:14–20.
10. Mojtabai R, Mauro C, Wall MM, Barry CL, Olfson M. Private health insurance coverage of drug use disorder treatment: 2005–2018. *PLoS One*. 2020;15(10):e0240298.
11. Mark TL, Yee T, Levitt KR, Camacho-Cook J, Cutler E, Carroll CD. Insurance financing increased for mental health conditions but not for substance use disorders, 1986–2014. *Health Aff*. 2016;35(6):958–65.
12. Tsai AC, Kiang MV, Barnett ML, Beletsky L, Keyes KM, McGinty EE, Smith LR, Strathdee SA, Wakeman SE, Venkataramani AS. Stigma as a fundamental hindrance to the United States opioid overdose crisis response. *PLoS Med*. 2019;16(11):e1002969.
13. Yates K, Lång U, Cederlöf M, Boland F, Taylor P, Cannon M, McNicholas F, DeVlyder J, Kelleher I. Association of psychotic experiences with subsequent risk of suicidal ideation, suicide attempts, and suicide deaths: a systematic review and meta-analysis of longitudinal population studies. *JAMA Psychiat*. 2019;76(2):180–9.
14. Hatzembuehler ML, Keyes KM, Narrow WE, Grant BF, Hasin DS. Racial/ethnic disparities in service utilization for individuals with co-occurring mental health and substance use disorders in the general population. *J Clin Psychiatry*. 2008;69(7):1112.
15. Anderson P, Baumberg B. *Alcohol in Europe*, vol. 2. London: Institute of Alcohol Studies; 2006. p. 73–5.
16. Miron JA, Zwiebel J. *Alcohol consumption during prohibition*. National Bureau of Economic Research; 1991.
17. Levine HG. The Committee of Fifty and the origins of alcohol control. *J Drug Issues*. 1983;13(1):95–116.
18. Kurtz E. Alcoholics anonymous and the disease concept of alcoholism. *Alcohol Treat Q*. 2002;20(3–4):5–39.
19. White AM, Castle IJP, Hingson RW, Powell PA. Using death certificates to explore changes in alcohol-related mortality in the United States, 1999 to 2017. *Alcohol Clin Exp Res*. 2020;44(1):178–87.
20. Metrebian N. *Influences on the prescribing of heroin for the treatment of opiate dependence in the United Kingdom*. London: University of London; 2005.

21. Strang J, Groshkova T, Metrebian N. European Monitoring Centre for Drugs and Drug Addiction. New heroin-assisted treatment: recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond. Luxembourg: Publications Office of the European Union; 2012.
22. Perneger T, Giner F, del Rio M, Mino A. Randomized trial of heroin maintenance programme for addicts who fail in conventional drug treatment. *BMJ*. 1998;317(7150):13–8.
23. Jiang R, Lee I, Lee TA, Pickard AS. The societal cost of heroin use disorder in the United States. *PLoS One*. 2017;12(5):e0177323.
24. Weinmeyer R. Needle exchange programs' status in US politics. *AMA J Ethics*. 2016;18(3):252–7.
25. Cohen A. How white users made heroin a public-health problem. *The Atlantic*. 2015.
26. Mack KA, Jones CM, Ballesteros MF. Illicit drug use, illicit drug use disorders, and drug overdose deaths in metropolitan and nonmetropolitan areas—United States. *Am J Transplant*. 2017;17(12):3241–52.
27. Peters DJ, Monnat SM, Hochstetler AL, Berg MT. The opioid hydra: understanding overdose mortality epidemics and syndemics across the rural-urban continuum. *Rural Sociol*. 2020;85(3):589–622.
28. Jones CM, Bekheet F, Park JN, Alexander GC. The evolving overdose epidemic: synthetic opioids and rising stimulant-related harms. *Epidemiol Rev*. 2020;42(1):154–66. <https://doi.org/10.1093/epirev/mxaa011>.
29. Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and geographic patterns in drug and synthetic opioid overdose deaths — United States, 2013–2019. *MMWR Morb Mortal Wkly Rep*. 2021;70:202–7. <https://doi.org/10.15585/mmwr.mm7006a4>.
30. Anderson AL, Li SH, Biswas K, McSherry F, Holmes T, Iturriaga E, Kahn R, Chiang N, Beresford T, Campbell J, Haning W. Modafinil for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2012;120(1–3):135–41.
31. Substance Abuse and Mental Health Services Administration: Center for Behavioral Health Statistics and Quality. Key substance use and mental health indicators in the United States: results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19–5068, NSDUH series H-54). Rockville: Substance Abuse and Mental Health Services Administration; 2019.
32. Winkelman TN, Admon LK, Jennings L, Shippee ND, Richardson CR, Bart G. Evaluation of amphetamine related hospitalizations and associated clinical outcomes and costs in the United States. *JAMA*. 2018;1(6):e183758.
33. United States. Public Health Service. Office of the Surgeon General, National Center for Chronic Disease Prevention, & Health Promotion (US). Office on Smoking. Preventing tobacco use among young people: a report of the surgeon general, vol. Vol. 10. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1994.
34. US Department of Health and Human Services. The health consequences of smoking—50 years of progress: a report of the surgeon general. Rockville: U.S. Department of Health and Human Services; 2014.
35. Substance Abuse and Mental Health Services Administration, National Mental Health Services Survey (N-MHSS): 2017. Data on Mental Health Treatment Facilities. BHSIS Series S-98, HHS Publication No. (SMA) 17-5049. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.
36. Maharajah HD, Abdool PS. Cultural aspects of suicide. *TheScientificWorldJOURNAL*. 2005;1:5.
37. Schmitt T. Stuff White People Like... To Keep: re-appropriation and whiteness in America. *Augsburg Honors Rev*. 2012;5(1):4.
38. United Nations Office on Drugs and Crime. World drug report 2020. 25 June 2020. <https://wdr.unodc.org/wdr2020/index.html>.
39. 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.

40. Dingle GA, Cruwys T, Frings D. Social identities as pathways into and out of addiction. *Front Psychol*. 2015.
41. Hussong AM, Ennett ST, McNeish D, Rothenberg WA, Cole V, Gottfredson NC, Faris RW. Teen social networks and depressive symptoms-substance use associations: developmental and demographic variation. *J Stud Alcohol Drugs*. 2018;79(5):770–80.
42. Copeland M, Fisher JC, Moody J, Feinberg ME. Different kinds of lonely: dimensions of isolation and substance use in adolescence. *J Youth Adolesc*. 2018;47(8):1755–70.
43. Fosnocht AQ, Lucerne KE, Ellis AS, Olimpo NA, Briand LA. Adolescent social isolation increases cocaine seeking in male and female mice. *Behav Brain Res*. 2019;359:589–96.
44. Rapiet R, McKernan S, Stauffer CS. An inverse relationship between perceived social support and substance use frequency in socially stigmatized populations. *Addict Behav Rep*. 2019;10:100188.
45. Wilkens C, Foote J. “Bad Parents,” “Codependents,” and other stigmatizing myths about substance use disorder in the family. In: *The stigma of addiction*. Springer; 2019. p. 33–53.
46. U.S. Department of Health and Human Services Final report: opioid use, misuse, and overdose in women. 2017.
47. American College of Obstetricians and Gynecologists (ACOG), American Society of Addiction Medicine (ASAM). Committee opinion: opioid abuse, dependence, and addiction in pregnancy, vol. 524. Committee on Health Care for Underserved Women and the American Society of Addiction Medicine; 2012. p. 1–7.
48. Substance Abuse and Mental Health Services Administration. SAMHSA’s Concept of Trauma and guidance for a traumainformed approach. 2014. <https://store.samhsa.gov/system/files/sma14-4884.pdf>
49. Embree JA. Prevalence of suicide attempts in a deaf population with co-occurring substance use disorder. *JADARA*. 2019;45(2):1–15.
50. Anderson ML, Chang BH, Kini N. Alcohol and drug use among deaf and hard-of-hearing individuals: a secondary analysis of NHANES 2013–2014. *Subst Abus*. 2018;39(3):390–7.
51. Moore D, Li L. Prevalence and risk factors of illicit drug use by people with disabilities. *Am J Addict*. 1998;7(2):93–102.
52. Peters RH, Bartoi MG, Sherman PB. Screening and assessment of co-occurring disorders in the justice system. Delmar: GAINS Center; 1997.
53. Gates ML, Turney A, Ferguson E, Walker V, Staples-Horne M. Associations among substance use, mental health disorders, and self-harm in a prison population: examining group risk for suicide attempt. *Int J Environ Res Public Health*. 2017;14(3):317.
54. Peters RH, Wexler HK, Lurigio AJ. Co-occurring substance use and mental disorders in the criminal justice system: a new frontier of clinical practice and research. *Psychiatr Rehabil J*. 2015;38:1–6.
55. Maguen S, Metzler TJ, Bosch J, Marmar CR, Knight SJ, Neylan TC. Killing in combat may be independently associated with suicidal ideation. *Depress Anxiety*. 2012;29(11):918–23.
56. Institute of Medicine. Substance use disorders in the US armed forces. Washington, DC: National Academies Press; 2013. <https://www.nap.edu/catalog/13441/substance-use-disorders-in-the-us-armed-forces>.
57. Dickerson DL, Spear S, Marinelli-Casey P, Rawson R, Li L, Hser YI. American Indians/Alaska natives and substance abuse treatment outcomes: positive signs and continuing challenges. *J Addict Dis*. 2010;30(1):63–74.
58. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. *JAMA*. 2018;320(8):815–24.
59. Cain C. Personal stories: identity acquisition and self-understanding in alcoholics anonymous. *Ethos*. 1991;19(2):210–53.
60. Kaskutas LA. Alcoholics anonymous effectiveness: faith meets science. *J Addict Dis*. 2009;28(2):145–57.

61. Ferri M, Amato L, Davoli M. Alcoholics anonymous and other 12-step programmes for alcohol dependence. *Cochrane Database Syst Rev.* 2006;(3):CD005032.
62. Litten RZ, Wilford BB, Falk DE, Ryan ML, Fertig JB. Potential medications for the treatment of alcohol use disorder: an evaluation of clinical efficacy and safety. *Subst Abus.* 2016;37(2):286–98.
63. Reif S, George P, Braude L, Dougherty RH, Daniels AS, Ghose SS, Delphin-Rittmon ME. Residential treatment for individuals with substance use disorders: assessing the evidence. *Psychiatr Serv.* 2014;65(3):301–12.
64. Suter M, Strik W, Moggi F. Depressive symptoms as a predictor of alcohol relapse after residential treatment programs for alcohol use disorder. *J Subst Abus Treat.* 2011;41(3):225–32.
65. Mason BJ. Emerging pharmacotherapies for alcohol use disorder. *Neuropharmacology.* 2017;122:244–53.
66. Burchi E, Makris N, Lee MR, Pallanti S, Hollander E. Compulsivity in alcohol use disorder and obsessive compulsive disorder: implications for neuromodulation. *Front Behav Neurosci.* 2019;13:70.
67. Philip NS, Sorensen DO, McCalley DM, Hanlon CA. Non-invasive brain stimulation for alcohol use disorders: state of the art and future directions. *Neurotherapeutics.* 2020;17(1):116–26.
68. Fullerton CA, Kim M, Thomas CP, Lyman DR, Montejano LB, Dougherty RH, et al. Medication-assisted treatment with methadone: assessing the evidence. *Psychiatr Serv.* 2014;65(2):146–57.
69. Maglione MA, Raaen L, Chen C, Azhar G, Shahidinia N, Shen M, et al. Effects of medication assisted treatment (MAT) for opioid use disorder on functional outcomes: a systematic review. *J Subst Abus Treat.* 2018;89:28–51.
70. Oesterle TS, Thusius NJ, Rummans TA, Gold MS. Medication-assisted treatment for opioid-use disorder. *Mayo Clin Proc.* 2019;94:2072–86. <https://doi.org/10.1016/j.mayocp.2019.03.029>.
71. Jones JL, Mateus CF, Malcolm RJ, Brady KT, Back SE. Efficacy of ketamine in the treatment of substance use disorders: a systematic review. *Front Psych.* 2018;9:277.
72. Ezquerra-Romano II, Lawn W, Krupitsky E, Morgan CJ. Ketamine for the treatment of addiction: evidence and potential mechanisms. *Neuropharmacology.* 2018;142:72–82.
73. Young JR, Smani SA, Mischel NA, Kritzer MD, Appelbaum LG, Patkar AA. Non-invasive brain stimulation modalities for the treatment and prevention of opioid use disorder: a systematic review of the literature. *J Addict Dis.* 2020;38(2):186–99.
74. Sawynok J. The therapeutic use of heroin: a review of the pharmacological literature. *Can J Physiol Pharmacol.* 1986;64(1):1–6. <https://doi.org/10.1139/y86-001>. PMID: 2420426
75. Fischer B, Oviedo-Joekes E, Blanken P, Haasen C, Rehm J, Schechter MT, Strang J, van den Brink W. Heroin-assisted treatment (HAT) a decade later: a brief update on science and politics. *J Urban Health.* 2007;84(4):552–62.
76. Bernhardt N, Petzold J, Groß C, Scheck A, Pooseh S, Mayer-Pelinski R, Zimmermann US, Smolka MN, Pilhatsch M. Neurocognitive dysfunctions and their therapeutic modulation in patients with methamphetamine dependence: a pilot study. *Front Psych.* 2020;11:581.
77. Zweben JE, Cohen JB, Christian D, Galloway GP, Salinardi M, Parent D, Iguchi M. Psychiatric symptoms in methamphetamine users. *Am J Addict.* 2004;13(2):181–90.
78. Longo M, Wickes W, Smout M, Harrison S, Cahill S, White JM. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. *Addiction.* 2010;105(1):146–54.
79. Clark M, Featherstone R. Management of acute withdrawal and detoxification for adults who misuse methamphetamine: a review of the clinical evidence and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2019.
80. Morley KC, Cornish JL, Faingold A, Wood K, Haber PS. Pharmacotherapeutic agents in the treatment of methamphetamine dependence. *Expert Opin Investig Drugs.* 2017;26(5):563–78.

81. Colfax GN, Santos GM, Das M, Santos DM, Matheson T, Gasper J, Shoptaw S, Vittinghoff E. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. *Arch Gen Psychiatry*. 2011;68:1168–75.
82. Chaiton M, Diemert L, Cohen JE, Bondy SJ, Selby P, Philipneri A, Schwartz R. Estimating the number of quit attempts it takes to quit smoking successfully in a longitudinal cohort of smokers. *BMJ Open*. 2016;6(6):e011045.
83. Antonelli M, Fattore L, Sestito L, Di Giuda D, Diana M, Addolorato G. Transcranial magnetic stimulation: a review about its efficacy in the treatment of alcohol, tobacco and cocaine addiction. *Addict Behav*. 2021;114:106760.