Background

Definitions and Terminology

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines substance use disorders as a constellation of recurrent pathological cognitive, behavioral, and physiological symptoms arising from the ongoing use of a substance.[1,2] Previously used terms of abuse and dependence are not recommended now when describing persons with substance use disorders.

Predictors of Substance Use Disorders

Substance use disorders generally arise in adolescence, with both genetic and environmental factors clearly active in its development. Different drugs produce different effects on the user, but important shared features include a dysregulation of brain reward pathways and an overactive brain stress system, which together reinforce use of the substance to achieve a pleasurable high, even if pursuing this high incurs great cost or negative consequences for the user.[3] Research has demonstrated that neurobiological differences in self-control become evident in early childhood and may predispose some individuals to substance use disorders.[4] Although no specific neurological testing, imaging, or laboratory evaluation can accurately predict who will develop a substance use disorder, accurate identification of predictive markers remains an area of active investigation.

Data Sources for Substance Use in United States

A primary source of statistical information for substance use disorders in the general United States population originates from the National Survey on Drug Use and Health (NSDUH), which is an annual survey of the civilian, non-institutionalized population of the United States aged 12 years and older; the survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) within the Department of Health and Human Services, and was most recently published in September 2015.[5] Since its establishment in 1992, SAMHSA has led public health efforts to advance behavioral health, specifically tasked with making information, services, and research about substance use and mental illness more accessible. Prevalence estimates for substance use disorders in persons living with HIV infection are derived from several different published studies, as there is no comparable annual survey for the population of individuals living with HIV.

DSM-5 Classification

Amid considerable controversy, the DSM-5 has combined the DSM-IV categories of substance abuse and substance dependence under the single heading of substance use disorders, which is classified by severity based on the number of symptom criteria (out of a total of 11) that are met: mild (2 to 3 criteria), moderate (4 to 5 criteria), and severe (more than 6 criteria).[1,2]
Impaired Control

- Taking the substance in larger amounts and for longer than intended
- Wanting to cut down or quit but not being able to do it
- Spending a lot of time obtaining, using, or recovering from use of the substance
- Craving or a strong desire to use the substance

Social Impairment

- Repeatedly unable to carry out major obligations at work, school, or home due to substance use
- Continued substance use despite persistent or recurring social or interpersonal problems caused or made worse by substance use
- Stopping or reducing important social, occupational, or recreational activities due to substance use

Risk Use of the Substance

- Recurrent use of the substance in physically hazardous situations
- Consistent use of the substance despite acknowledgment of persistent or recurrent physical or psychological difficulties from using the substance

Pharmacologic Criteria

- Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount. (Does not apply for diminished effect when used appropriately under medical supervision)
- Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal (Does not apply when used appropriately under medical supervision)

Screening Tools

Although screening for alcohol abuse is often integrated in primary care settings, screening for abuse of other drugs is less standardized. The following summarizes available screening tools that can potentially be used to evaluate for cannabis use disorder:

- **DAST**: The Drug Abuse Screening Test (DAST), first developed in 1982, is available in 10-item, 20-item, and 28-item versions; all versions are self-administered and have moderate to high levels of sensitivity, specificity, and validity.[6] Answers to this test are binary (yes/no), with different cutoff scores recommended with different versions and different populations.[6] The length of this test has proven to be a barrier to primary care screening, however, and subsequently other instruments have been trialed.

- **CAGE**: Conjoint screening tests that inquire simultaneously about alcohol and other drugs are available; the CAGE-AID, for example, consists of the same 4 CAGE questions for alcohol that have been expanded in scope to include drug use.[7]

- **Opiod Risk Tool**: The Opiod Risk Tool (ORT) is an 11-item screening tool specifically for opioid addiction.[8]

- **TICS**: An even briefer, two-item conjoint screening, known as TICS, has a sensitivity and specificity of nearly 80% in detecting current substance abuse problems.[9] A single-question screen—“How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?”—has been proven to have similar sensitivity and specificity for the detection of drug use and drug use disorders as the lengthier DAST, and is superior to conjoint screening in that it specifically identifies drug
More recently, the 4-item Substance Use Brief Screen (SUBS) has become available for screening primary care patients for tobacco, alcohol, and other drug use.[10] This is the only brief, self-administered, comprehensive screening instrument test that has been validated in the primary care setting and may facilitate screening of primary care populations.[11]

- **ASSIST**: The World Health Organization (WHO) has also developed the ASSIST (Alcohol, Smoking, and Substance Involvement Screening Test) to detect substance use and related problems in the primary care setting.[12] The ASSIST covers 12 items related to recent and lifetime use, dependence symptoms, substance-related problems, and intravenous use and addresses 10 categories of substances (tobacco, alcohol, cannabis, cocaine, stimulants, inhalants, sedatives/hypnotics, hallucinogens, opiates, and “other drugs”). A disadvantage to this tool is its length, but it has been effectively modified for use as a routine screening tool in some clinical settings, and it may be especially useful for screening patient populations with heavier polysubstance use (i.e. persons with HIV infection) compared with other primary care populations. New technologies allowing for patient-reported outcomes may allow for more such screening tools to be incorporated efficiently into busy HIV primary care clinics.[13,14,15]

**Overview**

The extensive body of literature informing the DSM-5 classification of substance use disorders will be applied throughout this lesson to substance use disorders among persons with HIV infection. This Core Concept will review the epidemiology of substance use in persons with HIV infection, examine the risk factors that predispose individuals to substance use disorders, and discuss current diagnostic and treatment paradigms for the most common substance use disorders in the United States.
Epidemiology of Substance Use in United States

Estimates of Substance Use Disorders in the United States

Data from the 2014 National Survey on Drug Use and Health (NSDUH) found that approximately 21.5 million people (8.1% of the population) aged 12 years and older in the United States had a substance use disorder in the past year, including 17 million with an alcohol use disorder and 7.1 million with an illicit drug use disorder, and 4.2 million with a marijuana use disorder (Figure 1).[5] In the same year, according to the NSDUH, approximately 21% of persons aged 12 years and older in the United States were cigarette smokers.[5] Smoking estimates were slightly lower in the National Health Interview Survey (NHIS), another annual nationally representative survey, which reported that 17% of adults in the United States were current smokers in 2014.[16] This discrepancy is likely due to the fact that the NHIS collects data only for adults aged 18 years and older, whereas the NSDUH collects data for persons beginning at age 12. Both of these surveys likely underestimate the prevalence of substance use disorders because they omit homeless and incarcerated populations that have higher rates of substance use disorders than the general population.

Estimates of Substance Use Disorders in Persons with HIV

Multiple studies and surveys have demonstrated high rates of substance use among persons living with HIV infection in the United States.[17,18] For example, individuals with HIV smoke at more than twice the rate of those without HIV, and the prevalence of tobacco smoking among persons with HIV infection in some series is as high as 50 to 70%.[19] In addition, use of alcohol and other substances are higher in persons with HIV infection compared to the general population. Data from the HIV Cost and Services Utilization Survey (HCSUS), a national probability survey of adults with HIV infection receiving medical care in the United States in 1996, found that 40% of persons with HIV infection used illicit drugs other than marijuana, with 12% meeting criteria for drug dependence; heavy drinking was also found to be twice as common among people in care for HIV compared with the general population.[18,20] The Medical Monitoring Project (a surveillance system that assesses behaviors and clinical characteristics of persons with HIV infection who have received outpatient medical care) estimated that in the 2009 data collection cycle, 27% of persons with HIV infection used noninjection illicit drugs, 2% used injection drugs, and 12 to 18% engaged in binge drinking in the past 30 days.[21] Although the metrics used to evaluate substance use in each study are different, with some studies reporting use in the past 30 days and others reporting use in the past 3 or 12 months, it is clear that substance use is prevalent among persons with HIV infection and higher than in the general U.S. population.[17]
Impact of Substance Use Disorders on HIV Metrics

Substance Use Disorders and Impact on HIV Transmission

Recent studies have provided overwhelming evidence that persons with HIV who take antiretroviral therapy and consistently maintain undetectable plasma HIV RNA levels do not transmit HIV sexually to others, even with condomless sex.\[22, 23, 24\] Thus, any substance use problem that interferes with antiretroviral medication adherence can impact transmission of HIV and have a significant public health consequence. In particular, certain substance use disorders in persons with HIV have been consistently linked to decreased adherence with antiretroviral medications and to activities that enhance the likelihood of HIV transmission to sex and needle-sharing partners uninfected with HIV.\[25, 26, 27, 28\] For example, the Medical Monitoring Project found that 24% of individuals with HIV reported using alcohol with sex, and 12% reported using noninjection drug use with sex; in this same survey, among the individuals with HIV who used injection drugs, 67% used them in the context of sex.\[21\] The Multicenter AIDS Cohort Study reported that methamphetamine use increased the number of condomless anal receptive sex partners, and several other studies, including a review of 61 studies, confirmed that men with HIV who have sex with men and use methamphetamine are more likely to report sex activities that place them at higher risk of acquiring HIV, such as condomless anal intercourse, or being high on alcohol or drugs at last sex act with a non-main partner.\[29, 30, 31\]

Substance Use Disorders and Impact on HIV Care

Substance use also serves as a barrier to care for many individuals who abuse alcohol and illicit drugs.\[28, 32, 33\] Several studies have shown that persons with HIV infection who use illicit substances are more likely to miss clinic appointments, use the emergency room for care, have poor medication adherence, and experience food and housing insecurity.\[34, 35, 36\] Antiretroviral medication adherence problems in individuals with substance use may have serious consequences, including suboptimal virologic control and potential emergence of virologic resistance. Studies have shown that when individuals with HIV infection stop using illicit substances, health utilization and antiretroviral adherence patterns are similar to non-substance users; in particular, retention in opioid treatment programs by those who have opioid use disorders predicts long-term virologic success, thereby emphasizing the importance of securing access to substance use treatment programs.\[35, 37\]

Substance Use and HIV Disease Progression

Alcohol, tobacco smoking, and illicit drug use can also impact HIV disease progression independent of non-adherence behaviors. Tobacco smoking has been shown to increase immune activation and decrease T-cell function in persons with HIV infection, and current smokers are less likely to have an undetectable HIV viral load compared to smokers who quit.\[38, 39\] A study of women with HIV infection starting antiretroviral therapy found that smokers had poorer virologic and immunologic responses to antiretroviral therapy, greater virologic rebound and immunologic failure, higher risk of death, and higher rate of progression to AIDS.\[40\] Heavy alcohol use, crack cocaine, and heroin use all have been linked to immune dysregulation, lower CD4 cell counts, impaired viral control, and higher AIDS-related mortality.\[41, 42, 43, 44, 45, 46, 47\] Methamphetamine has been shown to increase HIV replication in animal models.\[48\] An exception to this pattern is that cannabis has recently been found to lower HIV plasma viral load through its immunomodulatory properties, although its effect on disease progression is unknown.\[49\]
Tobacco Use Disorder

Tobacco Use Prevalence Among US Adults

Tobacco use is a worldwide epidemic and is the leading preventable cause of death, disease, and disability in the United States. The National Health Information Survey found that the prevalence of smoking among U.S. adults in 2014 was 16.8%, which represents a decline from 20.9% in 2005 (Figure 2). Significant disparities in smoking prevalence persist, with highest prevalence rates in Native Americans/Alaskan Natives, multiracial adults, persons living under the poverty line, and those with lowest educational attainment. Although cigarette smoking has declined, the prevalence of other tobacco use (cigars, smokeless tobacco) has not changed, with 21.3% of U.S. adults using some sort of tobacco product every day.

Tobacco Use Prevalence in Adults with HIV Infection

Individuals with HIV smoke at more than twice the rate of those without HIV. Among persons with HIV who engaged in medical care in 2009, 42.4% were current smokers, 20.3% were former smokers, and 37.3% had never smoked. In addition, adults with HIV are less likely to quit smoking compared with the general adult population.

Risk Factors

Individuals with psychiatric and/or other substance use disorders are at increased risk of smoking, and smoking rates have declined significantly less among persons with mental illness compared with those without mental illness. In addition, tobacco use disorder has a strong degree of heritability, and differences in nicotine blood levels and nicotine metabolism varies among individuals, especially among certain ethnicities (i.e. African American males have higher blood nicotine levels for a given number of cigarettes).

Screening and Treatment

Tobacco use is typically a chronic problem and often requires behavioral support, pharmacologic therapy, and multiple attempts to quit. The U.S. Preventive Services Task Force (USPSTF) issued an updated recommendation statement in 2014 on Behavioral and Pharmacotherapy Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Women. The key points in this recommendation are summarized as follows:

- The 5A’s: Ask about tobacco use at every visit, Advise all tobacco users to quit, Assess willingness to quit, Assist the patient in quitting (medications, counseling), and Arrange follow-up contact.
- Physician and nurse counseling, as well as telephonic tobacco counseling, have been effective as a component of smoking cessation programs.
- Nicotine replacement therapy, sustained-release bupropion, and varenicline all reliably increase long-term smoking abstinence rates when compared with placebo.
- Combining two types of nicotine replacement therapy increases abstinence rates more than use of a single nicotine replacement therapy.
- Abstinence rates for individuals using nicotine replacement therapy versus bupropion SR or varenicline do not differ significantly.
- Four studies have found lower abstinence rates with bupropion SR compared with varenicline, but the results did not reach statistical significance in all studies.
- The combination of behavioral interventions and pharmacotherapy appears to be more effective than either approach alone.
- There are no high-quality studies that evaluate the efficacy of using e-cigarettes (also referred to as electronic nicotine delivery systems, or ENDS) for smoking cessation; the two
available studies, which were conducted outside the United States, had conflicting results on abstinence rates.

- For pregnant women who smoke, the USPSTF recommends behavioral interventions but found insufficient safety and efficacy data to recommend the use of any pharmacologic treatments.
- For smokers who are not yet ready to quit using tobacco products, harm reduction strategies are gaining increasing research support, including long-term use of nicotine replacement products or smoke-free products, which are a safer alternative to tobacco smoking.

Of note, the USPSTF guideline includes several different strategies under the heading of behavioral interventions, including in-person counseling and support, telephone counseling, provision of self-help materials, and motivational interviewing.[57] Intensive counseling has been found to be more effective than brief counseling, and several studies of internet-based and mobile phone-based interventions have shown positive results.[58,59] A Cochrane review found that motivational interviewing, which is a patient-centered style of communication that is aimed to help people explore and resolve ambivalence about behavior change, may be helpful in assisting patients to quit smoking.[60] In a recent randomized control trial that compared motivational interviewing to brief advice or health education, however, motivational interviewing was only somewhat more effective than brief advice and less effective than delivering health education, which is a less complex and more practical intervention for most primary care settings.[61] The 2008 USPSTF clinical practice guideline for treating tobacco use and dependence provided specific suggestions for the clinical use of pharmacotherapies for smoking cessation (Table 1).[56] Additional information for providers, including advice on how to integrate tobacco cessation into office practice, guides for group visits and pharmacologic therapies, and coding and billing tools, is available through the Patient Care resource for Tobacco and Nicotine Prevention and Control on the website of the American Academy of Family Physicians.

**Treatment Considerations for Persons with HIV Infection**

Unfortunately, there is a lack of randomized controlled trial data evaluating the efficacy of interventions for smoking cessation in this population, and the HIVMA Primary Care Guidelines do not address specific interventions related to smoking cessation. There are no significant drug interactions between varenicline and antiretroviral medications, though interactions can occur between bupropion and antiretroviral medications that may result in lower bupropion levels.
Alcohol Use Disorder

Prevalence among Adults in U.S.

The 12-month prevalence for alcohol use disorder among the general United States adult population in 2014 was 12.3% for adults aged 18 to 25 years, and 5.9% for adults aged 26 years and older.\[5\] In addition, 11.7% of current adult users aged 12 years and older report heavy alcohol use, defined as drinking 5 or more drinks on the same occasion on 5 or more days in the last month. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) recommends that women of all ages and men older than 65 years consume no more than seven alcoholic drinks per week and no more than three per day (men age 65 years and younger should consume no more than 14 drinks per week and no more than 4 drinks per day); these limits reflect the fact that people who drink over recommended limits, even if they do not meet criteria for alcohol use disorder, are at significant risk for alcohol-related problems.\[62\]

Prevalence among Adults with HIV Infection in U.S.

Literature reviews suggest a similar prevalence rate of current alcohol use disorder among persons with HIV, but higher lifetime prevalence rates. In the HIV Cost and Services Utilization Study (HSCUS), which was the first representative study to provide estimates of alcohol use among persons receiving medical care for HIV, 53.4% of adults with HIV reported drinking alcohol in the past 4 weeks, which is similar to the overall drinking rate among U.S. adults.\[20\] In this study, however, 8% of the survey respondents with HIV reported heavy drinking (defined as 5 or more drinks on at least 4 days in the previous month), which is double the national average for heavy drinking.\[20\] The Medical Monitoring Project, reporting data from the 2009 to 2010 period, found similar rates to the initial HSCUS: 50.7% of persons with HIV engaged in medical care drank alcohol in the past 4 weeks (with an average daily consumption of 3.1 drinks), and even more individuals reported binge drinking in the past 30 days (17.8% of men and 12.6% of women) when compared with those in the HSCUS survey.\[21\]

Risk Factors

Alcohol use disorder has a significant genetic component, with rates three to four times higher in individuals with a close relative with alcohol use disorder.\[63\] The risk for developing alcohol use disorder also depends on personal experiences with alcohol, peer influences, cultural attitudes toward drinking, and personal strategies for coping with stress.\[2\] Individuals with bipolar disorder, impulsivity, schizophrenia, personality disorders, anxiety, and depression are also at increased risk for developing an alcohol use disorder.

Screening Tools

Multiple screening instruments have been developed to identify patients with alcohol use disorders who present in primary care settings. Two instruments perform consistently better than others: the CAGE and AUDIT.\[64\] The CAGE is a 4-question screening test that works well at detecting lifetime alcohol abuse and dependence, but is not sensitive for detecting heavy drinking and does not distinguish between past and present alcohol use.\[64, 65\] In comparison, the AUDIT (Alcohol Use Disorders Identification Test) is a 10-item questionnaire that was developed specifically to identify heavy drinking in addition to alcohol abuse and dependency. The AUDIT better identifies at-risk, harmful, or hazardous drinking patterns.\[64\] A brief, 3-item version of the full AUDIT, called AUDIT-C, has been found to have similar sensitivity and specificity as the full AUDIT for detecting hazardous drinking.\[64, 65\] The National Institute of Alcohol Abuse and Alcoholism (NIAAA) recommends a single prescreening question about binge drinking for individuals who drink any alcohol at all; any individual with one ore more days of heavy drinking in the past year is considered an at-risk drinker.\[66\]
Screening Recommendations

The United States Preventive Services Task Force (USPSTF) recommends screening all patients aged 18 years and older for alcohol misuse in the primary care setting.[67,68] The USPSTF recommends using the AUDIT, AUDIT-C, or NIAAA single prescreening binge drinking question. The USPSTF also recommends that patients who screen positive for risky or hazardous drinking should be provided with brief behavioral counseling interventions (these include face-to-face, web-based, telephonic, or written counseling materials, and can last from 5 to 15 minutes); this recommendation is informed by a robust systematic review demonstrating the efficacy of behavioral counseling interventions in improving behavioral outcomes, including reducing overall consumption as well as reducing heavy drinking days.[67,68].

Diagnostic Criteria

The DSM-5 defines alcohol use disorder by the presence of at least two symptoms (from a list of 11 symptoms as defined in the DSM-5) related to evidence of impaired control, social impairment, risky use, and pharmacological criteria. Many more individuals will meet criteria for at-risk drinking, which includes drinking more than 4 drinks per day (or more than 14 in a week) for men and more than 3 drinks per day for women (or more than 7 per week).[66]

Treatment Considerations

Evidence shows that combining psychosocial interventions with pharmacotherapy is the optimal approach for treating alcohol use disorders.[69,70,71] There are four U.S. FDA-approved medications for the treatment of alcohol use disorder: acamprosate, disulfiram, oral naltrexone, and extended-release naltrexone injection (Figure 4).[72,73] Although there have been many studies comparing one or more medications with placebo, and some studies comparing individual medications to one another, there is no conclusive data to support the choice of one particular agent over another and so the choice of agent should be guided by patient characteristics and preference.[71,74,75] This also applies to individuals with HIV infection since there are no specific guidelines for pharmacologic treatment of alcohol use disorders in persons with HIV. Naltrexone has been shown to be safe for use in individuals with HIV infection and even potentiates the anti-HIV activity of some antiretroviral medications.[76,77,78] To guide clinicians in primary care and general medical settings in the proper medication treatment of alcohol use disorders, the Substance Abuse and Mental Health Services Administration (SAMHSA) has published a Treatment Improvement Protocol,[75] and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) has published a Clinician’s Guide entitled “Helping Patients Who Drink Too Much”. [66] Medication treatments for alcohol use disorder are the same for persons with HIV infection as for those without HIV infection.

Acamprosate

Acamprosate is an oral medication approved by the U.S. FDA in 2004 for the maintenance of abstinence from alcohol in patients dependent on alcohol who are abstinent at treatment initiation. The mechanism of action of acamprosate is not well understood, but it is thought to counteract imbalances that occur between the glutamatergic and GABAergic systems associated with chronic alcohol exposure and alcohol withdrawal; the primary beneficial effect of acamprosate to reduce the negative symptoms in the period that follows soon after alcohol withdrawal.[73,79] The recommended dose of acamprosate is 666 mg three times daily (given as two 333 mg delayed-release tablets three times daily). Although evidence with acamprosate has been mixed, a large meta-analysis of randomized, placebo-controlled trials found that acamprosate had a small but significant effect on promoting abstinence compared with placebo—eight people would need to be treated to achieve one additional case of abstinence (NNT=7.5).[80] Trials in Europe have shown more benefit with acamprosate than those conducted in the United States, for unknown reasons (Figure 5).[81,82] Several advantages with acamprosate include good patient tolerance, ability to
use in patients with liver disease, no tapering of doses required at the time of discontinuation, minimal overdose risk, and ability to use concomitantly with opioid therapy. The most common side effect is diarrhea. A baseline evaluation of renal function should be performed prior to prescribing acamprosate and severe renal impairment (creatinine clearance less than or equal to 30 mL/min) is a contraindication for the use of acamprosate. For individuals with moderate renal impairment (creatinine clearance 30-50 mL/min), the dose of acamprosate should be reduced to 333 mg three times daily. There are no identified drug interactions between acamprosate and antiretroviral therapies used to treat HIV.

**Disulfiram**

Disulfiram was FDA-approved in 1951 as the first medication approved to treat alcohol dependence. Disulfiram is taken as an oral medication once daily on a regular basis. Disulfiram works by blocking the enzyme aldehyde dehydrogenase (Figure 6), which results in acetaldehyde levels rising within 10 to 30 minutes of alcohol ingestion, thereby triggering a “disulfiram-alcohol reaction”. The nature of this reaction varies based on individual characteristics of the patient, as well as on the amounts of alcohol and disulfiram consumed, and symptoms can range from sweating and tachycardia to respiratory collapse, seizures, and death. Disulfiram is meant to act as a deterrent to further alcohol consumption, and disulfiram has been shown to be effective, particularly in supervised treatment settings. The first dose of disulfiram should not be administered until the individual has been abstinent for at least 12 hours or they have a documented blood alcohol level of zero. The initial dosing is 500 mg once daily for 2 weeks and then maintenance dosing is given; the average maintenance dose is 250 mg per once daily and range is 125 to 500 mg once daily. Rare side effects with disulfiram include optic neuritis, peripheral neuropathy, polyneuritis, and hepatitis. There are multiple potential drug interactions that can occur with disulfiram, including medical contraindications to its use, so patients who are considering disulfiram should be carefully screened and counseled about the medication’s risks and benefits. Of particular importance to persons with HIV infection, certain antiretroviral medications affect disulfiram levels: efavirenz has been shown to increase the activity of disulfiram on aldehyde dehydrogenase while atazanavir decreases the activity of disulfiram. Disulfiram should not be used in patients taking ritonavir oral solution, as this formulation contains alcohol and may precipitate an alcohol-disulfiram reaction. Despite these interactions, disulfiram remains a viable option for the treatment of alcohol disorders for some persons with HIV infection.

**Naltrexone Oral and Extended-Release Injectable Naltrexone**

Naltrexone is an opioid antagonist that mediates the rewarding effects of alcohol and attenuates cravings. Although the exact mechanism of how naltrexone works to reduce alcohol consumption is not completely understood, the presumed major effect is via blockade of opiate receptors that play a role in the reward effects of alcohol. Naltrexone is currently available both as oral naltrexone (50 mg once daily) and extended-release injectable naltrexone (380 mg IM every 4 weeks). Oral naltrexone was approved by the U.S. FDA in 1994 for alcohol dependence or alcoholism. In a large, meta-analysis of randomized, placebo-controlled trials, oral naltrexone was found to have a small but significant effect in reducing craving and relapse: nine people would need to be treated to prevent one additional case of return to heavy drinking (NNT=9). Most of the studies in this meta-analysis were published prior to the U.S. FDA approval in 2006 of extended-release injectable naltrexone. Subsequently, two multi-center, double-blind, placebo-controlled trials in the United States confirmed that extended-release injectable naltrexone can reduce heavy drinking and increase abstinence rates (Figure 7). In these trials, however, the secondary outcomes in each trial were not as promising: one trial showed no difference in the time study subjects returned to heavy drinking and the other trial showed no reduction in risky drinking. Advantages observed with naltrexone include mild side effects (particularly nausea) and low abuse potential. There is a black box warning about potential hepatotoxicity with use of both forms of naltrexone, but the risk appears to be small and linked to higher doses of the medication as well as to underlying liver disease. Furthermore, the risk of liver toxicity is likely lower.
with injectable naltrexone since it avoids first-pass liver metabolism. Because of its mechanism of action that includes blocking opiate receptors, neither oral nor injectable naltrexone should be used in patients who use opioids or receive treatment with methadone or buprenorphine. Naltrexone given to someone actively using opiates could precipitate severe drug withdrawal. In addition, patients who discontinue naltrexone can subsequently have enhanced effects of opiates. There are no clinically significant drug interactions between naltrexone and antiretroviral medications used for the treatment of HIV.

**Topiramate**

Topiramate is not currently approved for treatment of alcohol use disorder, but multiple studies support its efficacy for improving abstinence rates and reducing alcohol craving, heavy drinking, and gamma-glutamyl transferase (GGT) levels (a biomarker of alcohol use). In addition, topiramate has also been shown to reduce smoking in alcoholic smokers.

**Gabapentin**

Gabapentin is also not yet approved for treatment of alcohol use disorder but may be another effective treatment option. In a 12-week, double-blind, placebo-controlled trial involving 150 participants, gabapentin (900 mg to 1800 mg/day) was found to be safe and effective in treating alcohol dependence (and reducing relapse-related symptoms including insomnia, dysphoria, and craving).
Cannabis Use Disorder

Prevalence of Cannabis Use Disorder

Cannabis (marijuana) is the most widely used psychoactive substance in the United States, with a 12-month prevalence estimate in 2014 of 4.9% among adults aged 18 to 25 years, and 0.9% among adults aged 26 years and older.[5] Reported lifetime prevalence (“ever used”) is 8.5%.[95] Several multicenter cohorts in the United States have found marijuana prevalence rates among persons with HIV that ranged from 24 to 38%, though these data do not distinguish between cannabis use and cannabis use disorder.[28,96]

Risk Factors

Risk factors for cannabis use disorder include being male, Native American, divorced or widowed, and having lower income.[5] In addition, mood disorders, anxiety disorders, and personality disorders are positively associated with cannabis use disorder, as are alcohol and other substance use disorders. Conduct disorder in childhood is a risk factor for the development of cannabis use disorder (as well as other substance use disorder), as is an unstable home environment and having a family member with cannabis use disorder.

Diagnostic Criteria

The DSM-5 defines cannabis use disorder by the presence of at least two symptoms (from a list of 11 symptoms as defined in the DSM-5) related to evidence of impaired control, social impairment, risky use, and pharmacological criteria.

Treatment Considerations

No medications have been shown to be consistently effective for the treatment of cannabis use disorder; buspirone was effective in one clinical trial but overall, anxiolytics and antidepressants (SSRIs, mixed action, and atypical) have not been proven to improve cannabis dependence.[97,98] Cognitive behavioral therapy and motivational interviewing or motivational enhancement therapy have been shown to improve outcomes (cannabis use, severity of dependence, cannabis problems).[99] Several programs have been established to help guide treatment of cannabis users, including the brief marijuana dependency counseling (BMDC) program; this is a 12-week multidisciplinary intervention developed by the Center for Substance Abuse Treatment that involves motivational enhancement therapy, cognitive behavioral therapy, and case management.[100] SAMHSA has also developed Brief Counseling for Marijuana Dependence: A Manual for Treating Adults – 2005.[101] Separate resources are available for treatment of youth with cannabis use disorders.
Stimulant Use Disorder

Prevalence among U.S. Adults

The 12-month prevalence for cocaine use disorder in 2014 was 0.5% among adults ages 18 to 25 years, and 0.3% among adults older than 26 years.[5] The 2014 National Survey on Drug Use and Health (NSDUH) does not include rates for amphetamine-type use disorder, but it does report usage data: in 2014, 0.2% of adults aged 18 to 25 years, and 0.2% of adults aged 26 years and older, reported methamphetamine use. According to 12-month prevalence estimates in the DSM-5 (which was published in 2013), amphetamine-type stimulant use disorder among adults 18 years of age and older was 0.2%.[2]

Prevalence among U.S. Adults with HIV Infection

Estimates of cocaine use among adults with HIV are disparate; in a longitudinal cohort of persons with HIV engaged in care at 8 clinical sites, 8.5% reported crack-cocaine use, whereas other cohort studies with inclusion criteria that favored higher numbers of drug users have found cocaine usage rates of up to 40 to 50%. [28, 42, 96] Estimates of methamphetamine use among adults with HIV range from 10 to 23%, though even higher rates have been found in men with HIV who have sex with men.[102] One study conducted among men who have sex with men in Los Angeles found very strong associations between methamphetamine use and HIV, with an HIV prevalence rate of 42% in men who have sex with men who used methamphetamine at least once per month for 6 months. The highest HIV prevalence rates were found among men who have sex with men seeking intensive outpatient treatment and residential treatment (61% and 85%, respectively).[103]

Risk Factors

Risk factors for stimulant use disorder include psychiatric comorbidities (in particular, bipolar disorder, schizophrenia, and antisocial personality disorder), other substance use disorders, prenatal exposure to cocaine, experiencing community violence in childhood, and living in an unstable home.[2] Men who have sex with men also represent a discreet risk group for stimulant use disorder, particularly methamphetamine use and its associated high-risk sexual behavior.[104, 105, 106]

Screening Tools

As noted earlier, a variety of screening instruments are available for detecting drug use and dependency. Instruments range from comprehensive inventories (DAST), to 4-item and 2-item conjoint screening tests for both alcohol and drug use (CAGE-AID, TICS), to single-question screening.[6, 7, 9, 10] The 4-item Substance Use Brief Screen (SUBS) may offer the best option for brief yet comprehensive screening for past-year unhealthy stimulant use in primary care populations.[11]

Diagnostic Criteria

The DSM-5 category of stimulant use disorder includes problems associated with the use of one or more of the following substances: methamphetamine, amphetamines or cocaine (but not caffeine or nicotine). The DSM-5 defines stimulant use disorder by the presence of at least two symptoms (from a list of 11 symptoms as defined in the DSM-5) related to evidence of impaired control, social impairment, risky use, and pharmacological criteria.

Treatment Considerations

Behavioral strategies, including cognitive behavioral therapy, motivational interviewing, and contingency management (a system of providing incentives for positive reinforcement, such as
delivery of vouchers in exchange for abstinence) are the primary intervention for stimulant use disorders, though no single approach has been proven to be most effective.[107,108] The Substance Abuse and Mental Health Services Administration (SAMHSA) developed an intensive, outpatient cognitive-behavioral treatment approach called the Matrix Model, which has been effectively tailored to meet the needs of different populations (men who have sex with men, for example).[109,110] Materials about the Matrix Model are available from SAMHSA but are geared toward counselors and substance users, rather than primary care providers. No pharmacologic treatment has been approved for the treatment of stimulant use disorder. Multiple medications have been investigated, including antipsychotics (risperidone, olanzapine, reserpine, aripiprazole, psychostimulants (dexamphetamine, bupropion, methylphenidate, modafinil, antidepressants, baclofen, and ondansetron; to date, none have been proven effective at achieving abstinence though there have been significant methodological limitations to the studies, including small numbers of patients and patients with mixed substance use disorders.[111,112,113] One small study evaluating whether mirtazapine would decrease methamphetamine use among men who have sex with men did have positive results, finding that participants assigned to mirtazapine therapy had fewer methamphetamine-positive urine tests compared with participations taking placebo, despite low-to-moderate medication adherence.[114] In general, there is a high rate of relapse among individuals who complete methamphetamine treatment programs.[115]
Opioid Use Disorder

Prevalence among U.S. Adults

The 12-month prevalence of heroin use disorder in 2014 was 0.5% among adults aged 18 to 25 years and 0.2% among adults aged 26 and older, and the 12-month prevalence of pain reliever use disorder was 1.2% among adults aged 18 to 25 and 0.6% among adults aged 26 years and older. These numbers likely underestimate the true prevalence of these opioid use disorders due to the large proportion of incarcerated persons who struggle with this disorder.[5] Even so, the rate of past-year heroin use among non-Hispanic whites increased 114% between the 2002 to 2004 period and the 2011 to 2013 period.[116] The rate of heroin use has also increased sharply in the 18 to 25 year-old age group and is rising faster among women than men, though men still have overall higher rates of heroin use.[116] Non-medical use of opioid prescription medication has emerged as a particularly alarming problem in the United States in recent years, especially among young people. There has been a 250% increase in prescription drug abuse (opioids are the most commonly abused prescription drug) over the past 20 years and in 2013, 13% of 12th graders reported lifetime prescription opioid abuse.[117,118] The opioid epidemic is now having a significant impact on mortality statistics, particularly among persons in the 25 to 34-year-old age group and those living in certain geographic regions (West Virginia, New Mexico, New Hampshire, Kentucky, and Ohio had the highest rates in 2014).[119] The Centers for Disease Control and Prevention (CDC) has reported that since 2000, the rate of death from drug overdoses has risen 137%, including a 200% increase in the rate of overdose deaths involving opioids.[119] Of note, the rate of overdose deaths rose by 6.5% in just one year between 2013 and 2014, with 61% of the overdose deaths attributed to opioids.[119]

Prevalence among U.S. Adults with HIV Infection

The most recent National HIV Behavioral Surveillance System (NHBS) reported that the HIV prevalence among persons who inject drugs is 9%, which is more than 10 times the HIV prevalence in the United States overall; in the NHBS, most persons who were injecting drugs were injecting heroin, and most injected it on a daily basis.[120,121] Looking at opioid use more specifically among individuals with HIV, one multisite study reported a 14% prevalence of heroin use during the prior 12 months.[96] Another survey that examined overall drug use among individuals with HIV reported 3-month prevalence rates of 2% for opiate use, 10% for polydrug use (including heroin as one of the drugs), and 4% for injection drug use.[28] Interpretation of these data is complicated because injection drug use was not always distinguished from opioid use, and the studies inconsistently accounted for polydrug use, which typically includes heroin. Opioid use has also been linked to HIV epidemics in rural populations historically at low risk for HIV, illustrating the syndemic nature of this problem. For example, an outbreak of HIV in southeastern Indiana in 2015 was traced to syringe-sharing partners who were injecting the prescription opioid, oxymorphone.[122] Unlike previous epidemics of HIV among persons injecting drugs, which typically involved black urban men older than age 35, the Indiana outbreak reflected the demographics of the current opioid epidemic and was concentrated in white, rural, younger persons, half of whom were women.

Risk Factors

Genetic and environmental factors appear to predispose individuals to substance use disorders but clearly correlate with the development of an opioid use disorder. Heroin use disorders have traditionally been associated with ethnic minority populations in low-income settings, but are now becoming more common among white middle-class individuals (especially teenagers and women) as a consequence of nonmedical prescription-opioid use and increased heroin availability.[2,123] Other risk factors for heroin use include living in a populated city and other substance use within the previous year; in particular, abuse or dependency on opioid pain relievers is the strongest risk factor for developing a heroin use disorder.[116] Nonetheless, it is important to recognize that only a small percentage of individuals who use nonmedical prescription opioids initiate heroin use; other factors,
including the low cost of pure heroin, are contributing to the growing epidemic.[123]

**Screening Tools**

As noted earlier, a variety of screening instruments are available for detecting drug use and dependency. Screening instruments include the 10-item Drug Abuse Screening Test (DAST), the 11-item Opioid Risk Tool (ORT), the 4-item and 2-item conjoint screening tests for both alcohol and drug use (CAGE-AID and TICS), and the single-question screening.[6,7,9,10] The 4-item Substance Use Brief Screen (SUBS) may offer the best option for brief yet comprehensive screening for past-year unhealthy drug use in primary care populations.[11]

**Diagnostic Criteria**

The DSM-5 defines opioid use disorder by the presence of at least two symptoms (from a list of 11 symptoms as defined in the DSM-5) related to evidence of impaired control, social impairment, risky use, and pharmacological criteria.

**Treatment Considerations**

Opioid use disorder is a medical disorder, and medication-assisted treatment plays a central role in helping patients overcome this disorder. In contrast, behavioral interventions and/or detoxification, without medication-assistant treatment, have poor outcomes with high rates of relapse.[124,125] Pharmacologic therapies for opioid use disorder include three categories: opioid agonists, opioid partial agonists, and opioid antagonists.[126] Opioid agonists and partial agonists are used for maintenance therapy (also called opioid replacement therapy or opioid substitution therapy). The Substance Abuse and Mental Health Services Administration (SAMHSA) has published a Treatment Improvement Protocol (TIP 43) for medication-assisted treatment for opioid use disorders.[127] A brief overview of the key medication options is provided below, but providers interested in offering medication-assisted treatment for opioid addiction should consult the TIP and also their local addiction specialists.

**Methadone Maintenance Therapy**

Methadone maintenance therapy is the most established form of treatment for opioid dependency and involves daily dosing of methadone through a methadone clinic; treatment is usually for 12 months or longer, with longer duration of treatment associated with greater likelihood of abstinence.[128] Methadone is a synthetic long-acting opioid agonist, which has a half-life of 24 to 36 hours and is usually administered daily when used as opioid replacement therapy.[127] Methadone relieves drug-craving, withdrawal symptoms, dampens the euphoric and sedating effects of heroin, and, at stable dosages, does not cause euphoria or sedation. Methadone is available in many formulations but the liquid form is typically used in the United States. Standard initiation dosages of methadone are low, but are titrated upward to achieve reduced symptoms of withdrawal without sedation. The goal for methadone dosing is generally in the 60 to 120 mg per day to eliminate the craving for heroin.[129] Methadone is a relatively safe drug, and when used during maintenance therapy, the most common adverse events are perspiration and constipation.[5] Additional possible complications of methadone maintenance therapy include cardiovascular effects (prolongation of QT interval and torsade de points), respiratory depression, decreased sexual function, and central nervous system effects.[127,130] Methadone maintenance therapy is associated with significantly reduced heroin use and has been found to be superior to buprenorphine (discussed below) in retaining people in treatment.[131] Whether methadone or buprenorphine is selected, improved outcomes appear to be correlated with a lower treatment threshold, flexible dose titration and duration of therapy that is focused on a harm reduction (i.e. retaining patients in care even in the setting of poor adherence to therapy) rather than on abstinence alone.[132]
Buprenorphine and Buprenorphine-Naloxone

Buprenorphine is a partial opioid agonist that can be prescribed in an outpatient office setting to reduce the craving and use of opioids and it offers a better safety profile than methadone.[133] Buprenorphine has high opioid receptor affinity, allowing it to block other opioids. The half-life of buprenorphine is 4 to 6 hours; it can be prescribed for use on a daily basis; if the dose is doubled or tripled, dosing can be extended to every other day or three-times weekly.[127] Typical doses of buprenorphine range from 8 to 16 mg daily, which is equivalent to approximately 60 mg of methadone.[127] A buprenorphine-naloxone fixed dose formulation (8 mg/2 mg and 2 mg/0.5 mg) is also available to decrease the risk of abuse, diversion, and overdose (since naloxone is an opioid antagonist that blocks the opioid activity of buprenorphine if it is injected).[126,134] In 2004, the SAMHSA CSAT issued Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction that addresses key issues related to prescribing buprenorphine; this publication has not been updated since 2004.

- **Physician Requirement**: Physicians interested in providing buprenorphine or buprenorphine-naloxone treatment in their practice settings need to receive a waiver from the Center for Substance Abuse Treatment (CSAT). Most physicians without prior addiction certification will need to complete 8 hours of training on the treatment of opioid-addicted patients and these trainings are now offered online or at all-day conferences.
- **Nurse Practitioners and Physician Assistants Requirement**: In July 2016, section 303 of the Comprehensive Addiction and Recovery Act (CARA) was signed into law and this legislation provides nurse practitioners and physician assistants the ability to apply for a waiver to prescribe buprenorphine and/or buprenorphine-naloxone if they have completed the 24 hours of required training. This waiver process requires completion of the Waiver Notification Form and submission of copies of training certificates. For detailed information regarding this process see (1) the SAMSA information page Qualify for Nurse Practitioners and Physician Assistants Waiver and (2) the American Society of Addiction Medicine (ASAM) resource page Nurse Practitioners and Physician Assistants Prescribing Buprenorphine.
- **Buprenorphine Treatment Practitioner Locator**: The SAMHSA Buprenorphine web site provides a state-by-state Buprenorphine Treatment Practitioner Locator for medical providers authorized to treat opioid addiction with buprenorphine; this site it also provides links to buprenorphine training.

Naltrexone

Naltrexone is an opioid antagonist that is FDA-approved for relapse prevention of opioid use disorder and works by inhibiting the euphoric response to opioids.[126] Two formulations are available—naltrexone oral and extended-release naltrexone injection formulation. Naltrexone is well tolerated and does not carry a risk of abuse or overdose. A 50 mg dose of naltrexone attenuates or blocks opioid effects for 24 hours, and a 100 to 150 mg dose blocks opioid effects for up to 72 hours.[127] A large meta-analysis found that naltrexone was no more effective than placebo, even when combined with psychotherapy, but studies with the extended-release injectable formulation are more promising; two randomized controlled trials in Russia have demonstrated improved rates of retention in treatment and abstinence from opioid use with naltrexone-SR.[135,136]

Treatment Considerations for Persons with HIV

Because HIV primary care providers can obtain certification to prescribe buprenorphine, this medication option offers a significant advantage to persons with HIV who inject drugs, as they can now potentially receive comprehensive care for both their HIV and opioid use disorder from their primary HIV medical care provider.[137] Through the Buprenorphine and HIV Care Evaluation and Support Initiative (BHIVES), numerous studies have been published on efforts to integrate buprenorphine treatment into HIV care settings, with mixed success. [138,139] Challenges to integrated care have included lack of clinical support staff, administrative obstacles, competing
physician activities, stigma, and difficulties reaching marginalized patients.[140] Reimbursement problems, training and workforce deficits, and practical barriers to implementation, such as incorporating new procedures (i.e. urine toxicology) into established routines, are additional barriers.[141] Some models, however, found considerable success and have dramatically scaled up access to opioid substitution therapy in underserved communities that have high risk for opioid addiction. The Massachusetts Model of Office-Based Opioid Treatment with Buprenorphine (OBOT-B), which has been implemented into 14 community health centers across the state, provides a particularly successful model that relies on collaboration between nursing case managers and prescribing physicians.[140]

Among individuals with HIV who inject drugs, buprenorphine has been linked to improved engagement in care, and it is clear that mortality is lowest when antiretroviral therapy and opioid treatment are prescribed jointly.[142,143] Opioid substitution therapy with either methadone or buprenorphine is safe in individuals with HIV, as long as medication prescribers are aware of the relevant drug interactions that can raise or lower levels of opioid therapy. Several key drug interactions can potentially occur with the use of opioid replacement therapy and antiretroviral medications as summarized in the following list:[137]

- Possible opioid withdrawal from methadone can occur when individuals are taking certain non-nucleoside reverse transcriptase inhibitors or protease inhibitors; clinically relevant pharmacokinetic effects have been documented with efavirenz, nevirapine, rilpivirine, darunavir, atazanavir and lopinavir-ritonavir.
- Atazanavir should always be boosted with ritonavir if buprenorphine is administered.
- Cobicistat-boosted protease inhibitors have not been studied in combination with opioid substitution therapies.
- There are no significant pharmacokinetic interactions between methadone or buprenorphine and the integrase inhibitors raltegravir and elvitegravir; interactions between opioid substitution therapy with either dolutegravir or bictegravir have not been studied.
- Potential toxicity can occur when coadministering zidovudine with methadone.

### Harm Reduction Approach

Opioid substitution therapy is one of several practices that follow a harm reduction philosophy. Other such practices include syringe services, HIV prevention education, and overdose prevention strategies.

#### Syringe Services

The use of sterile needles and injection equipment, with each fix, is the most effective way for injection drug users to limit their risk of acquiring and transmitting HIV infection. With only minor exceptions, federal funding for needle exchange programs in the United States was prohibited from the 1980s until Congress modified this restriction in late 2015. Needle exchange (also called syringe services) remains a controversial topic. Opponents of syringe services argue that providing these programs condones and even encourages drug use, especially among youth; an early cohort study showed that a needle exchange program in Montreal was associated with a higher rate of HIV seroconversion, likely due to new social networks formed through the exchange, and this stigma has persisted.[144] Subsequently, multiple studies and reviews have concluded that providing sterile equipment to injection drug users actually leads to reductions in injecting risk behaviors, reduces the risk of HIV infection, and facilitates entry into drug treatment.[145,146,147,148] Vancouver, British Columbia has taken the harm reduction philosophy one step beyond syringe services by establishing InSite, North America’s only legal, supervised injection site (InSite).[149] InSite has reduced overdose deaths in the city and surrounding areas, reduced HIV and HCV risk behaviors, reduced use of medical resources (i.e. ambulances, emergency room visits), and has increased access to preventive, mental health, and primary care services.
**HIV Prevention Education**

In harm reduction programs, syringe services often provide a comprehensive set of services beyond basic needle exchange, including HIV counseling and testing, screening for sexually transmitted diseases, screening for tuberculosis, vaccination services, and referral to substance use treatment programs. It is extremely important to remember that persons who inject drugs can also acquire and transmit HIV via sexual contact and should be counseled about sexual risk reduction strategies. Many syringe services exchange sites can link interested persons who use drugs to formal education programs; a Cochrane review found that standard educational interventions, rather than multi-session psychosocial interventions, are a cost-effective way to reduce injection and sexual risk behavior.[150]

**Opioid Overdose Prevention Strategies**

Another harm reduction technique involves overdose education and distribution of naloxone to persons who use injection drugs as well as to their friends, family, and other community members. The strategy of training potential bystanders to prevent, recognize, and respond to overdose situations was piloted in 19 Massachusetts communities through the OEND (opioid education and nasal naloxone distribution) program, and between 2002 and 2009, the adjusted rate ratios of death attributed to opioid overdose decreased in communities with both low and high enrollment compared with communities without OEND implementation.[151] This is especially pertinent as the availability of naloxone has greatly expanded and is being widely promoted nationally for both heroin users and those prescribed higher doses of opioids for chronic pain conditions.[152] As of April 2016, all but 5 states (AK, KS, MO, MT, WY) had passed legislation improving layperson access to naloxone, while Good Samaritan laws, which encourage bystanders to summon emergency responders without concern for legal repercussions, continue to be expanded throughout the country.[153]

**Opioid Prescribing Practices**

The epidemic of opioid use is intertwined with the rise in opioid prescribing practices in the United States over the last few decades. Due to increasing concern that pain was being undertreated, the number of opioid prescriptions quadrupled between 1999 and 2013, followed by an increase in opioid use disorders and overdose deaths.[154] The high prevalence of acute and chronic pain syndromes among persons with HIV infection means that clinicians caring for patients with HIV/AIDS frequently have to balance pain management with the risk of iatrogenic opioid dependence and with underlying addiction.[155] However, in an online, anonymous, national survey of 106 clinicians providing HIV care, most providers did not follow recommended opioid prescribing practices and acknowledged limited confidence in their ability to identify opioid use disorders in their patients.[155] There are numerous initiatives underway to move away from the practice of prescribing opiates as well as strategies for making prescribing safer (written contracts for patients, prescribing protocols, routine use of urine toxicology, electronic health records, prescription drug monitoring programs, and more training for primary care medical providers. At the same time, primary care physicians, especially younger physicians, are increasingly reluctant to manage chronic pain in their patients, which is understandable but threatens to jeopardize pain management for those patients who truly need it. Clearly, there is an ongoing need to educate both clinicians as well as patients about the risks, benefits, and proper role for opioid pain medications.[156]
Hallucinogen Use Disorder

Prevalence among U.S. Adults

Hallucinogen use disorders are categorized by the type of hallucinogen used. For example, the DSM-5 divides hallucinogen use disorder into separate categories for those who use phencyclidine or a similar substance such as ketamine, and those who use other hallucinogens, such as mescaline, 3,4-methylenedioxymethamphetamine (MDMA) and popularly known as “ecstasy or Molly”, and lysergic acid diethylamide (LSD).[2] Of note, MDMA is classified as a hallucinogen though it is structurally similar to methamphetamine and has stimulant properties as well.[157] The National Survey on Drug Use and Health (NSDUH) divides hallucinogen use in a more practical manner, providing separate estimates for “any” hallucinogen use disorder and then, more specifically, for the most common LSD and ecstasy (MDMA) disorders. According to the NSDUH, among people aged 12 years and older in 2014, 0.4% (about 1.2 million persons) were current hallucinogen users; 0.1% (approximately 300,000 people) used LSD and 0.2% (approximately 600,000 people) used ecstasy.[5]

Prevalence among U.S. Adults with HIV Infection

Although prevalence rates are not available for hallucinogen use disorders among adults with HIV, evidence indicates that use of “club drugs” (which typically refers to a group of substances that includes the hallucinogens ketamine, MDMA, and LSD, as well as GHB, methamphetamine, and flunitrazepam) has been rising in the general population and especially among bisexual men and men who have sex with men who have HIV or at risk for HIV acquisition.[115, 157, 158]

Risk Factors

Risk factors for phencyclidine use disorder include low educational attainment, male gender, and living in the West or Northeast.[2] Use of other hallucinogens is linked to other substance use disorders (and early exposure to alcohol, tobacco, and cannabis), depression, drug use by peers, and high sensation-seeking behavior.[2] A recent population study that looked specifically at psychedelics (LSD, psilocybin, mescaline, peyote) found that psychedelic users were more likely to be younger, white, male, unmarried, with somewhat higher educational status, risk-takers, and more likely to have used other drugs; interestingly, this paper found no association between lifetime psychedelic use and increased likelihood of past year psychological distress, mental health treatment, depression, anxiety, or suicidality.[159]

Screening Tools

As noted earlier, a variety of screening instruments are available for detecting drug use and dependency. Instruments range from comprehensive inventories (DAST), to 4-item and 2-item conjoint screening tests for both alcohol and drug use (CAGE-AID, TICS), to single-question screening.[6, 7, 9, 10] The 4-item Substance Use Brief Screen (SUBS) may offer the best option for brief yet comprehensive screening for drug use in primary care populations.[11]

Diagnostic Criteria

The DSM-5 defines phencyclidine and hallucinogen use disorder by the presence of at least two symptoms (from a list of 11 symptoms as defined in the DSM-5) related to evidence of impaired control, social impairment, risky use, and pharmacological criteria.

Treatment Considerations

Behavioral interventions, such as intensive counseling and contingency management, are the
mainstay of treatment for persons with hallucinogen use disorders (or “club drug use” disorders).[115] No pharmacologic treatment is known to have any benefit. Clinicians should have awareness of significant interactions that can occur between club drugs and antiretroviral medications, particularly the pharmacologic boosters ritonavir and cobicistat; there are several published case reports of fatal drug interactions.[115,158]
Summary Points

- More than 25% of persons living with HIV in the United States meet criteria for one or more substance use disorders.
- Substance use disorders are linked to decreased adherence to antiretroviral medications, risk-taking behaviors, and HIV disease progression (independent of non-adherence behaviors).
- Combining psychosocial interventions with pharmacotherapy (acamprosate, disulfiram, oral naltrexone, or extended-release naltrexone injection) is the optimal approach for treating alcohol use disorders; all pharmacotherapies can be used to treat persons with HIV, keeping in mind that disulfiram has several clinically significant drug interactions with antiretroviral medications whereas acamprosate and naltrexone do not.
- There is a high rate of cannabis use among persons with HIV and treatment for cannabis use disorders should focus on behavioral therapies.
- The use of club drugs, which includes methamphetamine as well as hallucinogens such as LSD and MDMA (“ecstasy”), is a significant problem among bisexual men and men who have sex with men who are HIV-infected or at risk for HIV acquisition.
- Behavioral strategies are the primary intervention for stimulant and hallucinogen use disorders, though no single approach has been proven to be most effective and there is a high rate of relapse.
- The rise in opioid addiction has paralleled the rise in opioid prescribing habits over the past 15 years, and tackling the opioid epidemic will require educating clinicians and patients alike about the risks, benefits, and proper role of opioid pain medications.
- Medication-assisted treatment is a necessary and highly effective treatment for opioid use disorder, and includes three categories: opioid agonists (methadone), opioid partial agonists (buprenorphine), and though less effective, opioid antagonists (naltrexone).
- Among persons with HIV who inject drugs, both drug- and HIV-related mortality are lowest when antiretroviral therapy and medication-assisted treatment of opioid use disorder are prescribed jointly.
- Individuals with HIV who stop using illicit substances have excellent health utilization and antiretroviral adherence patterns, thereby emphasizing the importance of securing access to substance use treatment programs.
- Treatment strategies for substance use disorders should embrace a harm reduction philosophy in order to better retain in care those patients at highest risk for ongoing substance use and associated HIV risk behavior.
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Figures

Figure 1 Number of Persons Age 12 and Older with a Past Year Substance Disorder, United States, 2014

Abbreviations: SUD = substance use disorder  
Note: SUD refers to dependence or abuse in the past year related to the use of alcohol or illicit drugs in that same period. Estimated numbers of people having disorders for specific substances do not sum to the 21.5 million people with any SUD because people could have disorders associated with their use of more than one substance.

Figure 2 Percentage of Adults who were Current Cigarette Smokers*, National Health Interview Survey, United States, 2005-2014

*Persons who reported smoking ≥100 cigarettes during their lifetime and who, at the time of interview, reported smoking every day or some days.

Figure 3 Neurochemical Circuits Involved in Alcohol Dependence and Craving

This figure shows ethanol leading to increased dopamine levels in nucleus accumbens. Naltrexone works by blocking opioid receptors and causes a reduction in dopamine levels in the nucleus accumbens, which reduces the reward or pleasure associated with alcohol ingestion.

**Figure 4 U.S. FDA Approved Medications to Treat Alcohol Use Disorder**


<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate</td>
<td>666 mg three times daily</td>
<td>Dose reduction required with renal impairment</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>500 mg once daily for 1-2 weeks, then decrease to maintenance dose (range 125-500 once daily)</td>
<td>Not for use in persons actively drinking alcohol; avoid alcohol in other products</td>
</tr>
<tr>
<td>Oral Naltrexone</td>
<td>50 mg once daily</td>
<td>Cannot be given to patients taking opioids</td>
</tr>
<tr>
<td>Extended-Release Naltrexone</td>
<td>380 mg IM every 4 weeks; administer in gluteal area with 1.5 inch 20-gauge needle</td>
<td>Cannot be given to patients taking opioids</td>
</tr>
</tbody>
</table>
**Figure 5 Acamprosate in Persons with Alcohol Dependence**

This graph shows results of acamprosate versus placebo in 272 persons with alcohol dependence. Results are shown for day 60 during treatment, at week 48 (end-of-treatment), and week 96 (48 weeks post treatment).

Figure 6 Inhibition of Alcohol Metabolism by Disulfiram

Normal ethanol (alcohol) metabolism is shown in top figure, with conversion of ethanol to acetate. Disulfiram inhibits the enzyme aldehyde dehydrogenase, leading to accumulation of acetaldehyde, which is associated with adverse effects.

Normal Ethanol (Alcohol) Metabolism

- Ethanol (CH₃CH₂OH) undergoes metabolism by Alcohol dehydrogenase to form Acetaldehyde (CH₃CO).
- Acetaldehyde (CH₃CO) is then converted to Acetate (CH₃COO⁻) by Aldehyde dehydrogenase.

Inhibition of Ethanol (Alcohol) Metabolism

- Ethanol (CH₃CH₂OH) is converted to Acetaldehyde (CH₃CO) by Alcohol dehydrogenase.
- Acetaldehyde (CH₃CO) is not further converted to Acetate (CH₃COO⁻) by Aldehyde dehydrogenase due to the inhibition by Disulfiram.
Figure 7 Impact of Long-Acting Naltrexone on Median Heavy Drinking Days per Month

This graphic shows results from a 6-month, placebo-controlled study that randomized 624 alcohol-dependent adults to receive either placebo or one of two doses of extended release injectable naltrexone (190 mg per month or 380 mg every 4 weeks).

### Table 1.
**Suggestions for the Clinical Use of Pharmacotherapies for Smoking Cessation***

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Precautions, contraindications</th>
<th>Adverse effects</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td></td>
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<tr>
<td>Sustained release bupropion hydrochloride</td>
<td>History of seizure disorders</td>
<td>Insomnia</td>
<td>150 mg every morning for 3 days, then 150 mg twice daily (begin treatment 1-2 weeks pre-quit)</td>
<td>7 - 12 weeks, Maintenance up to 6 months</td>
</tr>
<tr>
<td></td>
<td>History of eating disorders</td>
<td>Dry Mouth</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>Mouth soresness</td>
<td>Dyspepsia</td>
<td>1-24 cigarettes/day: 2mg gum (up to 24 pieces/day)</td>
<td>Up to 12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 25 cigarettes/day: 4mg gum (up to 24 pieces/day)</td>
<td></td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>Local irritation of mouth and throat</td>
<td></td>
<td>6-16 cartridges/day</td>
<td>Up to 6 months</td>
</tr>
<tr>
<td>Nicotine lozenge</td>
<td>Nausea</td>
<td>Heartburn</td>
<td>First cigarette smoked ≥ 30 minutes after awakening: initiate with 2 mg lozenge</td>
<td>Up to 12 weeks</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>First cigarette smoked &lt; 30 min after awakening: initiate with 4 mg lozenge</td>
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<td>• Weeks 1-6: 1 lozenge every 1-2 hours</td>
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<td></td>
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<td>• Weeks 7-9: 1 lozenge every 2-4 hours</td>
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<td>• Weeks 10-12: 1 lozenge every 4-8 hours</td>
<td></td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>Nasal irritation</td>
<td></td>
<td>8-40 doses/day</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Nicotine 24-hour patch</td>
<td>Local skin reaction</td>
<td></td>
<td>If smokes ≥ 10 cigarettes per day</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>Precautions, contraindications</td>
<td>Adverse effects</td>
<td>Dosage</td>
<td>Duration</td>
</tr>
<tr>
<td>---------------------------------</td>
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<td>------------------------------------------------------------------------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
<td>• Weeks 1-4: 21 mg/24 hours&lt;br&gt;• Weeks 5 and 6: 14 mg/24 hours&lt;br&gt;• Weeks 7 and 8: 7 mg/24 hours</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If smokes &lt;10 cigarettes per day&lt;br&gt;• Weeks 1-6: 14 mg/24 hours&lt;br&gt;• Weeks 7 and 8: 7 mg/24 hours</td>
<td></td>
</tr>
<tr>
<td>Nicotine 16-hour patch</td>
<td></td>
<td>Local skin reaction</td>
<td>If smokes ≥15 cigarettes per day&lt;br&gt;• Weeks 1-8: 25 mg/16 hours&lt;br&gt;• Weeks 9 and 10: 15 mg/16 hours&lt;br&gt;• Weeks 11 and 12: 10 mg/16 hours</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If smokes &lt;15 cigarettes per day&lt;br&gt;• Weeks 1 to 8: 15 mg/16 hours&lt;br&gt;• Weeks 9-12: 10</td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>Significant kidney disease</td>
<td>Nausea, trouble sleeping</td>
<td>Begin treatment 1 week pre-quit</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>Precautions, contraindications</td>
<td>Adverse effects</td>
<td>Dosage</td>
<td>Duration</td>
</tr>
<tr>
<td>-----------------</td>
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</tr>
<tr>
<td>Patients on dialysis</td>
<td>Abnormal or vivid/strange dreams, Depressed mood and other psychiatric symptoms</td>
<td></td>
<td>• 0.5 mg/day for 3 days, then • 0.5 mg twice/day for 4 days, then • 1 mg twice/day</td>
<td></td>
</tr>
</tbody>
</table>

* The information contained in this table is not comprehensive; see package inserts for additional safety information. Much of the content in this table is based on information in the 2008 U.S. Public Health Service Clinic Practice Guideline for Treating Tobacco Use and Dependence.

Source:
