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In the Clinic®

Substance Use Disorders

Epidemiology

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Management

"Substance use disorders" refers to a spectrum of aberrant behaviors related to use of psychoactive substances, which can alter normal brain activity and have wide-ranging consequences for a person's health and well-being. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), lists 11 criteria for alcohol and other substance use disorders (1). These criteria primarily relate to whether the patient has experienced consequences or a loss of control over substance use.

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Notably, the emphasis on severity in the new DSM-5 nomenclature has replaced the DSM-IV's focus on the distinction between "substance abuse" and "substance dependence."

The DSM-V's emphasis on severity removes some of the confusion between the term "substance dependence" and physical dependence, a state in which the body has adapted to long-term use of a substance and experiences withdrawal in its absence. While most patients with severe substance use disorders are physically dependent, this dependence alone is not sufficient for the diagnosis. The term "addiction" remains in widespread use and refers to the long-term, neurobiological disease that overlaps with moderate or severe substance use disorders as defined in the DSM-5 (2).

Epidemiology

How common are substance use disorders?

Alcohol use and other substance use disorders, excluding tobacco, contribute to more than 90 000 deaths in the United States annually (3). Despite such dire consequences, these conditions are often inadequately addressed in outpatient care. And yet, substance use disorders have much in common with other medical conditions that are commonly treated in primary care and other medical settings: genetic, environmental, and behavioral roots; enduring biological changes that lead to a chronic, relapsing and remitting course; and response to both medical and behavioral treatment (4).

Alcohol use disorders remain the most common substance use disorder in the United States. Nearly 30% of Americans 18 years of age or older exceed recommended limits for alcohol consumption and can be considered "at-risk" or "risky" drinkers (5). Fewer, but still a substantial minority, have consumption patterns indicative of an alcohol use disorder (AUD). The 12-month and lifetime prevalences of AUD among adults in the United States are 14% and 29%, respectively (6).

Approximately 22.3 million Americans aged 12 years or older were current users of illicit drugs in 2013, representing 9.4% of the population. According to the 2013 National Survey on Drug Use and Health, marijuana was by far the most commonly used drug (7.5%), followed in descending order by prescription drugs (2.5%, most of which were opioids), cocaine (0.6%), hallucinogens (0.5%), inhalants (0.2%), and heroin (0.1%) (7). Of note, prescription opioid use disorders in the United States are increasing and seem to be a gateway to the use of heroin, which is both cheaper and more abundant in some parts of the country. One consequence is an epidemic of opioid overdoses, with those involving prescription opioids increasing 3-fold, and heroin overdoses increasing 5-fold from 2001 to 2013 (8). Methamphetamine ("crystal meth"), use of which has declined slightly, is uncommon on a population level but remains a major problem in some regions of the country. In addition, concern about designer drug use in young adults is increasing; these drugs include synthetic cannabinoids (also known as K2 or "spice"), which were used more commonly than any drug except cannabis among high school seniors in 2013, and substituted

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cathiones, including mephredone or "bath salts" (9).

What are the risk factors?

Studies suggest that genetic polymorphisms may contribute to as much as 40% to 60% of an individual's risk for addiction (10, 11). Environmental factors, particularly in childhood or adolescence, are also important, including age of first exposure to alcohol or drugs (12) and adverse childhood experiences (13). Finally, substance use disorders are commonly associated with psychiatric comorbidities, including depression, anxiety, and bipolar disorder. These conditions may contribute to an individual's vulnerability to addiction; in addition, anxiety and depressive symptoms may be a consequence of long-term substance use.

Prevention

What personal, community, and health system measures are effective in preventing substance use disorders?

Parents who model abstinence or modest alcohol consumption are a positive influence on their children (12). Parents and children should be aware that early use of drugs or alcohol is a risk factor for later development of a substance use disorder.

Policy measures that have been effective in reducing underage drinking and other adverse drinking-related outcomes at all ages include price regulations (e.g., alcohol taxation and minimum pricing) and reduction in alcohol availability (e.g., age limits for purchase, restricting hours and days of sales, and marketing restrictions) (12, 14). Examples of community and policy measures being considered or implemented to reduce prescription drug abuse include initiatives to dispose of remaining controlled substance prescriptions, physician safe opioid prescribing education, restrictions on such pain clinic practices as directly dispensing opioid analgesics, and limitations on the quantity given in a first opioid prescription. As yet, evidence is limited about the effectiveness of these strategies, but in Florida, implementation of a prescription monitoring program in combination with pain clinic restrictions reduced the amount of total opioids prescribed and was associated with a decline in overdose deaths (15).

What health system measures are effective in reducing or preventing unhealthy substance use?

Screening, Brief intervention and Referral to Treatment (SBIRT) is an important tool for physicians and primary care teams to reduce alcohol use. Safe practices for opioid prescribing for chronic pain, including the use of prescription monitoring programs, are increasingly being implemented as a strategy aimed at reducing the burden of prescription opioid use disorders and/or overdose.

Unhealthy alcohol use is consumption at a level that has been determined in epidemiologic studies to have negative health consequences (16). Unhealthy alcohol use encompasses a spectrum from "risky" use to an alcohol use disorder (**Figure**). As defined in the United States, for men aged 65 years and younger, risky use means more than 4 drinks per occasion or more than 14 drinks per week; for men older than 65 years and women, risky use is more than 3 drinks per occasion or more than 7

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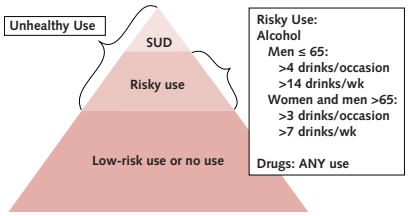
Figure. **Spectrum of substance use**



SUD = substance use disorder.

drinks per week (5, 16). Unhealthy alcohol use goes beyond risky use to become a disorder when a person experiences negative consequences and/or loss of control around their drinking, as defined in the DSM-5. For patients who have risky use, brief interventions in primary care can reduce the amount of alcohol consumed.

A systematic review of 12 studies found that in the subset of studies involving good-quality, brief, multicontact behavioral counseling interventions, participants reduced the average number of drinks per week by 13%–34% more than controls, and the proportion of participants drinking at moderate or safe levels was 10%–19% more than controls. Such multicontact interventions were more effective than single-contact interventions (16).

Of note, patients with risky use who do not have an alcohol use disorder benefit the most from screening and brief intervention; SBIRT benefits have not been demonstrated for persons with an alcohol use disorder, who should receive more extensive treatment (17).

SBIRT for alcohol is a U.S. Preventive Services Task Force grade B recommendation, meaning there is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial. In a primary care practice, SBIRT initially involves screening for unhealthy alcohol use using a validated tool (see Diagnosis). Patients who screen positive should have further assessment for an alcohol use disorder, and physicians or practice staff should conduct a brief investigation. This investigation is a conversation in which the provider uses motivational interviewing techniques to give feedback about the patient's level of alcohol use, offers advice, and elicits goals and next steps from the patient. If there is concern for an alcohol use disorder, the patient should be referred for further treatment. All patients with a positive screen should receive planned follow-up.

In contrast, brief interventions for drug use have not been shown to be effective.

The ASPIRE study randomly assigned 528 primary care patients with drug use to 1 of 2 brief counseling interventions or to no intervention. It found that no strategy decreased drug use at 6 months, regardless of the type of drug or severity of use (18). A second study of 868 patients with drug use randomly assigned to a single brief intervention with an attempted follow-up telephone booster, compared with a handout alone (control group), found that the brief intervention had no significant effect on drug use or addiction severity at 3, 6, 9, or 12 months (19).

Nonetheless, physicians should consider asking about drug use when observing deteriorating social functioning, finding a family history of substance use disorders, or diagnosing comorbidities often associated with substance use (e.g., hepatitis C, upper extremity abscess). Clinical cues, such as pancreatitis or unexplained elevated liver function test results, should also trigger investigation about alcohol use.

How can opioids for chronic pain be prescribed safely and effectively?

Physicians' prescribing practices over the past 2 decades have contributed to increasing rates of opioid use disorder and overdose in the United States. Clinical experience provides insight into which patients being considered for opioid medications for pain may be at risk for opioid use disorder, and recommendations to monitor patients for behaviors that could indicate opioid use disorder or prescription diversion have been made. But despite a growing body of literature, many gaps remain in our understanding of effective strategies (20).

Studies have yielded varying estimates of the proportion of patients treated with opioids for chronic pain who develop aber-

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rant behaviors that may indicate an opioid use disorder (21). Potential predictors include a history of substance use disorders or a mental health diagnosis, current cigarette smoking, family history of substance use disorders, and a history of legal problems. Possible tools to identify patients most at risk for aberrant use include the Screener and Opioid Assessment for Patients with Pain (SOAPP and SOAPP-R), Current Opioid Misuse Measure (COMM), Pain Medication Questionnaire (PMQ), and the Opioid Risk Tool (ORT). However, all of these tools have sensitivity below 40%, whereas specificity ranges from 70%–90% (22).

Physicians should also be aware that risk factors for prescription opioid overdose include concurrent benzodiazepine prescriptions and higher opioid doses, with the greatest effect found with doses over 100 mg morphine equivalents per day (23, 24).

Given the risks of opioid use disorder and overdose as well as diversion, long-term opioid treatment should be considered only for patients with moderate to severe pain that affects function and/or quality of life and for those in whom potential therapeutic benefits outweigh risks (20). Key principles for risk management of patients being considered for such treatment include optimization of alternatives to opioid treatment for chronic pain; assessing for risk for aberrant drug-related behaviors possibly using a standardized tool; structuring a treatment and monitoring plan commensurate with risk; considering a medication agreement (also known as a "contract"); regularly assessing opioid benefit, focusing on functional gains, with reevaluation of the decision to use opioids if little benefit is seen; and regularly assessing drug-related behaviors using urine drug testing, pill counts, and state prescription monitoring program data. If benefits are not commensurate with the risks, or if a pattern of aberrant drug-taking behaviors is seen, safe and effective methods for discontinuation (e.g., tapering as appropriate) and referrals for medication or counseling to treat opioid use disorder are indicated (20).

In addition, primary care providers should consider specialist assistance in treating patients with substance use and comorbid chronic pain or psychiatric disorders. State-wide regulations of physician opioid practices (e.g., limiting opioid doses prescribed in nonspecialty settings, requiring participation in a state prescription monitoring program before dispensing a first prescription), while controversial, will probably continue to influence physician behaviors regarding pain management.

Prevention... Screening and brief interventions for unhealthy alcohol use have been shown to reduce the quantity of alcohol that patients use, as well as social and medical costs. When managing chronic pain, physicians should optimize alternatives to opioids. When considering opioid treatment initiation, they should evaluate patients for risk factors for misuse, adjusting treatment and monitoring accordingly. Monitoring should include regular urine drug tests, pill counts, and review of state prescription monitoring program data, as well as regular assessment of benefit.

CLINICAL BOTTOM LINE

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Diagnosis

Patients present to physicians with substance use disorders in various ways. They may have medical complications of substance use or symptoms suggestive of substance intoxication (e.g., sedation, slurred speech) or withdrawal (e.g., unexplained tachycardia, restlessness). Primary care patients may come to the clinic explicitly for help with a substance use disorder or for management of withdrawal. In addition, alcohol use disorders are increasingly identified through routine screening questions asked by physicians or other staff, as screening becomes more routine in primary care settings.

The single-item alcohol question endorsed by The National Institute on Alcohol Abuse and Alcoholism is a practical tool in clinical settings. It asks how many times the patient has consumed alcohol over the recommended limits. A response of one or more is 82% sensitive and 79% specific for unhealthy alcohol use (i.e., the spectrum from risky drinking to alcohol use disorder) (25), and the patient should be further assessed for an alcohol use disorder. The Alcohol Use Disorder Identification Test (AUDIT)-C is a 3-item survey that is similarly sensitive and more specific for unhealthy use with cut-off scores of 4 for men and 3 for women (26). The AUDIT, from which the AUDIT-C is derived, is a 10-question survey being increasingly used in primary care settings that can be used as a follow-up to the single-item question or alone as an initial screening tool. Although the optimal cut-offs are still under debate, recent data support 3 for women and 5 for men for a diagnosis of risky drinking (rather than 8, which is traditionally used for both men and women), and a cut-off of 13 for women or 15 for men suggestive of an alcohol use disorder (27). The CAGE tool asks whether patients have ever felt the need to Cut down on use, felt Annoyed by others who criticized their drinking, felt Guilty about their drinking, or needed a drink first thing the morning (an "Eye-opener"). It assesses lifetime rather than current patterns of alcohol use but is easily remembered for further assessment of a patient with a positive single-item screening test.

Although the evidence base does not support screening and brief intervention for drug use, the validated single-item drug question endorsed by the National Institute on Drug Abuse is an efficient tool that asks, "How many times in the last year have you used an illegal drug, or a prescription medication for a nonmedical reason (for example, because of the experience or feeling it caused)?" (28). The Drug Abuse Screening Test (DAST-10) can be used as an initial screening device or to follow up on the single-item question for patients who may have a problem with drug use (28).

When a physician is concerned about a substance use disorder, other key aspects of the history include past or current use of other psychoactive substances; prior treatments and the response to treatment; overdose history; any risky behaviors, such as driving while intoxicated or sharing needles; psychiatric history; family history of substance use disorders; current social situation and supports; and readiness for change. The physical examination should look for complications, such as abscesses or cirrhosis. For patients with an alcohol or opioid use disorder and probable physical dependence who report recently stopping use, both the history and physical

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examination enable the assessment of a CIWA (Clinical Institute Withdrawal Assessment, used for alcohol withdrawal) (**Appendix Table 1**, available at www.annals.org) or COWS (Clinical Opiate Withdrawal Scale) (**Appendix Table 2**, available at www.annals.org) score. Laboratory evaluation is often important to further assess for complications of substance use, such as hepatitis C.

Complications

Alcohol

Alcohol is hepatotoxic, and unhealthy levels of consumption are associated with liver disease, including acute alcoholic hepatitis, alcoholic fatty liver disease, and cirrhosis. Alcohol was estimated to contribute to half of the deaths from cirrhosis globally in 2010 (29). Additionally, unhealthy alcohol use is associated with cardiovascular disease, including hypertension and cardiomyopathy, as well as pancreatitis, gastritis, esophagitis, bone marrow suppression, peripheral neuropathy, chronic infectious diseases, pneumonia, and several types of cancer, including those of the mouth, esophagus, throat, liver, and breast (30). Alcohol use complicates care and is associated with increased morbidity in individuals with HIV and hepatitis C infections. It is associated with psychiatric and behavioral conditions, including depression and sleep disturbance and is a major risk factor for trauma. Patients who use alcohol are more likely to experience violence, including intimate partner violence (31). Finally, withdrawal can be fatal. It is associated with significant morbidity, including seizures and delirium tremens, which manifests as delirium that may be accompanied by marked autonomic hyperactivity with fever, tachycardia, hypertension, agitation, and diaphoresis.

Injection drugs

The act of injecting heroin and other drugs is associated with local infections, such as abscesses and cellulitis, as well as blood-borne infections. Blood-borne infections may be bacterial (e.g., endocarditis, pneumonia, osteomyelitis, septic arthritis) or viral (e.g., HIV, hepatitis C and B) (32). The prevalence of HIV among people who inject drugs has been declining in the United States due to safer injection practices. The incidence of new hepatitis C infections in the United States declined in the 1990s, possibly because of safer injection practices as well as screening of the blood supply, but rates plateaued in the 2000s and newer data suggest increasing rates, especially among young injection drug users (33).

Opioids

In addition to the complications of opioid injection itself, other problems include common physical symptoms, such as nausea and constipation, and effects of hypothalamic-pituitary-adrenal axis suppression, such as amenorrhea, low bone density, and loss of libido. Patients receiving long-term opioids for pain may have opioid-related hyperalgesia, in which nociceptive receptors are sensitized and painful stimuli are experienced as being more severe. As noted, overdose is becoming increasingly common.

Cocaine

Because it inhibits reuptake of norepinephrine as well as dopamine and serotonin, cocaine causes a variety of complications. Cardiac ischemia is common, and cocaine is estimated to contribute to one fourth of myocardial infarctions among patients younger than 45 years (34). Other complications include cerebrovascular and renal disease. Intranasal use can lead to chronic rhinitis and perforation of the nasal septum. Smoking crack cocaine can lead to a wide range of

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both acute and chronic pulmonary complications, including acute pulmonary toxicity or "crack lung," which involves diffuse alveolar damage and hemorrhagic alveolitis.

Methamphetamine

Methamphetamine increases synaptic availability of norepinephrine, dopamine, and serotonin and, like cocaine, is associated with cardiotoxicity. This drug causes acute behavioral effects, including irritability; anger; panic; and, in some cases, psychosis that may recur during periods of abstinence (35). There is some evidence for neurotoxicity and cognitive decline; however, the long-term clinical significance of these symptoms is still uncertain.

Marijuana

Long-term marijuana use has a range of medical and neuropsychiatric effects. The smoke has many of the same combustible particles as tobacco smoke. Thus, long-term use can lead to pulmonary complications, such as cough, sputum production, bronchitis, and asthma exacerbation (36). Whether marijuana is associated with lung cancer or other cancers is under debate—the quality of the studies has generally been variable and they have yielded mixed results. Cannabis-related hyperemesis has been increasingly described and can cause significant distress. Regular marijuana use in adolescents may be associated with abnormal development of certain neural pathways, including those involved in reward, executive function, and alertness; several studies have found an association between heavy marijuana use and reduced cognitive function, although controversy remains (37, 38). Finally, studies have linked marijuana use to depression, anxiety, and psychosis, although whether these associations are causal remains under debate (36).

Designer drugs

The most commonly used designer drugs—synthetic cannabinoids—are usually smoked, and in rare instances cause seizures, acute renal failure, and myocardial infarction in the short-term setting. Long-term effects are not well-known, but the hyperemesis associated with marijuana seems uncommon. Substituted cathinones, or "bath salts," which are usually taken intranasally, increase extracellular levels of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin by facilitating extracellular release and reuptake inhibition. Intoxicated patients may present with muscle spasm, bruxism, and palpitations, and most will be found to have tachycardia and hypertension. Short-term complications include cardiac arrhythmias, myocarditis, hyponatremia (probably due to a combination of sweating and antidiuretic hormone secretion), and rhabdomyolysis. Psychiatric effects are common (9).

Oral health effects

Oral health problems are common in patients with substance use disorders. Although they are often related to poor self-care and dental hygiene, some drugs have specific dental effects. Heavy methamphetamine use is particularly known to cause profound tooth decay.

Complications... Substance use disorders have myriad medical complications. Unhealthy alcohol use can cause or exacerbate liver disease as well as causing or contributing to a host of other medical conditions. Injection drug use is associated with local and systemic bacterial infections and blood-borne viruses, including HIV and hepatitis C. Cocaine is known for its cardiovascular effects. Marijuana leads to pulmonary complications; it is also associated with neurocognitive impairment that may be particularly serious in adolescents.

CLINICAL BOTTOM LINE

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How should withdrawal be approached in the outpatient setting?

Goals of withdrawal management (also known as detoxification) include managing symptoms, preventing serious complications, and bridging patients to treatment to achieve long-term recovery.

Substance use withdrawal can be managed in the outpatient setting in selected patients. They must be highly motivated, be ready for change, and have some degree of home support available. Because withdrawal management is not substance use treatment, but a means to prepare a patient for treatment, there must be a plan in place for ongoing care.

Alcohol

Because alcohol withdrawal has a particularly high potential for morbidity and mortality, experts have proposed the following additional criteria for outpatient detoxification: CIWA scores of 8 to 15 *without* seizures or delirium tremens (disorientation, hallucinations, fever, drenching sweats, severe tachycardia [e.g., pulse >120 beats/min], or hypertension [e.g., >160/100 mm Hg]); ability to take oral medications; presence of a reliable family member or close contact who can stay with the patient throughout the detoxification period (usually 3–5 days) and monitor for worsening symptoms; ability to commit to daily medical visits; no unstable medical condition; not psychotic, suicidal, or significantly cognitively impaired; not pregnant; no concurrent other substance use that may lead to withdrawal; and no history of delirium tremens or alcohol withdrawal seizures. Relative contraindications for ambulatory detoxification are age older than 60 years or evidence of alcohol-related end-organ damage (39).

For the selected group of patients who are candidates for outpatient alcohol withdrawal, physicians may prescribe benzodiazepines to manage symptoms and prevent the complications of withdrawal. The optimum medication regimen in the outpatient setting is unknown. A fixed-dose schedule in which a benzodiazepine is given every few hours, or a loading-dose approach in which a long-acting benzodiazepine is given to provide a tapering effect, can be effective and practical in the outpatient setting. Commonly used benzodiazepines include the long-acting agents diazepam or chlordiazepoxide. Oxazepam or lorazepam are shorter-acting and less commonly used but are recommended in patients with impaired liver function because they are not metabolized by the liver.

Opioids

Whether and how to treat opioid withdrawal symptoms among outpatients depends on the patient's treatment goals and treatment availability. Patients who are experiencing withdrawal and are interested in methadone or buprenorphine treatment can be referred immediately for such care. Patients should be in at least mild withdrawal at the time of initiation of buprenorphine treatment because it is a partial agonist, and patients generally need to be abstinent from short-acting opioids for at least 12 hours and long-acting opioids for 12–36 hours. Because naltrexone is a full opioid antagonist, patients need to be abstinent from opioids for 3–7 days before initiation of the oral medication, depending on the half-life of the opioids used, and for at least 7 days before initiation of intramuscular formulation. Thus, patients awaiting naltrexone treatment usually require management of withdrawal symptoms during the waiting period, as may patients referred for buprenorphine or methadone who are not able to access care right away. Although these patients often require the structure and supervision of an inpatient setting during this transition, outpatient management is possible in some cases. Symptoms can generally be managed in the outpatient setting with at least partial improvement with nonopioid medications, such as clonidine for anxiety, nonsteroidal anti-inflammatory drugs for muscle cramps, dicyclomine for abdominal cramping, and antidiarrheal medications.

Benzodiazepines

Benzodiazepine withdrawal may manifest as tremors, anxiety, perceptual disturbances, dysphoria, psychosis, and in some cases seizures. Patients with severe withdrawal should be managed as inpatients so that intravenous benzodiazepines can be given and titrated to effect. However, after this, patients motivated to stop their use can receive a gradually tapering benzodiazepine dose in the outpatient setting over several months, assuming they have monitoring and support in place (40).

What medications are available for treatment?

Pharmacotherapy, ideally combined with counseling, can be effective in the management of opioid or alcohol use disorders, and the option of medication should be reviewed with all patients with at least moderate disease severity (**Table**).

Alcohol

Medications approved by the U.S. Food and Drug Administration (FDA) for alcohol use disor-

Table. **Medical Treatment for Substance Use Disorders**

Medication	*Uses*	*Maintenance dosing*	*Side effects and risks*	*Precautions*	*Notes*
Alcohol					
Oral naltrexone	Maintenance	50 mg/d by mouth	Nausea, headache, dizziness, elevated transaminase levels	Periodic monitoring of liver enzymes is recommended. Impaired metabolism in liver disease.	
IM naltrexone	Maintenance	380 mg IM every 4 wk	Nausea, fatigue, dizziness, injection site reaction	Periodic monitoring of liver enzymes is recommended. Impaired metabolism in liver disease.	`
Acamprosate	Maintenance	666 mg by mouth 3 times/d	Diarrhea, nervousness, fatigue	Contraindicated with creatinine clearance ≤30 mL/min; reduce dose if creatinine clearance 30–50 mL/min.	Safe in decompensated liver disease.
Disulfiram	Maintenance	Weeks 1–2: 500 mg by mouth daily, 250 mg by mouth daily thereafter	Drowsiness, metallic taste, headache, peripheral neuropathy, rare fulminant hepatitis	Do not administer until the patient has been abstinent from alcohol for at least 12 h due to highly unpleasant adverse reaction. Contraindicated in severe myocardial disease or known coronary occlusion; psychosis; pregnancy; or rubber, nickel or cobalt allergy.	Unlikely to be effective outside of structured settings or in patients not highly motivated for self-change.
Opioids					
Methadone	Inpatient withdrawal management; maintenance	Most effective at doses of 60 mg or more by mouth daily	Sedation, prolongation of the QTc interval, nausea, constipation, weight gain, edema, amenorrhea, decreased bone density, decreased libido. Risk for respiratory depression and overdose.	Prolonged, variable half-life with incomplete cross-tolerance with other opioids; requires low initiation dose (30 mg or less) and slow titration (10 mg or less dose increases every 3 d or longer). Potential for drug interactions with inducers or inhibitors of P450 system. Obtain baseline EKG in persons with risk factors for QTc prolongation; dose reduction and EKG monitoring or alternative treatment is recommended for patients with QTc ≥500 msec.	U.S. Schedule II. For outpatient addiction treatment, only available through state-licensed programs. For pain treatment, available from licensed prescribers.
Buprenorphine–naloxone	Inpatient withdrawal management; maintenance	Sublingual buprenorphine 2 mg/naloxone 0.5 mg–buprenorphine 24 mg/naloxone 6 mg daily (generic dosages; dosage varies in newer brand-name formulations)	Nausea, constipation, headache, insomnia. Rarely associated with overdose, usually in combination with other sedating agents.	Risk for precipitated opioid withdrawal if initiated too soon in opioid-tolerant patient after last use of full opioid agonist; patients should be experiencing at least moderate withdrawal at first dose (typically ≥12 h after last heroin dose, more for longer-acting agents). May be less effective in severe liver disease due to increased bioavailability of naloxone. Periodic monitoring of liver enzymes is recommended.	U.S. Schedule III. Can be prescribed only by physicians who have taken a federally mandated course and received federal waiver. Naloxone is an opioid antagonist with poor sublingual bioavailability and is intended to block buprenorphine's effect only if the tablet is crushed and injected.
Buprenorphine	Inpatient withdrawal management; maintenance, particularly for pregnant women	2 mg–24 mg sublingually daily	Nausea, constipation, headache, insomnia. Rarely associated with overdose, usually in combination with other sedating agents.	Risk for precipitated opioid withdrawal if initiated too soon after last use of full opioid agonist, as above. Periodic monitoring of liver enzymes is recommended.	Schedule III. Can be prescribed only by physicians who have taken a federally mandated course and received federal waiver. Preferred over buprenorphine–naloxone for pregnant women; pregnant women may need higher doses.

Table–Continued

Medication	*Uses*	*Maintenance dosing*	*Side effects and risks*	*Precautions*	*Notes*
IM naltrexone	Maintenance	380 mg IM every 4 wk	Nausea, fatigue, dizziness, injection site reaction.	Risk for precipitated withdrawal if taken <7 d after last opioid dose (urine drug testing and naloxone challenge may be used to assess risk). Risk for overdose if dose is missed and patient relapses, due to waning opioid tolerance. Periodic monitoring of liver enzymes is recommended. Impaired metabolism in liver disease.	Some variability in length of time for full opioid blockade reported.
Oral naltrexone	Sometimes given as bridge before IM naltrexone; can be considered for maintenance in highly supervised settings	Bridge to IM naltrexone, or maintenance: 25 mg by mouth on d 1, if no withdrawal symptoms occur, start 50 mg daily on d 2	Nausea, headache, dizziness, elevated transaminase levels	Risk for precipitated withdrawal if taken <3–6 d after use of short-acting opioids, or <7 d for long-acting opioids. Periodic monitoring of liver enzymes is recommended. Impaired metabolism in liver disease.	Sometimes used as a bridge while awaiting insurance approval for IM naltrexone. Daily dosing limits effectiveness as a maintenance treatment for opioid dependence but may be effective in settings with enforced adherence.

EKG = electrocardiogram; IM = intramuscular.

ders include naltrexone, acamprosate, and disulfiram. Naltrexone is a μ-opioid antagonist that may reduce the pleasurable effects of alcohol intake. When given in oral form, naltrexone has been found in numerous studies to modestly reduce the risk for heavy drinking compared with placebo.

A 2010 meta-analysis of 50 randomized trials with 7793 alcohol-dependent participants found that naltrexone reduced the risk for heavy drinking to 83% of the risk in the placebo group (relative risk [RR], 0.83 [95% CI, 0.76–0.90]) and decreased drinking days by about 4% (41).

Naltrexone is also effective as a sustained-release injection, given monthly (42).

It is contraindicated in patients receiving long-term opioids. Nausea can occur with both formulations but may be more problematic with the oral formulation. Liver function tests should be done at baseline and periodically. Drug levels are higher in persons with cirrhosis, particularly when decompensated; the risks and benefits of naltrexone use should be carefully considered before initiation in persons with decompensated cirrhosis.

Acamprosate is an alternative to naltrexone that is believed to modulate glutamate neurotransmission and reduce symptoms associated with abstinence. European studies found acamprosate efficacious in terms of abstinence duration compared with controls (43). However, the large COMBINE study of 1383 recently abstinent patients in the United States did not find acamprosate to be effective compared with naltrexone or a behavioral intervention (44). Compliance is limited by the 3-times-daily dosing, but it is safe for persons with hepatic dysfunction.

Disulfiram is an aversive agent that inhibits aldehyde dehydrogenase. When alcohol is consumed it causes a buildup of acetaldehyde in the blood, leading to uncomfortable symptoms, such as sweating, flushing, nausea, and palpitations. Other medications under evaluation for alcohol use disorders include topiramate, baclofen, gabapentin, and ondansetron.

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Opioids

For opioid use disorder, treatment is most effective when it includes medication (45, 46). Three agents are currently FDA-approved for maintenance treatment. The oldest, methadone, is a long-acting full opioid agonist and a Schedule II substance that, when used for outpatient addiction, is almost exclusively provided at a licensed opioid treatment program.

A 2009 Cochrane review of methadone for opioid use disorder compared with no medication treatment included 11 randomized trials. Patients receiving methadone were less likely to use heroin (RR, 0.66 [CI, 0.56–0.78]) than patients who were not (46).

While effective, methadone can be associated with risk for excessive sedation, and rarely with respiratory depression. These risks increase in patients receiving other sedating medications, such as benzodiazepines (47). Side effects include nausea, constipation, weight gain, edema, and suppression of the hypothalamic-pituitary-adrenal axis.

Additionally, methadone can prolong the QTc interval and thus may be a risk factor for torsades de pointes. The approach to monitoring risk for this condition is controversial. However, a panel convened by the Substance Abuse and Mental Health Services Administration (SAMHSA) and a second group representing the American Pain Society, The College of Problems of Drug Dependence, and the Heart Rhythm Society recommended that a baseline electrocardiogram (EKG) be obtained in patients with risk factors for QTc interval prolongation, based on medical or family history, and concurrent medications (48, 49). Both groups agreed that risk becomes more significant at QTc lengths greater than 500 ms. Although the optimum strategy for patients with a QTc interval >500 ms is debated, at the very least physicians should review risks with the patient and seek alternatives to methadone treatment or ways to minimize risk, along with regular EKG monitoring.

Methadone is metabolized by the hepatic cytochrome P450 isoenzyme system, and thus physicians should be aware of the potential for a change in methadone levels if patients take medications that inhibit or induce this enzyme. Fluconazole (and related drugs) and ciprofloxacin are commonly used P450 inhibitors, whereas carbamazepine, rifampin, efavirenz, nevirapine, and nafcillin are examples of inducers. Notably, whereas ritonavir is a well-known inhibitor of the 3A4 isoform of cytochrome P450, in vivo it decreases methadone plasma concentrations, through unclear mechanisms (50).

Buprenorphine is a partial mu-opioid receptor agonist usually provided in combination with naloxone as a sublingual medication. Naloxone is an opioid antagonist that is minimally bioavailable when taken sublingually as prescribed; thus its presence in the combined product is designed to deter parenteral use of the medication. Buprenorphine alone is commonly used for pregnant women because of limited data regarding the safety of naloxone in pregnancy. Buprenorphine and buprenorphine-naloxone are Schedule III medications and can be prescribed by providers who have taken a federally mandated training course and received a waiver from SAMHSA and an additional Drug Enforcement Agency identification number.

A 2008 Cochrane review of buprenorphine for maintenance therapy for heroin addiction included 24 studies and 4497 participants. Buprenorphine was superior to placebo in terms of retention in treatment (RR, 1.50 [CI, 1.19–1.88] for low-dose therapy) and suppressed opioid use at doses of 16 mg and greater. Buprenorphine was less effective than methadone for retention in therapy at low or flexible

doses (RR, 0.80 [CI, 0.68–0.95]) but was similarly effective at higher doses (45).

Buprenorphine has a strong affinity for the opioid receptor, and buprenorphine-containing medication can thus precipitate withdrawal if opioids are still present because the buprenorphine displaces the full agonist from the μ receptor. Thus, patients should be in mild-to-moderate withdrawal and be given a low dose when buprenorphine is administered for the first time. Many providers supervise this induction process.

Side effects are generally mild. Respiratory depression and sedation are extremely rare given that buprenorphine is a partial agonist; overdose has been reported but usually seems to occur in combination with other sedating agents, such as benzodiazepines and alcohol, or when taken intravenously at high doses (51). Medication interactions are uncommon.

More limited data support the use of sustained-release naltrexone in patients with opioid use disorder, which is currently FDA-approved as a monthly injection at the same dose as for alcohol use disorders. Although the oral formulation of this agent is also approved for treatment of opioid use disorders, the need for daily dosing limits its usefulness except for certain settings in which adherence can be enforced. Unlike methadone and buprenorphine, naltrexone does not provide any reinforcing effect and the patient typically continues to crave opioids (52). Experts recommend that naltrexone primarily be considered for highly motivated patients and/or those living in structured treatment environments.

Sustained-release naltrexone should not be given until the patient has been abstinent from opioids for at least 7 days to avoid precipitating withdrawal. Physicians should warn patients about the risk for overdose if naltrexone treatment is stopped, due to waning tolerance.

When deciding which medication to recommend to a patient with an opioid use disorder, the physician should take into account the patient's preference and experience with medication for opioid use disorder, as well his or her medical comorbidities, co-occurring diagnoses, and need for more or less structured treatment.

Cocaine

No medications are currently FDA-approved to treat cocaine use disorders. Studies are examining topiramate, tiagabine, modafinil, and disulfiram.

What other treatments are available for substance use disorders?

Particularly for opioid use disorders, medication alone is effective for many patients (53). However, a number of patients, whether they have chosen to take medication or not, find psychosocial treatment helpful not only in achieving sobriety but in rebuilding other aspects of their lives. These forms of treatment include counseling, such peer-support groups as Alcoholics Anonymous, and residential treatment. While data support specific counseling techniques, such as contingency management and motivational interviewing for some substance use disorders, evidence for peer-support groups is more limited (54). Nonetheless, higher-quality studies of Alcoholics Anonymous tended to show positive effects (55). There are no high-quality studies comparing residential treatment to lower levels of care.

For patients who continue to use substances, how can physicians help reduce harms?

"Harm reduction" refers to the policies, programs, and practices that can reduce the harms associated with substance use for people who are unable or unwilling to stop. Physicians should discuss relevant evidence-based harm reduction strategies with all patients actively using substances.

Needle exchange services reduce HIV and hepatitis C transmission among patients who use injection drugs (56). Such programs often offer additional services, such as provision of other clean drug paraphernalia, education about safer injection practices, and HIV and hepatitis C testing, and referral to care. Physicians should be familiar with how to refer patients using injection drugs for these services.

For patients with opioid use disorders, there is emerging evidence that improving the availability of intranasal naloxone reduces overdose deaths (57). In many communities, substance use treatment and needle exchange programs now give out intranasal naloxone, and first responders, such as police officers and emergency medical technicians, carry the medication. Increasingly, physicians may prescribe naloxone to patients who are at risk for opioid overdose, including those prescribed opioids for chronic pain, and diagnosed with or in recovery from opioid use disorder. Patients whose family or friends are opioid users may also be prescribed intranasal naloxone. The intent of the prescription is to enable individuals to perform a bystander rescue or have one performed on them.

Preventive health care can also reduce the harms associated with substance use. For example, immunization against hepatitis A and B and tetanus are important in patients who inject drugs, while pneumonia vaccination is indicated in patients with alcohol use disorders (as well as smokers). Preexposure prophylaxis against HIV infection with tenofovir, which was shown to be effective in injection drug users in Thailand,

should be considered for high-risk patients (58).

Targeted counseling about behaviors can also play a role in harm reduction. For example, primary care physicians should counsel patients with unhealthy alcohol or drug use to avoid driving after use. A physician might offer birth control, condom counseling, and frequent testing for sexually transmitted infections to young women with heroin use disorders who sell sex to obtain drugs, in addition to continuing to engage the patient around discussions about her readiness for change. Finally, physicians should address tobacco use in patients with substance use disorders, just as they would with other patients. Tobacco is a major cause of morbidity and mortality among patients who are actively using drugs and alcohol, as well as those in recovery; no evidence convincingly suggests that tobacco cessation worsens substance use outcomes or causes relapse.

What are the medical–legal issues of substance use disorders?

Given the prescription opioid use epidemic, individual states have passed or are considering legislation that affects how physicians prescribe opioids and other controlled substances; physicians should stay abreast of new requirements and local training opportunities.

Physicians working with patients with substance use disorders should be cognizant of Title 42, part 2 of the Code of Federal Regulations (42 CFR Part 2), which requires a higher degree of confidentiality around substance use treatment than standard medical information. To promote relationships between physicians and external substance use treatment providers, and facilitate routine and efficient communication, practices should incorporate 42 CFR Part 2–compliant language into standard clinic release of information forms as long as the regulation remains in effect.

What is the role of primary care physicians vs. addiction physicians and other specialists in care for persons with substance use disorders?

Primary care physicians have central roles related to prevention, diagnosis, and management of unhealthy substance use and substance use disorders, including screening and brief intervention, safe and effective opioid prescribing for pain, identifying and managing medical comorbidities of substance use disorders, and helping patients reduce the harm associated with any ongoing substance use. Increasingly, many primary care physicians are also treating patients with substance use disorders, in addition to referring them to addiction medicine or addiction psychiatry subspecialists and/or treatment programs. Physicians are gaining expertise and obtaining waivers to prescribe buprenorphine and some provide naltrexone for opioid use disorders. Although primary care physicians have been slow to embrace pharmacotherapy for alcohol use disorders, they are ideally positioned to do so, either by initiating treatment on their own or by continuing medications started elsewhere.

Primary care physicians should seek the advice of addiction specialists when working with particularly complex patients who have suspected or confirmed substance use disorders. For patients who have also been diagnosed with a mental health condition, especially serious disorders, such as bipolar disorder or schizophrenia, close collaboration with psychiatry is needed. Pain specialists can be helpful in optimizing nonopioid treatments of chronic pain in patients in whom long-term opioid treatment are high risk or who are already receiving high doses of opioid analgesics.

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Management... Withdrawal management is a necessary bridge to further treatment for many patients. Outpatient management of withdrawal is appropriate only for patients who are highly motivated for recovery and have ample support at home. Medications are an important treatment option for both alcohol and opioid use disorders and should be offered to all patients with conditions of at least moderate severity. Psychosocial treatments, such as motivational interviewing-based counseling, seem to be effective for many patients. Patients in early recovery, or who are not ready to stop substance use, should be educated about harm reduction, such as needle exchange programs.

CLINICAL BOTTOM LINE

In the Clinic Tool Kit

Substance Use Disorders

Clinical Guidelines

www.jpain.org/article/S1526-5900(08)00831-6/abstract
Guidance on use of long-term opioid therapy in chronic noncancer pain from the American Pain Society and the American Academy of Pain Medicine

Clinical Education Resources

www.pcssmat.org
Training modules and webinars on treatment of opioid use disorders, with a focus on the use of medication, as well as opportunities for new prescribers to receive mentorship from Providers' Clinical Support System for Medication Assisted Treatment
www.bu.edu/aodhealth/
Free online newsletter summarizing the latest clinically relevant research on alcohol, illicit drugs, and health

Guidelines for Safe Opioid Prescribing

https://www.scopeofpain.com/
Web-based provider education on safe opioid prescribing
https://www.acponline.org/education_recertification/cme/safe_opioid_prescribing.htm
Online training program about best practices for opioid prescribing from the American College of Physicians

Patient Education Resources

www.drugabuse.gov/patients-families
National Institute on Drug Abuse
https://www.nlm.nih.gov/medlineplus/ency/article/001522.htm
Overview of substance use disorders from MedlinePlus
www.samhsa.gov/find-help
Includes behavioral health treatment services locator and tools to help patients locate nearby buprenorphine and methadone treatment providers from the Substance Abuse and Mental Health Services Administration

WHAT YOU SHOULD KNOW ABOUT SUBSTANCE USE DISORDERS

What Are Substance Use Disorders?

If alcohol or drugs are having a negative effect on your life, you may have substance use disorder. Substance use disorder can cause damage your health and relationships. It can also cause problems at work, home, or school. Many people with substance use disorder are not able to stop using drugs or alcohol, even if they want to.

What Are the Warning Signs of Substance Use Disorder?

You may have substance use disorder if you:

- Use large amounts of drugs or alcohol or for a longer amount of time than you planned
- Have trouble cutting down on your use of drugs or alcohol
- Spend a lot of time trying to get drugs or alcohol
- Take a long time to recover from drug or alcohol use
- Have strong cravings or urges to use drugs or alcohol
- Have trouble at work, school, or home because of drugs or alcohol
- Continue to use drugs or alcohol even if it causes problems for you
- Feel like you need to use more drugs or alcohol than before to get the same effects
- Have withdrawal when you don't use drugs or alcohol

How Is It Diagnosed?

- Your doctor will ask questions about your substance use.
- You may fill out a series of questions. This can help your physician make a diagnosis.
- You may have blood tests to check for health problems caused by drugs or alcohol.

How Is Substance Use Disorder Treated?

- Some medicines can be helpful in treating substance use disorder. These medicines may be prescribed by your doctor or another health care provider.
- Group or one-on-one counseling can help you better manage your substance use disorder.
- Self-help groups, such as Alcoholics Anonymous (AA) or Narcotics Anonymous (NA), and day programs are helpful for many people.
- Some choose an overnight treatment program to get more support.
- Talk to your doctor about how to get the care you need. If you are not ready to stop using drugs or alcohol, talk to your doctor. They can help you learn about ways to reduce the effect of substance use on your health.

Questions for My Doctor

- Is my substance use affecting my health?
- What is the best treatment for me?
- If I don't get treatment, what will happen?
- Are there medicines that could help me? Which ones might be right for me?
- Should I go to a long-term treatment program?
- I need emotional support. Where can I turn?

For More Information

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American College of Physicians
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National Institute on Alcohol Abuse and Alcoholism
www.niaaa.nih.gov/alcohol-health

National Institute on Drug Abuse
www.drugabuse.gov/patients-families

Substance Abuse and Mental Health Services Administration
www.samhsa.gov

Patient Information

Appendix Table 1. **Clinical Opiate Withdrawal Scale (COWS)***

Resting pulse rate (beats/min)
Measured after patient is sitting or lying for 1 minute
0: 80 or below
1: 81–100
2: 101–120
4: 120

Sweating
Over past half hour not accounted for by room temperature or patient activity
0: No report of chills or flushing
1: Subjective report of chills or flushing
2: Flushed or observable moistness on face
3: Beads of sweat on brow or face
4: Sweat streaming off face

Restlessness
Observation during assessment
0: Able to sit still
1: Reports difficulty sitting still, but is able to do so
3: Frequent shifting or extraneous movements of legs/arms
5: Unable to sit still for more than a few seconds

Pupil size
0: Pupils pinned or normal size for room light
1: Pupils possibly larger than normal for room light
2: Pupils moderately dilated
5: Pupils so dilated that only the rim of the iris is visible

Bone or joint aches
If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored
0: Absent
1: Mild, diffuse discomfort
2: Patient reports severe diffuse aching of joints/ muscles
4: Patient is rubbing joints or muscles and is unable to sit still because of discomfort

Runny nose or tearing
Not accounted for by cold symptoms or allergies
0: Absent
1: Nasal stuffiness or unusually moist eyes
2: Nose running or tearing
4: Nose constantly running or tears streaming down cheeks

Gastrointestinal upset
Over past half hour
0: No symptoms
1: Stomach cramps
2: Nausea or loose stool
3: Vomiting or diarrhea
5: Multiple episodes of diarrhea or vomiting

Tremor
Observation of outstretched hands
0: None
1: Felt but not observed
2: Slight tremor observable
4: Gross tremor or muscle twitching

Yawning
Observation during assessment
0: None
1: Yawning once or twice during assessment
2: Yawning ≥ 3 times/assessment
4: Yawning several times/min

Anxiety or irritability
0: None
1: Patient reports increasing irritability or anxiousness
2: Patient obviously irritable, anxious
4: Patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh
0: Skin is smooth
3: Piloerection of skin can be felt or is visible
5: Piloerection is prominent

Score: 5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; >36 = severe.
** From 59. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003;35:253-9. [PMID: 12924748]*

Appendix Table 2. **Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)***

Nausea and vomiting
Ask: "Do you feel sick to your stomach? Have you vomited?"
Observation:
0: No nausea and no vomiting
1: Mild nausea with no vomiting
2:
3:
4: Intermittent nausea with dry heaves
5:
6:
7: Constant nausea, frequent dry heaves and vomiting

Tremor
Arms extended and fingers spread apart. Observation:
0: No tremor
1: Not visible, but can be felt fingertip to fingertip
2:
3:
4: Moderate with patient's arms extended
5:
6:
7: Severe, even with arms not extended

Paroxysmal sweats
Observation:
0: No sweat visible
1: Barely perceptible sweating, palms moist
2:
3:
4: Beads of sweat obvious on forehead
5:
6:
7: Drenching sweats

Anxiety
Ask: "Do you feel nervous?"
Observation:
0: No anxiety, at ease
1: Mildly anxious
2:
3:
4: Moderately anxious or guarded, so anxiety is inferred
5:
6:
7: Equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

Agitation
Observation:
0: Normal activity
1: Somewhat more than normal activity
2:
3:
4: Moderately fidgety and restless
5:
6:
7: Paces back and forth during most of the interview or constantly thrashes about

Tactile disturbances
Ask: "Do you have any itching, pins and needles sensations, burning, numbness or do you feel bugs crawling on/under your skin?"
Observation:
0: None
1: Very mild itching, pins and needles, burning or numbness
2: Mild itching, pins and needles, burning or numbness
3: Moderate itching, pins and needles, burning or numbness
4: Moderately severe hallucinations
5: Severe hallucinations
6: Extremely severe hallucinations
7: Continuous hallucinations

Continued on following page

Appendix Table 2—Continued

Auditory disturbances
Ask: "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"
Observation:
0: Not present
1: Very mild harshness or ability to frighten
2: Mild harshness or ability to frighten
3: Moderate harshness or ability to frighten
4: Moderately severe hallucinations
5: Severe hallucinations
6: Extremely severe hallucinations
7: Continuous hallucinations

Visual disturbances
Ask: "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
Observation:
0: Not present
1: Very mild sensitivity
2: Mild sensitivity
3: Moderate sensitivity
4: Moderately severe hallucinations
5: Severe hallucinations
6: Extremely severe hallucinations
7: Continuous hallucinations

Headache, fullness in head
Ask: "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0: Not present
1: Very mild
2: Mild
3: Moderate
4: Moderately severe
5: Severe
6: Very severe
7: Extremely severe

Orientation and clouding of sensorium
Ask: "What day is this? Where are you? Who am I?"
0: Oriented and can do serial additions†
1: Cannot do serial additions or is uncertain about date
2: Disoriented for date by no more than 2 calendar days
3: Disoriented for date by more than 2 calendar days
4: Disoriented for place and/or person

Score: 0–7 = no withdrawal; 8–15 = mild withdrawal; 16–20 = moderate withdrawal; >20 = severe withdrawal.
** From 60. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84:1353-7. [PMID: 2597811]*
† Serial additions—ask patient to add by 7s.