

# 10 - Chapter 7

# Substance Related and Addictive Disorder

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## Chapter 7 Substance- Related and Addictive Disorders

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## 76 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS

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**Substance Use Disorders** Substance use disorders are characterized by a problematic pattern of substance use that leads to some form of functional impairment or distress. Keep in mind that frequent use of a substance does not necessarily indicate a substance use disorder unless it is causing problems for the patient.

**DIAGNOSIS AND DSM-5 CRITERIA** Substance use disorders are characterized by a problematic pattern of substance use causing impairment or distress, as manifested by at least two of the following within a 12-month period: ■ Using substance more than originally intended. ■ Persistent desire or unsuccessful efforts to cut down on use. ■ Significant time spent in obtaining, using, or recovering from substance. ■ Craving to use substance. ■ Failure to fulfill obligations at work, school, or home. ■ Continued use despite social or interpersonal problems due to the substance use. ■ Limiting social, occupational, or recreational activities because of substance use. ■ Use in dangerous situations (e.g., driving a car). ■ Continued use despite subsequent physical or psychological problem (e.g., drinking alcohol despite worsening liver problems). ■ Tolerance (needing higher amounts of the substance to achieve the desired effect or experiencing diminished effects when repeating the same dose). ■ Withdrawal (a substance-specific syndrome occurring when a patient stops or reduces heavy/prolonged substance use). Note that these criteria remain the same regardless of what substance(s) the patient is using. The disorder may be classified as mild, moderate, or severe depending on the number of criteria met.

**EPIDEMIOLOGY** ■ One-year prevalence of any substance use disorder in the United States is approximately 8%. ■ More common in men than women. ■ Alcohol and nicotine are the most commonly used substances.

**PSYCHIATRIC SYMPTOMS** ■ Mood symptoms are common among persons with substance use disorders. ■ Psychotic symptoms may occur with

some substances. ■ Personality disorders and psychiatric comorbidities (e.g., major depression, anxiety disorders) are common among persons with substance use disorders. ■ It is often challenging to decide whether psychiatric symptoms are primary or substance-induced. Many patients may use substances to self-medicate for undertreated psychiatric symptoms. **SUBSTANCE-RELATED AND ADDICTIVE DISORDERS WARDS TIP** It is possible to have a substance use disorder without having physiological dependence (i.e., without having withdrawal or tolerance). **WARDS TIP** Substance-induced mood symptoms improve during prolonged abstinence, whereas primary mood symptoms persist.

**78 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS ACUTE INTOXICATION AND WITHDRAWAL**  
**KEY FACT** Withdrawal symptoms of a drug are usually the opposite of its intoxication effects. For example, alcohol is sedating, but alcohol withdrawal can cause brain excitation and seizures.  
**DETECTION OF SUBSTANCE USE** See Table 7-1. **TREATMENT OF SUBSTANCE USE DISORDERS** **TABLE 7-1.** Direct Testing for Substance Use Phencyclidine (PCP) Marijuana Urine detection: Both the intoxicated and withdrawing patient can present difficulties in diagnosis and treatment. Since it is common for persons to abuse several substances at once, the clinical presentation is often confusing, and signs/symptoms may be atypical. Always be on the lookout for use of multiple substances. ■ Behavioral counseling should be part of every substance use disorder treatment. See Table 7-2. ■ Psychosocial treatments are effective and include motivational intervention (MI), cognitive-behavioral therapy (CBT), contingency management, and individual and group therapy. ■ For severe substance use disorders, residential (usually 28-day) “rehab” programs are common; some patients may choose to do partial hospitalization or intensive outpatient programming. **Alcohol** ■ Stays in system for only a few hours. ■ Breathalyzer test, commonly used by law enforcement. ■ Blood/urine testing more accurate. ■ Urine screening for metabolite (ethyl glucuronide) — not useful for assessing acute intoxication, but can indicate alcohol use over the preceding 2–5 days. **Cocaine** ■ Urine drug screen positive for 2–4 days (up to 8 days for heavy users). **Amphetamines** ■ Urine drug screen positive for 1–3 days. ■ Most assays have poor sensitivity and/or specificity. ■ Urine drug screen positive for 4–7 days. ■ OTC cold medications may yield false positive. ■ Creatine kinase (CK) and aspartate aminotransferase (AST) are often elevated. **Sedative/hypnotics** In urine and blood for variable amounts of time. **Barbiturates:** ■ Short-acting (pentobarbital): 24 hours ■ Long-acting (phenobarbital): 3 weeks **Benzodiazepines:** ■ Short-acting (e.g., lorazepam): up to 5 days ■ Long-acting (diazepam): up to 30 days **Opioids** ■ Urine drug test remains positive for 1–3 days, depending on opioid used. ■ Routine screening tests detect morphine, which is the eventual metabolite of all natural opioids. ■ Buprenorphine, synthetic opioids (methadone, fentanyl, tramadol) and semi-synthetic opioids (oxycodone, hydrocodone) will not be detected on routine screening (order separate assay). ■ After a single use, about 3 days. In heavy users, up to 4 weeks (THC is released from adipose stores).

**79 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS** ■ Community-based groups such as SMART Recovery, Alcoholics Anonymous (AA), and Narcotics Anonymous (NA) should also be encouraged as part of the treatment. ■ Pharmacotherapy is available for some drugs of abuse, and will be discussed later in this chapter as relevant to a particular substance. **Alcohol (EtOH)** ■ Alcohol activates gamma-aminobutyric acid (GABA), dopamine, and serotonin receptors in the central nervous system (CNS). It inhibits glutamate receptor activity and voltage-gated calcium channels. GABA receptors are inhibitory, and glutamate receptors are excitatory; thus, alcohol is a potent CNS depressant. ■ Lifetime prevalence of alcohol use disorder in the United States is 5% of women

and 12% of men. ■ Alcohol is metabolized in the following manner:

1. Alcohol → acetaldehyde (enzyme: alcohol dehydrogenase).
  2. Acetaldehyde → acetic acid (enzyme: aldehyde dehydrogenase). These enzymes are upregulated in heavy drinkers. Some populations produce less aldehyde dehydrogenase due to genetic variation, resulting in flushing and nausea with alcohol use.
- INTOXICATION Clinical Presentation** ■ The absorption and elimination rates of alcohol are variable and depend on many factors, including age, sex, body weight, chronic nature of use, TABLE 7-2.
- Stages of Change**
- | Stage            | Definition                                                                                                                                                                  | Example                                                                                                                                                                                 |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Precontemplation | Patients do not view their addiction as a problem. They may see substance use as helpful and/or enjoyable.                                                                  | A college student who drinks heavily feels that they need alcohol to overcome social anxiety and enjoy parties. They do not identify any negative consequences from their use.          |
| Contemplation    | The patient begins to think about cutting down or stopping altogether. They recognize potential benefits of making a change, but may be ambivalent or feel unable to do so. | The student misses several deadlines due to hangovers from drinking the night before. They think cutting down on alcohol might improve their grades, but aren't sure they want to stop. |
| Preparation      | The patient plans for the process of change. They collect information, and may experiment with very small changes.                                                          | The student begins researching self-help strategies for reducing alcohol intake. They look up campus resources for individual and group therapy.                                        |
| Action           | The patient takes direct steps toward reducing or stopping substance use.                                                                                                   | The student begins attending substance-use-focused groups on campus, and talks with their primary care doctor about starting naltrexone.                                                |
| Maintenance      | The patient has successfully made significant behavior change, and works to avoid relapse.                                                                                  | The student continues to drink, but limits themselves to 1-2 drinks per day, and only consumes alcohol on weekends.                                                                     |
| Relapse          | After a successful period of remission, patients resume substance use (or fall back into unhealthy patterns of use).                                                        | After graduating, the student is unemployed. They begin drinking again to cope with stress and unstructured time, and quickly escalates to near daily use.                              |
- Alcohol is the most common co-ingestant in drug overdoses. **WARDS TIP** Most adults will show some signs of intoxication with BAL >100 and obvious signs with BAL

“ 150 mg/dL. KEY FACT

80 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS **WARDS QUESTION** Q: What is the average rate of alcohol metabolism? A: Between 15 and 35 mg/dL per hour. **KEY FACT** Ethanol, along with methanol and ethylene glycol, can be a cause of anion gap metabolic acidosis. **Treatment KEY FACT** Males with substance use disorders, especially alcohol, have higher rates of perpetrating domestic violence. **WARDS QUESTION** Q: What are the typical features of Wernicke's encephalopathy? A: The classic triad is confusion (altered mental status), ataxic gait, and oculomotor findings (typically nystagmus or gaze palsies). **WITHDRAWAL** TABLE 7-3. **Clinical Presentation of Alcohol Intoxication Effects**

| BAL                                                                           | Effects       |
|-------------------------------------------------------------------------------|---------------|
| Impaired fine motor control                                                   | 20-50 mg/dL   |
| Impaired judgment and coordination                                            | 50-100 mg/dL  |
| Ataxic gait and poor balance                                                  | 100-150 mg/dL |
| Lethargy, difficulty sitting upright, difficulty with memory, nausea/vomiting | 150-250 mg/dL |
| Coma (in the novice drinker)                                                  | 300 mg/dL     |
| Respiratory depression, death possible                                        | 400 mg/dL     |

duration of

consumption, food in the stomach, and the state of nutrition and liver health. ■ In addition to the above factors, the effects of EtOH also depend on the blood alcohol level (BAL). Serum EtOH level or an expired air breathalyzer can determine the extent of intoxication. As shown in Table 7-3, patients with high tolerance may show diminished effects at a given BAL. ■ Monitor: Airway, breathing, circulation, glucose, electrolytes, acid-base status. ■ Give parenteral thiamine (to prevent or treat Wernicke's encephalopathy) and folate. Remember thiamine must be given before glucose, as it's a necessary cofactor for glucose metabolism. ■ Naloxone may be necessary to reverse effects of co-ingested opioids. ■ A computed tomography (CT) scan of the head may be necessary to rule out subdural hematoma or other brain injury. ■ The liver will eventually metabolize alcohol without any other interventions. ■ Severely intoxicated patients may require mechanical ventilation with attention to acid-base balance, temperature, and electrolytes while they are recovering. ■ Gastrointestinal evacuation (e.g., gastric lavage, induction of emesis, and charcoal) is not indicated in the treatment of EtOH overdose unless a significant amount of EtOH was ingested within the preceding 30-60 minutes. A 42-year-old man has routine surgery for a knee injury. After 72 hours in the hospital he becomes anxious, flushed, diaphoretic, hypertensive, and tachycardic. What most likely accounts for this patient's symptoms? Alcohol withdrawal. Treatment? Benzodiazepines (chlordiazepoxide [Librium] or lorazepam [Ativan] are considered the drugs of choice). What are you most concerned about? Seizures, delirium tremens, autonomic instability, and cardiac arrhythmias. Remember that alcohol withdrawal can be fatal. Chronic alcohol use has a depressant effect on the CNS, and cessation of use causes a compensatory hyperactivity with glutamate excitotoxicity. Alcohol withdrawal is potentially lethal!

Clinical Presentation ■ Signs and symptoms of alcohol withdrawal syndrome include insomnia, anxiety, hand tremor, irritability, anorexia, nausea, vomiting, autonomic hyperactivity (diaphoresis, tachycardia, hypertension), psychomotor agitation, fever, seizures, hallucinations, and delirium tremens (see Table 7-4). ■ The earliest symptoms of EtOH withdrawal begin between 6 and 24 hours after the patient's last drink and depend on the duration and quantity of EtOH consumption, liver size, and body mass. ■ Generalized tonic-clonic seizures usually occur between 12 and 48 hours after cessation of drinking, with a peak around 12-24 hours. ■ About a third of persons with seizures develop delirium tremens (DTs). ■ Hypomagnesemia may predispose to seizures; thus, it should be corrected promptly. ■ Seizures are treated with benzodiazepines. Long-term treatment with anticonvulsants is not recommended for alcohol withdrawal seizures. Delirium Tremens ■ The most serious form of EtOH withdrawal. ■ Usually begins 48-96 hours after the last drink but may occur later. ■ While only 5% of patients who experience EtOH withdrawal develop DTs, there is a roughly 5% mortality rate (up to 35% if left untreated). ■ Physical illness predisposes to the condition. ■ Age >30 and prior DTs increase the risk. ■ In addition to delirium, symptoms of DTs may include hallucinations (most commonly visual), agitation, gross tremor, autonomic instability, and fluctuating levels of psychomotor activity. ■ It is a medical emergency and should be treated with adequate doses of benzodiazepines. Treatment ■ Benzodiazepines (lorazepam, diazepam, or chlordiazepoxide) should be given in sufficient doses to keep the patient calm and lightly sedated, then tapered down slowly. Carbamazepine or valproic acid can be used in mild withdrawal. TABLE 7-4. Timing of Alcohol Withdrawal Symptoms Syndrome Clinical Findings Onset After Last Drink  
Minor withdrawal Tremulousness, mild anxiety, headache, diaphoresis, palpitations, anorexia, gastrointestinal upset; normal mental status Seizures Single or brief flurry of generalized tonic-clonic seizures, short postictal period, status epilepticus rare 6 to 48 hours Alcoholic hallucinosis Visual, auditory, and/or tactile hallucinations with intact orientation and normal vital signs 12 to 48

hours Delirium tremens Delirium, agitation, tachycardia, hypertension, fever, diaphoresis 48 to 96 hours Source: Used, with permission, from Hoffman RS, Weinhouse GL. Management of moderate and severe alcohol withdrawal syndromes. <https://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes>. © 2021 UpToDate, Inc. and/or its affiliates. All Rights Reserved. SUBSTANCE-RELATED AND ADDICTIVE DISORDERS KEY FACT Risk of suicide attempts is higher among those with psychiatric disorders and concurrent substance use (especially alcohol). KEY FACT Delirium tremens is a dangerous form of alcohol withdrawal involving mental status and neurological changes. Symptoms include disorientation, agitation, visual and tactile hallucinations, and autonomic instability (increase in respiratory rate, heart rate, and blood pressure). It carries a 5% mortality rate but occurs in only 5% of patients that experience EtOH withdrawal. Patients often require ICU level of care; treatment includes supportive care and benzodiazepines. 6 to 36 hours

82 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS KEY FACT Confabulation—inventing stories of events that never occurred—is often associated with Korsakoff’s “psychosis,” or alcohol-induced neurocognitive disorder. Patients are unaware that they are “making things up.” Alcoholic Ketoacidosis ■ Parenteral thiamine, folic acid, and a multivitamin to treat nutritional deficiencies (“banana bag”). ■ Electrolyte and fluid abnormalities must be corrected. ■ Monitor withdrawal signs and symptoms with the Clinical Institute Withdrawal Assessment (CIWA) scale. ■ Providers must pay careful attention to the level of consciousness, and consider the possibility of traumatic injuries. ■ Check for signs of hepatic failure (e.g., ascites, jaundice, caput medusae, coagulopathy). ■ Frequently seen in the setting of alcohol cessation after an alcohol binge secondary to protracted vomiting and lack of oral intake. ■ Hallmark is ketosis without hyperglycemia and a negative alcohol level. ■ Laboratory studies reveal a high anion gap metabolic acidosis, ketonemia, and low levels of potassium, magnesium, and phosphorus. ■ Treatment consists of hydration with D5NS, and replacing electrolytes. Mr. Smith is a 42-year-old divorced man who arrives to the ED requesting treatment for alcohol detoxification. He began drinking at the age of 17. Although he initially drank only on the weekends, his alcohol use gradually progressed to drinking half a pint of whiskey daily by the age of 35. At that time, he arrived to his workplace intoxicated on several occasions and was referred to a 45-day inpatient alcohol addiction program. After completing the program, he was able to maintain sobriety for 7 years. However, 2 years ago he got divorced, was laid off from work, and ultimately relapsed into alcohol use. Mr. Smith is currently living with his older sister and states that his drinking is “out of control.” He had a DUI recently and has a court date in 2 weeks. He has tried to quit alcohol on his own on several occasions. However, when he stops drinking he feels “shaky, sweaty, anxious, and irritable” and thus resumes his alcohol intake. He also reports a history of a seizure 10 years ago, after he abruptly discontinued his alcohol use for a few days. Mr. Smith’s last drink was about 8 hours prior to his arrival at the ED. During the last month he has been feeling sad, with low energy, difficulty falling and staying asleep, low appetite, and difficulty concentrating. He denies suicidal ideation but has significant guilt over not being able to stop drinking. He denies a history of depression or anxiety, and has not received any other psychiatric treatment in the past. Upon presentation to ER the patient’s blood alcohol level was 110, he did not have symptoms of intoxication, and his urine drug screen was negative. Vital signs were significant for blood pressure of 150/90 and pulse of 110 bpm. Complete blood count and electrolytes were within normal limits. What is Mr. Smith’s most likely diagnosis? The patient has a diagnosis of alcohol use disorder, with current signs of withdrawal. It is clear that he has exhibited symptoms of tolerance and withdrawal, has been using

more alcohol than intended, and has made unsuccessful efforts to cut down. He also describes symptoms suggestive of a depressive disorder. The fact that his depressive symptoms began while abusing alcohol warrants a diagnosis of alcohol-induced depressive disorder. However, major depressive disorder should be ruled out once he remits his alcohol use. If his depressive symptoms are indeed substance-induced, they will improve and resolve with continuing sobriety.

What would be the next step in management? Given the Mr. Smith's heavy chronic alcohol use and history of complicated withdrawal (i.e., seizure), he should be admitted to an inpatient unit for close monitoring. Outpatient detoxification is not appropriate in this case. He will likely require a standing and PRN benzodiazepine (the particular benzodiazepine sometimes varies depending on hospital's protocol), as well as close monitoring for signs of withdrawal. **ALCOHOL USE DISORDER** ■ The AUDIT-C (Table 7-5) is used to screen for alcohol use disorder. ■ Biochemical markers are useful in detecting recent prolonged drinking; ongoing monitoring of biomarkers can also help detect a relapse. Most commonly used biomarkers are BAL, liver function tests ([LFTs]—aspartate aminotransferase [AST], alanine aminotransferase [ALT]), gamma-glutamyl transpeptidase (GGT), and mean corpuscular volume (MCV). Urine screening for ethyl glucuronide can indicate alcohol use in the 2–5 days prior to testing. Medications for Alcohol Use Disorder See Table 7-6. Long-Term Complications of Alcohol Intake ■ Wernicke's encephalopathy: ●Caused by thiamine (vitamin B1) deficiency resulting from poor nutrition. **TABLE 7-5. AUDIT-C Question #1: How often did you have a drink containing alcohol in the past year?** ■ Never (0 points) ■ Monthly or less (1 point) ■ Two to four times a month (2 points) ■ Two to three times per week (3 points) ■ Four or more times a week (4 points) **Question #2: How many drinks did you have on a typical day when you were drinking in the past year?** ■ 1 or 2 (0 points) ■ 3 or 4 (1 point) ■ 5 or 6 (2 points) ■ 7 to 9 (3 points) ■ 10 or more (4 points) **Question #3: How often did you have six or more drinks on one occasion in the past year?** ■ Never (0 points) ■ Less than monthly (1 point) ■ Monthly (2 points) ■ Weekly (3 points) ■ Daily or almost daily (4 points) The AUDIT-C is scored on a scale of 0–12 (scores of 0 reflect no alcohol use). In men, a score of 4 or more is considered positive; in women, a score of 3 or more is considered positive. **SUBSTANCE-RELATED AND ADDICTIVE DISORDERS** **WARDS TIP** At-risk or heavy drinking for men is more than 4 drinks per day or more than 14 drinks per week. For women, it is more than 3 drinks per day or more than 7 drinks per week. **KEY FACT** AST:ALT ratio  $\geq 2:1$  and elevated GGT suggest excessive long-term alcohol use; they take a few weeks to return to normal during abstinence.

**84 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS** ●Acute and can be reversed with thiamine therapy. ●Features: Ataxia (broad-based), confusion, ocular abnormalities (nystagmus, gaze palsies). ■ If left untreated, Wernicke's encephalopathy may progress to Korsakoff syndrome: ●Chronic amnestic syndrome. ●Reversible in only about 20% of patients. ●Features: Impaired recent memory, anterograde amnesia, compensatory confabulation (unconsciously making up answers when memory has failed). **Cocaine** Cocaine blocks the reuptake of dopamine, epinephrine, and norepinephrine from the synaptic cleft, causing a stimulant effect. Dopamine plays a role in the behavioral reinforcement ("reward") system of the brain. **INTOXICATION** ■ General: Euphoria, heightened self-esteem, increase or decrease in blood pressure, tachycardia or bradycardia, nausea, dilated pupils, weight loss, psychomotor agitation or depression, chills, and sweating. ■ Dangerous: Seizures, cardiac arrhythmias, hyperthermia, paranoia, and hallucinations (especially tactile). Since cocaine is an indirect sympathomimetic, intoxication mimics the fight-or-flight response. ■ Deadly: Cocaine's vasoconstrictive effect may result in myocardial infarction (MI),

intracranial hemorrhage, or stroke. **WARDS QUESTION Q:** What is the treatment for Wernicke's encephalopathy? **A:** High dose parenteral (IV or IM) thiamine should be given for 2–7 days, followed by daily oral thiamine. Give all patients with altered mental status thiamine before glucose, to avoid precipitating Wernicke–Korsakoff syndrome. Thiamine is a coenzyme used in carbohydrate metabolism. **WARDS TIP TABLE 7-6. Pharmacological Treatment of Alcohol Use Disorder Medication Mechanism Pros Cons** Naltrexone Opioid receptor antagonist; reduces cravings and the “high” associated with alcohol intoxication. First-line treatment. Will precipitate withdrawal in patients with physical opioid dependence. Can interfere with anesthesia (e.g., for acute injury or planned surgeries). Risk of LFT elevation. Available as an oral tablet (can be taken daily, or as-needed on drinking days), or monthly injection. Can allow some patients to engage in moderate alcohol use without escalating to binge drinking. Acamprosate Likely modulates glutamate transmission. First-line treatment. Contraindicated in severe renal disease. Can be used for patients with liver disease. Typically used for relapse prevention in patients who have already stopped drinking. Disulfiram Blocks aldehyde dehydrogenase, causing buildup of acetaldehyde and aversive symptoms (flushing, headache, nausea/vomiting, palpitations, shortness of breath). Second-line. Can be effective for highly motivated patients. Medication adherence can be an issue. Contraindicated in severe cardiac disease, pregnancy, psychosis. Must monitor LFTs. Topiramate Anticonvulsant; potentiates GABA and inhibits glutamate receptors. Second-line treatment. Reduces cravings for alcohol, and decreases alcohol use. Common adverse effects: impaired cognition (“DOPE-a-max”), nausea / weight loss, metabolic acidosis.

**Management** ■ For mild-to-moderate agitation and anxiety: Reassurance of the patient and benzodiazepines. ■ For severe agitation or psychosis: Antipsychotics (e.g., haloperidol). ■ Symptomatic support (i.e., control hypertension, arrhythmias). ■ Temperature of >102°F should be treated aggressively with an ice bath, cooling blanket, and other supportive measures. **COCAINE USE DISORDER** Treatment of cocaine use disorder: ■ There is no Food and Drug Administration (FDA)-approved pharmacotherapy for cocaine use disorder. ■ Off-label medications are sometimes used (naltrexone, modafinil, topiramate). ■ Psychological interventions (contingency management, relapse prevention, NA, etc.) are the mainstay of treatment. **WITHDRAWAL** ■ Abrupt abstinence is not life threatening. ■ Produces post-intoxication depression (“crash”): Malaise, fatigue, hypersomnolence, depression, anhedonia, hunger, constricted pupils, vivid dreams, psychomotor agitation, or retardation. Occasionally, these patients can become suicidal. ■ With mild-to-moderate cocaine use, withdrawal symptoms resolve within 72 hours; with heavy, chronic use, they may last for 1–2 weeks. ■ Treatment is supportive, but severe psychiatric symptoms may warrant hospitalization. **Amphetamines** ■ Classic amphetamines: ●Block reuptake and facilitate release of dopamine and norepinephrine from nerve endings, causing a stimulant effect. ●Examples: Dextroamphetamine (Dexedrine), methylphenidate (Ritalin), methamphetamine (Desoxyn, “ice,” “speed,” “crystal meth,” “crank”). ●Methamphetamines are easily manufactured in home laboratories using over-the-counter medications (e.g., pseudoephedrine). ●Methamphetamines are used medically in the treatment of narcolepsy, attention deficit/hyperactivity disorder (ADHD), binge eating, and occasionally depressive disorders. ■ Substituted (“designer,” “club drugs”) amphetamines: ●Release dopamine, norepinephrine, and serotonin from nerve endings. ●Examples: MDMA (“ecstasy”), MDEA (“eve”). ●Often used in dance clubs and raves. ●Have both stimulant and hallucinogenic properties. ●Serotonin syndrome is possible if designer amphetamines are combined with selective serotonin reuptake inhibitors (SSRIs). **SUBSTANCE-RELATED AND ADDICTIVE DISORDERS** **WARDS QUESTION Q:** Why should beta-

blockers be avoided for patients who regularly use cocaine? A: Cocaine has both alpha and beta-adrenergic effects. If a beta-blocker is given simultaneously, unopposed alpha-adrenergic activity can cause coronary vasoconstriction and induce myocardial infarction. KEY FACT Cocaine or amphetamines can both cause formication, a tactile hallucination of something crawling on or under the skin. KEY FACT Symptoms of amphetamine intoxication include euphoria, dilated pupils, increased libido, tachycardia, perspiration, grinding teeth, and chest pain.

86 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS INTOXICATION WARDS TIP Clinical Presentation Chronic amphetamine use leads to accelerated tooth decay (“meth mouth”). WARDS TIP Both amphetamine and PCP use can cause rhabdomyolysis. Look for elevated creatine kinase (CK) and monitor closely for acute kidney injury. Treatment is mostly supportive and emphasizes - hydration. Phencyclidine (PCP) KEY FACT Ketamine (“special K”) can produce tachycardia, tachypnea, hallucinations, and amnesia. INTOXICATION Clinical Presentation KEY FACT PCP intoxication symptoms— RED DANES Rage Erythema (redness of skin) Dilated pupils Delusions Amnesia Nystagmus Excitation Skin dryness Treatment WITHDRAWAL KEY FACT Nystagmus (especially rotary) is very common in PCP intoxication. ■ Amphetamine intoxication causes symptoms similar to those of cocaine (see above). ■ MDMA and MDEA may induce sense of closeness to others. ■ Overdose can cause hyperthermia, dehydration (especially after a prolonged period of dancing in a club), rhabdomyolysis, and renal failure. ■ Complications of their long half-life can cause ongoing psychosis, even during abstinence. ■ Amphetamine withdrawal can cause prolonged depression. Treatment Rehydrate, correct electrolyte balance, and treat hyperthermia. PCP, or “angel dust,” is a dissociative, hallucinogenic drug that antagonizes N-methyl-d-aspartate (NMDA) glutamate receptors and activates dopaminergic neurons. It can have stimulant or CNS depressant effects, depending on the dose taken. ■ PCP can be smoked as “wet” (sprinkled on cigarette) or as a “joint” (sprinkled on marijuana). ■ Ketamine is similar to PCP, but is less potent. Ketamine is sometimes used as a “date rape” drug, as it is odorless and tasteless. ■ Effects include agitation, depersonalization, hallucinations, synesthesia (one sensory stimulation evokes another—e.g., hearing a sound causes one to see a color), impaired judgment, memory impairment, combativeness, nystagmus (rotary, horizontal, or vertical), ataxia, dysarthria, hypertension, tachycardia, muscle rigidity, and high tolerance to pain. ■ Overdose can cause seizures, delirium, coma, and even death. ■ Monitor vitals, temperature, and electrolytes, and minimize sensory stimulation. ■ Use benzodiazepines (lorazepam) to treat agitation, anxiety, muscle spasms, and seizures. ■ Use antipsychotics (haloperidol) to control severe agitation or psychotic symptoms. No withdrawal syndrome, but “flashbacks” (recurrence of intoxication - symptoms due to release of the drug from body lipid stores) may occur.

Sedative-Hypnotics Agents in the sedative-hypnotics category include benzodiazepines, barbiturates, zolpidem, zaleplon, gamma-hydroxybutyrate (GHB), meprobamate, and others. These medications, especially benzodiazepines, are highly abused in the United States, as they are more readily available than other drugs such as cocaine. ■ Benzodiazepines (BZDs): ●Commonly used in the treatment of anxiety disorders. ●Easily obtained via prescription from physicians’ offices and emergency departments. ●Potentiate the effects of GABA by modulating the receptor, thereby increasing frequency of chloride channel opening. ■ Barbiturates: ●Used in the treatment of epilepsy and as anesthetics. ●Potentiate the effects of GABA by binding to the receptor and increasing duration of chloride channel opening. ●At high doses, barbiturates act as direct GABA agonists, and therefore have a lower margin of safety relative to BZDs. Overdose can be lethal.

● They are synergistic in combination with BZDs (as well as other CNS depressants such as alcohol); respiratory depression can occur. **INTOXICATION Clinical Presentation** ■ Intoxication with sedatives produces drowsiness, confusion, hypotension, slurred speech, incoordination, ataxia, mood lability, impaired judgment, nystagmus, respiratory depression, and coma or death in overdose. ■ Symptoms are synergistic when combined with EtOH or opioids/narcotics. ■ Long-term sedative use may lead to dependence and may cause depressive symptoms. **Treatment** ■ Maintain airway, breathing, and circulation. Monitor vital signs. ■ Activated charcoal and gastric lavage to prevent further gastrointestinal absorption (if drug was ingested in the prior 4–6 hours). ■ For barbiturates only: Alkalinize urine with sodium bicarbonate to promote renal excretion. ■ For benzodiazepines only: Flumazenil in overdose. ■ Supportive care—Improve respiratory status, control hypotension. **WITHDRAWAL** Abrupt abstinence after chronic use can be life threatening. While physiological dependence is more likely with short-acting agents, longer-acting agents can also cause dependence and withdrawal symptoms. **CLINICAL PRESENTATION** Signs and symptoms of withdrawal are the same as these of EtOH withdrawal. Tonic-clonic seizures may occur and can be life threatening. **SUBSTANCE-RELATED AND ADDICTIVE DISORDERS KEY FACT** PCP intoxication is associated with violence, more so than other drugs. **KEY FACT** Gamma-hydroxybutyrate (GHB) is a CNS depressant that produces confusion, dizziness, drowsiness, memory loss, respiratory distress, and coma. It is commonly used as a date-rape drug. **WARDS QUESTION Q:** Which substances of abuse have potentially fatal withdrawal syndromes? **A:** Alcohol, benzodiazepines, and barbiturates. **WARDS TIP** Flumazenil is a very short-acting BZD antagonist used for treating BZD overdose. Use with caution when treating overdose, as it may precipitate seizures. **KEY FACT** The opioid dextromethorphan is a common ingredient in cough syrup.

**88 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS Treatment KEY FACT** Infection secondary to needle sharing is a common cause of morbidity from street heroin usage. **Opioids KEY FACT** Opioid intoxication: Nausea, vomiting, sedation, decrease in pain perception, decrease in gastrointestinal motility, pupil constriction, and respiratory depression (which can be fatal). **INTOXICATION Clinical Presentation KEY FACT** Meperidine is the exception to opioids producing miosis. “Demerol Dilates pupils.” **Treatment KEY FACT** ■ Ventilatory support may be required. Naloxone is the treatment of choice for opiate overdose. **OPIATE USE DISORDER WARDS TIP WITHDRAWAL** Classic triad of opioid overdose—Rebels Admire Morphine Respiratory depression Altered mental status Miosis ■ Benzodiazepines (stabilize patient, then taper gradually). ■ Carbamazepine or valproic acid taper not as beneficial. ■ Opioid medications and drugs of abuse stimulate mu, kappa, and delta opiate receptors (normally stimulated by endogenous opiates), and are involved in analgesia, sedation, and dependence. Examples include heroin, oxycodone, codeine, dextromethorphan, morphine, methadone, and meperidine (Demerol). ■ Opioids also have effects on the dopaminergic system, which mediates their addictive and rewarding properties. ■ Prescription opioids (OxyContin [oxycodone], Vicodin [hydrocodone/ acetaminophen], and Percocet [oxycodone/acetaminophen])—not heroin—are the most commonly used opioids. ■ Behaviors such as losing medication, “doctor shopping,” and running out of medication early should alert clinicians of possible misuse. ■ Opioids are associated with more deaths (usually due to unintentional overdose) than any other drug. ■ Opioid intoxication causes drowsiness, nausea/vomiting, constipation, slurred speech, constricted pupils, seizures, and respiratory depression, which may progress to coma or death in overdose. ■ Meperidine and monoamine oxidase inhibitors taken in combination may cause serotonin syndrome: hyperthermia, confusion, hypertension or hypotension, and hyperreflexia. ■ Ensure adequate airway, breathing, and

circulation. ■ In overdose, administration of naloxone (an opioid antagonist) will improve respiratory depression but may cause severe withdrawal in an opioid-dependent patient. ■ Patients at risk of opioid overdose should be prescribed a naloxone (Narcan) kit to keep at home for emergencies. See Table 7-7 for treatment of opioid use disorder. ■ While not life threatening, abstinence in the opioid-dependent individual leads to an unpleasant withdrawal syndrome characterized by dysphoria, insomnia, lacrimation, rhinorrhea, yawning, weakness, sweating, piloerection, nausea/vomiting, fever, dilated pupils, abdominal cramps, arthralgia/myalgia, hypertension, tachycardia, and craving.

89 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS ■ Treatment includes: ●Moderate symptoms: Symptomatic treatment with clonidine (for autonomic signs and symptoms of withdrawal), nonsteroidal anti-inflammatory drugs (NSAIDs) for pain, loperamide for diarrhea, dicyclomine for abdominal cramps, promethazine for nausea, etc. ●Severe symptoms: Detox with buprenorphine or methadone. ●Monitor degree of withdrawal with COWS (Clinical Opioid Withdrawal Scale), which uses objective measures (i.e., pulse, pupil size, tremor) to assess withdrawal severity. Hallucinogens Hallucinogenic drugs of abuse include psilocybin (mushrooms), mescaline (peyote cactus), and lysergic acid diethylamide (LSD). Pharmacological effects vary, but LSD is believed to act on the serotonergic system. Hallucinogens do not cause physical dependence or withdrawal, though users can rarely develop psychological dependence.

INTOXICATION ■ Effects include perceptual changes (illusions, hallucinations, body image distortions, synesthesia), labile affect, dilated pupils, tachycardia, hypertension, hyperthermia, tremors, incoordination, sweating, and palpitations. TABLE 7-7. Pharmacological Treatment of Opioid Use Disorder Medication Mechanism Pros Cons Methadone Full agonist at mu-opioid receptor. Administered once daily. Long half life. Restricted to federally licensed substance abuse treatment programs. Can cause QTc interval prolongation: screening electrocardiogram is indicated, particularly in patients with high risk of cardiac disease. Presenting to the methadone clinic for regular pickups can be helpful for patients who benefit from daily structure and access to group therapy or case management. Patients can still use other opioids on top of methadone. Buprenorphine Partial opioid receptor agonist—can precipitate withdrawal if used too soon after full opioid agonists. Sublingual preparation that is safer than methadone, as its effects reach a plateau and make overdose unlikely. In the outpatient setting, can only be prescribed by a physician with a special waiver on their controlled substances license. Combined formulation (buprenorphine-naloxone, or Suboxone) prevents intoxication from intravenous or intranasal use. Naltrexone Competitive opioid antagonist, precipitates withdrawal if used within 7 days of heroin use Available as daily oral medication or monthly depot injection. It is a good choice for highly motivated patients such as health care professionals. Adherence is an issue for oral formulation. Risk of LFT elevation. Can interfere with anesthesia (e.g., for acute injuries or surgical procedures). Naloxone Competitive opioid antagonist, used in treatment of overdose. Can be life-saving for patients or their peers, and should routinely be prescribed for all patients with opioid use disorder (especially for those who are receiving medication-assisted treatment). Does not reduce opioid use or treat symptoms of opioid use disorder. Very short half-life; patients must be educated about need to call EMS or present to ED after it's administered (even if the overdose appears to be reversed). Rapid recovery of consciousness following the administration of intravenous (IV) naloxone (a potent opioid antagonist) is consistent with opioid overdose. WARDS TIP Eating large amounts of poppy seed bagels or muffins can result in a urine drug screen that is positive for opioids. KEY FACT

90 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS KEY FACT Remember the withdrawal symptoms of opiates: flu-like symptoms (body aches, anorexia, rhinorrhea, fever), diarrhea, anxiety, insomnia, and piloerection. These are not life threatening. WITHDRAWAL Marijuana KEY FACT An LSD flashback is a spontaneous recurrence of symptoms mimicking a prior LSD “trip” that may last for minutes to hours. INTOXICATION KEY FACT Dronabinol is a pill form of THC that is FDA-approved for certain indications. WITHDRAWAL ■ Treatment: Supportive and symptomatic. Inhalants ■ Usually lasts 6–12 hours, but may last for several days. ■ May have a “bad trip” that consists of marked anxiety, panic, and psychotic symptoms (paranoia, hallucinations). ■ Treatment: Monitor for dangerous behavior and reassure patient. Use benzodiazepines as first-line for agitation (can use antipsychotics if needed). No withdrawal syndrome is produced, but with long-term LSD use, patients may experience flashbacks later in life. ■ Cannabis (“marijuana,” “pot,” “weed,” “grass”) is the most commonly used illicit substance in the world. ■ The main psychoactive component which produces the “high” in cannabis is THC (tetrahydrocannabinol). ■ Cannabinoid receptors in the brain inhibit adenylate cyclase. ■ Marijuana has shown some efficacy in treating nausea and vomiting in chemotherapy patients, increasing appetite in AIDS patients, in chronic pain (from cancer), and lowering intraocular pressure in glaucoma. A specific class of compounds found in marijuana, cannabidiols (CBDs), is currently being studied for management of pain, seizures, and anxiety/depression. ■ Marijuana causes euphoria, anxiety, impaired motor coordination, perceptual disturbances (sensation of slowed time), mild tachycardia, anxiety, conjunctival injection (red eyes), dry mouth, and increased appetite (“the munchies”). ■ Cannabis-induced psychotic disorders with paranoia, hallucinations, and/or delusions may occur. There is no overdose syndrome for marijuana use. ■ Cannabis use disorder occurs in approximately 10% of those who use (up to 50% of daily users). ■ Chronic use may cause respiratory problems such as asthma and chronic bronchitis, immunosuppression, cancer, and possible effects on reproductive hormones. ■ Treatment: Supportive, psychosocial interventions (e.g., contingency management, groups). ■ Withdrawal symptoms may include irritability, anxiety, restlessness, aggression, strange dreams, depression, headaches, sweating, chills, insomnia, and low appetite. ■ Inhalants include a broad range of drugs that are inhaled and absorbed through the lungs.

■ Inhalants generally act as CNS depressants. ■ Most commonly used by preadolescents or adolescents; rate of use is similar between boys and girls (but rare in adult females). ■ Examples: Solvents, glue, paint thinners, fuels, isobutyl nitrates (“huffing,” “laughing gas,” “rush,” “bolt”). INTOXICATION ■ Effects: Perceptual disturbances, paranoia, lethargy, dizziness, nausea/vomiting, headache, nystagmus, tremor, muscle weakness, hyporeflexia, ataxia, slurred speech, euphoria, hypoxia, clouding of consciousness, stupor, or coma. ■ Acute intoxication: 15–30 minutes. May be sustained with repeated use. ■ Overdose: May be fatal secondary to respiratory depression or cardiac arrhythmias. ■ Long-term use may cause permanent damage to CNS (e.g., neurocognitive impairment, cerebellar dysfunction, Parkinsonism, seizures), peripheral neuropathy, myopathy, aplastic anemia, malignancy, metabolic acidosis, urinary calculi, glomerulonephritis, myocarditis, MI, and hepatotoxicity. ■ Treatment: Monitor airway, breathing, and circulation; may need oxygen with hypoxic states. ■ Identify solvent because some (e.g., leaded gasoline) may require chelation. WITHDRAWAL A withdrawal syndrome does not usually occur, but symptoms may include irritability, sleep disturbance, anxiety, depression, nausea, vomiting, and craving. Caffeine Caffeine is the most commonly used psychoactive substance in the United States, usually in the form of coffee, tea, or energy drinks. It acts as an adenosine antagonist, causing increase in cyclic adenosine monophosphate (cAMP) and stimulating the release of excitatory neurotransmitters.

**OVERDOSE** ■ More than 250 mg (2 cups of coffee): Anxiety, insomnia, muscle twitching, rambling speech, flushed face, diuresis, gastrointestinal disturbance, restlessness, excitement, and tachycardia. ■ More than 1 g: May cause tinnitus, severe agitation, visual light flashes, and cardiac arrhythmias. ■ More than 10 g: Death may occur secondary to seizures and respiratory failure. ■ Treatment: Supportive and symptomatic. **WITHDRAWAL** ■ Caffeine withdrawal symptoms occur in 50–75% of caffeine users if cessation is abrupt. ■ Withdrawal symptoms include headache, fatigue, irritability, nausea, vomiting, drowsiness, muscle pain, and depression. ■ Usually resolves within 1½ weeks. **SUBSTANCE-RELATED AND ADDICTIVE DISORDERS**

**92 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS Nicotine** **WARDS TIP** Cigarette smoking during pregnancy is associated with low birth weight, SIDS, and a variety of postnatal morbidities. **TREATMENT OF NICOTINE DEPENDENCE** FDA-approved pharmacotherapy: ■ Relapse after abstinence is common. **Gambling Disorder** **DIAGNOSIS AND DSM-5 CRITERIA** ■ Nicotine is derived from the tobacco plant, and stimulates nicotinic receptors in autonomic ganglia of the sympathetic and parasympathetic nervous systems. It is highly addictive through its effects on the dopaminergic system. ■ Nicotine use causes both tolerance and physical dependence (i.e., prominent craving and withdrawal). ■ Cigarette smoking is the leading cause of preventable morbidity and mortality in the United States, posing many health risks including chronic obstructive pulmonary disease (COPD), cardiovascular diseases, and various cancers. ■ Current smoking prevalence is about 15% of U.S. adults. ■ Effects: Restlessness, insomnia, anxiety, and increase in gastrointestinal motility. ■ Withdrawal symptoms: Intense craving, dysphoria, anxiety, poor concentration, increase in appetite, weight gain, irritability, restlessness, and insomnia. ■ Varenicline (Chantix): α4β2 nicotinic cholinergic receptor (nAChR) partial agonist that mimics the action of nicotine, reducing the rewarding aspects and preventing withdrawal symptoms. ■ Bupropion (Zyban): Antidepressant inhibits reuptake of dopamine and norepinephrine; helps reduce craving and withdrawal symptoms. ■ Nicotine replacement therapy (NRT): Available as transdermal patch, gum, lozenge, nasal spray, and inhaler. ■ Behavioral support/counseling should be part of every treatment. Persistent and recurrent problematic gambling behavior, as evidenced by four or more of the following in a 12-month period:

1. Preoccupation with gambling.
2. Need to gamble with increasing amount of money to achieve pleasure.
3. Repeated and unsuccessful attempts to cut down on or stop gambling.
4. Restlessness or irritability when attempting to stop gambling.
5. Gambling when feeling distressed (depressed, anxious, etc.).
6. Returning to reclaim losses after gambling (“get even”).
7. Lying to hide level of gambling.
8. Jeopardizing relationships or job because of gambling.
9. Relying on others to financially support gambling.

**EPIDEMIOLOGY/ETIOLOGY** ■ Prevalence: 0.4–1.0% of adults in the United States. ■ Men represent most of the cases. ■ More common in young adults and middle-aged, and lower rates in older adults. ■ Similar to substance use disorders, the course is marked by periods of abstinence and relapse. ■ Increased incidence of mood disorders, anxiety disorders, substance use disorders, and personality disorders. ■ Etiology may involve genetic, temperamental, environmental, and neurochemical factors. ■ One-third may achieve recovery without treatment. **TREATMENT** ■

Participation in Gamblers Anonymous (a 12-step program) is the most common treatment. ■ Cognitive-behavioral therapy has been shown to be effective, particularly when combined with Gamblers Anonymous. ■ Important to treat comorbid mood disorders, anxiety disorders, and substance use disorders where appropriate. SUBSTANCE-RELATED AND ADDICTIVE DISORDERS

#### 94 SUBSTANCE-RELATED AND ADDICTIVE DISORDERS NOTES