Chapter 72: Substance Use Disorders: Alcohol, CNS Depressants, Stimulants, Nicotine

INTRODUCTION

Substance use disorder (SUD) is a lifelong illness that consists of intoxication and withdrawal from the substance that may cause euphoria. Because this illness affects brain and behavior, it results in the inability to limit or control the use of legal and illegal substances.

PATHOPHYSIOLOGY

- The true etiology behind SUD is unknown. In general, it is felt that there needs to be a triad of the right patient, with the right genetic risk factors, being exposed to the right medication or substance in order for a SUD to occur.

CENTRAL NERVOUS SYSTEM DEPRESSANTS: CLINCAL PRESENTATION

Alcohol Use Disorder

- **Table 72-1** relates the effects of **alcohol** to the blood alcohol concentration (BAC).
- Alcohol withdrawal includes (1) a history of cessation or reduction in heavy and prolonged alcohol use and (2) the presence of two or more of the symptoms of alcohol withdrawal.
- There is 14 g of alcohol in 12 oz of beer, 5 oz of wine, or 1.5 oz (one shot) of 80-proof whiskey. This amount will increase the BAC by approximately 20–25 mg/dL (4.3–5.4 mmol/L) in a healthy 70-kg (154-lb) man. Deaths generally occur when BACs are greater than 400–500 mg/dL (87–109 mmol/L).
- Absorption of alcohol begins in the stomach within 5–10 minutes of ingestion. Peak concentrations are usually achieved 30–90 minutes after finishing the last drink.
- Alcohol is metabolized by alcohol dehydrogenase to acetaldehyde, which is metabolized to carbon dioxide and water by aldehyde dehydrogenase. Catalase and the microsomal alcohol oxidase system are also involved.
- Most clinical laboratories report BAC in milligrams per deciliter. In legal cases, results are reported in percentage (grams of alcohol per 100 mL of whole blood). Thus, a BAC of 150 mg/dL = 0.15% = 34 mmol/L.

TABLE 72-1

Specific Effects of Alcohol Related to Blood Alcohol Concentration

BAC (%)[a] (mmol/L)	Type of Impairment	Effect(s)
0.0–0.05 (0–12)	Mild	Mild speech/memory/attention/coordination/balance impairment, relaxation, sleepiness
0.06–0.15 (13–34)	Increased	Impaired speech/memory/attention/coordination/balance, risk of aggression, significantly impaired driving skills, increased risk of injury to self and others, moderate memory impairment
0.16–0.30 (35–65)	Severe	Impaired speech/memory/attention/coordination/reaction time, balance significantly impaired, driving skills dangerously impaired, judgment and decision making dangerously impaired, blackouts, vomiting and signs of alcohol poisoning common, loss of consciousness
0.31–0.45 (66–98)	Life-threatening	Loss of consciousness, danger of life-threatening alcohol poisoning, significant risk of death

[a]Grams of ethyl alcohol per 100 mL of whole blood.

BAC, blood alcohol concentration.

Benzodiazepines and Other Sedative–Hypnotic Misuse

- Benzodiazepine intoxication is manifested as slurred speech, poor coordination, swaying, drowsiness, hypotension, nystagmus, and confusion.
- Likelihood and severity of withdrawal are a function of dose and duration of exposure. Gradual tapering of dosage is necessary to minimize withdrawal and rebound anxiety.
- Signs and symptoms of benzodiazepine withdrawal are similar to those of alcohol withdrawal, including dizziness, flu-like symptoms, impaired memory and concentration, nausea, vomiting, nightmares, visual disturbances, convulsions, muscle pain, anxiety, agitation, restlessness, confusion, irritability, hallucinations, delirium, seizures, and cardiovascular collapse. Withdrawal from short-acting benzodiazepines (eg, **oxazepam, lorazepam**, and **alprazolam**) has an onset within 12–24 hours of the last dose. **Diazepam, chlordiazepoxide**, and **clorazepate** have elimination half-lives (or active metabolites with elimination half-lives) of 24 to more than 100 hours. Thus, withdrawal may be delayed for up to 7 days after their discontinuation.
- **Flunitrazepam** (Rohypnol) is most commonly ingested orally, frequently in conjunction with alcohol or other drugs. Often called a *date-rape drug*, it has been given to women (without their knowledge) to lower their inhibitions.
- Zolpidem is reported to have little liability for physical dependence, but tolerance and withdrawal have been reported.

Carisoprodol

- **Carisoprodol** is used for muscle spasms and back pain. **Meprobamate** is one of its metabolites.
- It can cause drowsiness, dizziness, vertigo, ataxia, tremor, irritability, headache, syncope, insomnia, tachycardia, postural hypotension, nausea, agitation, depression, weakness, and confusion.
- Overdose can cause stupor, coma, respiratory depression, and death.

DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (*DSM-5*) defines SUD as "problematic pattern of substance use leading to clinically significant impairment or distress as manifested by at least two of eleven criteria occurring in the preceding 12-month period." See Diagnosis section in Chapter 69 for greater detail.
- The CAGE questionnaire or alcohol use disorders identification test (AUDIT) can be used to assess alcohol dependence/abuse.

TREATMENT

- Goals of Treatment: The goals include cessation of use of the drug, termination of drug-seeking behaviors, and return to normal functioning. The goals of treatment of withdrawal include prevention of progression to life-threatening severity, thus enabling comfort and functionality conducive to participation in a treatment program.

Nonpharmacologic Therapy

- Treatment of drug dependence or addiction is primarily behavioral. The goal is complete abstinence, and treatment is a lifelong process. Most drug-dependence treatment programs embrace treatment based on the Alcoholics Anonymous approach (ie, a 12-step model).

Pharmacologic Therapy

Alcohol Use Disorder

Intoxication

- In treating acute intoxications of central nervous system depressants, support of vital functions is critical.
- When toxicology screens are desired, blood or urine should be collected immediately upon arrival for treatment.

Withdrawal

- Treatment of withdrawal for alcohol is summarized in **Table 72-2**.
- Most clinicians agree that symptom-triggered treatment with benzodiazepines is the standard of care for alcohol detoxification.
- A common approach is the front-loading method using a long-acting benzodiazepine such as **diazepam** 10–20 mg or **chlordiazepoxide** 100 mg, repeated every 1–2 hours until the patient is sedated. The short-acting benzodiazepine lorazepam is also preferred because it can be administered IV, intramuscularly, or orally with predictable results (**Table 72-2**). Address fluid, electrolyte, and vitamin deficiencies as in **Table 72-2**.
- With symptom-triggered therapy, medication is given when the patient has symptoms and the Clinical Institute Withdrawal Assessment–Alcohol, Revised (CIWA-AR) score is ≥8. Various benzodiazepines may be used (**Table 72-2**) depending on patient-specific factors (ie, age and liver function). The patient should be reassessed hourly with continued doses given if the score is ≥8. The assessment timeframe can be extended to every 4–8 hours once the patient appears stable and their CIWA-AR score is <8.
- Alcohol withdrawal seizures do not require anticonvulsant drug treatment unless they progress to status epilepticus. Treat patients with seizures supportively. An increase in the dosage and slowing of the tapering schedule of the benzodiazepine used for detoxification or a single injection of a benzodiazepine may be necessary to prevent further seizure activity.

TABLE 72-2

Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Alcohol Withdrawal

Drug/Route	Dosage Range	Indication	Monitoring	Duration of Dosing	Level of

	Per Day (Unless Otherwise Stated)				Evidence for Efficacy[a]
Multivitamin oral/IV	1 tablet	Malnutrition	Diet	At least until eating a balanced diet at caloric goal	B3
Thiamine oral/IV	100 mg	Deficiency	CBC, WBC, nystagmus	Empiric ×5 days. More if evidence of deficiency	B2
Crystalloid fluids IV (NS or D5–0.45 NS with 20 mEq [mmol] of KCl per liter)	50–100 mL/hr	Dehydration	Weight, electrolytes urine output, nystagmus if dextrose	Until intake and outputs stabilize and oral intake is adequate	A3
Clonidine oral (Catapres)	0.05–0.3 mg Consider dose reduction in the elderly	Autonomic tone rebound and hyperactivity, hypertensive urgency	Shaking, tremor, sweating, blood pressure	3 days or less	B2
Clonidine transdermal (Catapres-TTS)	TTS-1 to TTS-3 Consider dose reduction in the elderly	Autonomic tone rebound and hyperactivity	Shaking, tremor, sweating, blood pressure	1 week or less. One patch only	B3
Antipsychotics oral/IV haloperidol (Haldol)	2.5–5 mg every 2–4 hours	Agitation unresponsive to benzodiazepines, hallucinations (tactile, visual, auditory, or otherwise), or delusions	Subjective response plus rating scale (CIWA-Ar or equivalent), ECG	Individual doses as needed	B1
Antipsychotics, atypical Quetiapine (Seroquel) oral Aripiprazole (Abilify) oral/IV	25–200 mg; dosage adjustment is necessary in hepatic impairment 5–15 mg	Agitation unresponsive to benzodiazepines, hallucinations, or delusions in patients intolerant of conventional antipsychotics	Subjective response plus rating scale (CIWA-Ar or equivalent)	Individual doses as needed in addition to scheduled antipsychotic	C3
Benzodiazepines (BZD) Lorazepam (Ativan) oral/IV/IM Chlordiazepoxide (Librium) oral Diazepam (Valium) oral/IV/IM Oxazepam (Serax) oral	0.5–8 mg 25–300 mg 5–40 mg 15–30 mg	Tremor, anxiety, diaphoresis, tachypnea, dysphoria, seizures	Subjective response plus rating scale (CIWA-Ar or equivalent)	Individual doses as needed. Underdosing is more common than overdosing	A2
Dexmedetomidine (Precedex) IV	0.2 mcg/kg/hr, titrate based on	Adjunct to BZD for autonomic hyperactivity, sympathetic symptom	Tremor, blood pressure, heart rate	5 days or less	B2

	response	control			
Phenobarbital (Luminal) oral/IV	30–260 mg	Adjunct to BZD, promotes BZD binding to $GABA_A$ receptor	Sedation, respiratory depression, blood pressure	5 days or less	B2
Alcohol oral		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3
Alcohol IV		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3

[a]Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.

CBC, complete blood count; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; D5, dextrose 5%; ECG, echocardiogram; KCl, potassium chloride; NS, normal saline; WBC, white blood cell count.

Quality of evidence: (1) evidence from more than one properly randomized controlled trial; (2) evidence from more than one well-designed clinical trial with randomization, from cohort or case-control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; and (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Dependence

- **Table 72-3** shows dosing and monitoring of drug therapy for alcohol dependence.
- **Disulfiram** deters a patient from drinking by producing an aversive reaction if the patient drinks. It inhibits aldehyde dehydrogenase in the pathway for alcohol metabolism, allowing acetaldehyde to accumulate, resulting in flushing, vomiting, headache, palpitations, tachycardia, fever, and hypotension.

  ✔ Severe reactions include respiratory depression, arrhythmias, MI, seizures, and death. Inhibition of the enzyme continues for as long as 2 weeks after stopping disulfiram.

  ✔ Prior to starting disulfiram, obtain baseline liver function tests (LFTs), and repeat at 2 weeks, 3 months, and 6 months, then twice yearly. Wait at least 24 hours after the last drink before starting disulfiram, usually at a dose of 250 mg/day.

- **Naltrexone** reduces craving and the number of drinking days. Do not prescribe it to patients currently dependent on opioids because it can precipitate severe withdrawal syndrome. A depot formulation allows monthly administration in a usual dose of 380 mg intramuscularly.

  ✔ Naltrexone is hepatotoxic and contraindicated in patients with hepatitis, liver failure, or serum aminotransferase levels greater than five times normal. LFTs should be done at baseline and 1–3 months after starting therapy, then annually. Use with caution in patients with moderate-to-severe renal impairment.

  ✔ Side effects include nausea, headache, dizziness, nervousness, insomnia, and somnolence.

- **Acamprosate** is a glutamate modulator that reduces alcohol craving.

  ✔ The most common acamprosate side effect is diarrhea.

TABLE 72-3

Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Alcohol Dependence

Drug	Dosage Range Per Day	Indication	Monitoring	Duration of Dosing	Level of Evidence for Efficacy[a]
Disulfiram (Antabuse)	250–500 mg; use with caution in patients with hepatic disease or insufficiency	Deterrence	Facial flushing, liver enzymes	Indefinite	B2
Acamprosate (Campral)	999–1998 mg and higher (333 mg tablets) Dosage adjustment necessary in renal impairment	Craving	Patient-reported craving, renal function	Indefinite	A1
Naltrexone (ReVia)	50–100 mg; dosage adjustment may be needed in renal and liver impairment	Craving	Patient-reported craving	Indefinite	A1
Naltrexone (Vivitrol)	380 mg intramuscularly once every 4 weeks Risk of hepatotoxicity lower compared to oral formulation due to lack of first pass effect	Craving	Patient-reported craving	Indefinite	B2
Anticonvulsants (eg, lamotrigine [Lamictal], topiramate [Topamax], carbamazepine [Tegretol], valproic acid [Depakote], gabapentin [Neurontin])	Seizure disorder doses	Craving	Patient-reported craving, plasma drug levels	Indefinite	B2
Antidepressants (eg, clomipramine [Anafranil], bupropion [Wellbutrin], doxepin [Sinequan], fluoxetine [Prozac])	Depression doses	Craving, depression, anxiety	Patient-reported craving	Indefinite	B2

[a]Strength of recommendations: A, B, and C, good, moderate, and poor evidence to support recommendation, respectively.

Quality of evidence: (1) evidence from more than one properly randomized controlled trial; (2) evidence from more than one well-designed clinical trial with randomization, from cohort or case-control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; and (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

Benzodiazepine Misuse and Dependence

Intoxication

- **Flumazenil** can be used for benzodiazepine overdoses and is contraindicated when cyclic antidepressant use is known or suspected because of seizure risk. Use with caution when benzodiazepine physical dependence is suspected, as it may precipitate withdrawal.

Withdrawal

- For benzodiazepine withdrawal, use the same drugs and dosages that are used for alcohol withdrawal (see **Table 72-3**).
- The onset of withdrawal from long-acting benzodiazepines may be up to 7 days after discontinuation of the drug. Initiate treatment at usual doses and maintain this dose for 5 days. Then taper over 5 days. Alprazolam withdrawal may require a more gradual taper of the benzodiazepine used for detoxification.

EVALUATION OF THERAPEUTIC OUTCOMES

Alcohol Withdrawal and Dependence

- Treating alcohol withdrawal takes precedence over the treatment of alcohol dependence.
- Close monitoring of withdrawal symptoms is essential to avoid progression to severe withdrawal.
- Patient counseling on potential adverse effects of medications used for alcohol dependence, followed by close monitoring and follow-up are necessary to assess therapeutic response and adherence.

Benzodiazepine Withdrawal

- Gradual taper of benzodiazepines should occur over 4–8 weeks and sometimes longer depending on the duration of use.
- Reduce the daily dose 10%–25% every 2 weeks to decrease the risk of severe withdrawal reactions and seizures.
- Minor abstinence symptoms (ie, anxiety, insomnia, irritability, sensitivity to light and sound, and muscle spasms) can remain for several weeks after the acute phase of withdrawal.

CENTRAL NERVOUS SYSTEM STIMULANTS: PATHOPHYSIOLOGY

- **Nicotine** is a ganglionic cholinergic-receptor agonist with dose-dependent pharmacologic effects, including stimulation and depression in the central and peripheral nervous systems; respiratory stimulation; skeletal muscle relaxation; catecholamine release by the adrenal medulla; peripheral vasoconstriction; and increased blood pressure, heart rate, cardiac output, and oxygen consumption. Low doses produce increased alertness and improved cognitive functioning. Higher doses stimulate the “reward” center in the brain. Cigarette smoking is the leading cause of preventable morbidity and mortality in the United States. It increases the risks of cardiovascular diseases, lung cancer, other cancers, and nonmalignant respiratory diseases.
- **Cocaine** may be the most behaviorally reinforcing of all drugs. Ten percent of people who begin to use the drug “recreationally” go on to heavy use. Pharmacologically it blocks reuptake of catecholamine neurotransmitters.

  ✔ The hydrochloride salt of cocaine is inhaled or injected. The high from snorting lasts 15–30 minutes. Smoking cocaine base (crack or rock) is almost instantly absorbed and causes intense euphoria. The high from smoking lasts 5–10 minutes. Tolerance to the “high” develops quickly. The elimination half-life of cocaine is 1 hour.

  ✔ In the presence of alcohol, cocaine is metabolized to cocaethylene, a longer-acting compound than cocaine with a greater risk for causing death.
- **Methamphetamine** (known as speed, meth, and crank) can be taken orally, rectally, intranasally, by IV injection, and by smoking. Inhalation or IV injection results in an intense rush that lasts a few minutes. Methamphetamine has a longer duration of effect than cocaine. Ephedrine and pseudoephedrine can be extracted from cold and allergy tablets and converted to methamphetamine. In the United States, federal law requires that pseudoephedrine-containing products be kept behind a counter and that identification be shown at the time of purchase.

- **3,4-methylenedioxymethamphetamine (MDMA; Ecstasy or Molly)** is usually taken by mouth as a tablet, capsule, or powder, but it can also be smoked, snorted, or injected; if taken by mouth, effects last 4–6 hours.

CLINICAL PRESENTATION

Nicotine Withdrawal

- Abrupt cessation of nicotine results in withdrawal symptoms usually within 24 hours, including anxiety, cravings, difficulty concentrating, frustration, irritability, hostility, insomnia, and restlessness.

Cocaine Intoxication and Withdrawal

- Signs and symptoms of cocaine intoxication include agitation, euphoria, loquacity, sweating or chills, nausea, tachycardia, arrhythmias, respiratory depression, mydriasis, altered blood pressure, and seizures. Adverse effects seen with use include ulceration of nasal mucosa and nasal septal collapse.
- Withdrawal symptoms begin within hours of discontinuation and last up to several days. Signs and symptoms of withdrawal include fatigue, sleep disturbances, nightmares, depression, drug craving, changes in appetite, bradyarrhythmias, myocardial infarction (MI), and tremors.

Methamphetamine

- Intoxication may present as increased wakefulness, increased physical activity, decreased appetite, dental caries, increased respiration, hyperthermia, euphoria, irritability, insomnia, confusion, tremors, anxiety, paranoia, aggressiveness, convulsions, increased heart rate and blood pressure, stroke, and death.
- Individuals in withdrawal may exhibit depression, cognitive impairment, drug craving, dyssomnia, and fatigue, but they are usually not in acute distress. Duration of withdrawal ranges from 2 days to several months. Occurrence of delirium suggests withdrawal from another drug (eg, **alcohol**).

Ecstasy (MDMA) Use

- MDMA stimulates the CNS, causes euphoria and relaxation, and produces a mild hallucinogenic effect. It can cause muscle tension, nausea, impaired memory, impaired attention and reasoning, impaired incidental learning, chills, sweating, panic, anxiety, depression, hallucinations, convulsions, and paranoid thinking. It increases heart rate and blood pressure and destroys serotonin (5-HT)–producing neurons in animals. It is considered to be neurotoxic in humans.

DIAGNOSIS

- See Diagnosis section in Chapter 69 for greater detail.

TREATMENT

- Goals of Treatment: The goals include cessation of use of the drug, termination of drug-seeking behaviors, and return to normal functioning.

Nonpharmacologic Therapy

Nicotine Use Disorder

- The Agency for Healthcare Research and Quality (AHRQ) and the United States Preventive Services Task Force (USPSTF) have developed treatment guidelines that use the 5 As (**A**sk about smoking, **A**dvise the person to quit through clear individualized messages, **A**ssess the patient's willingness to quit, **A**ssist in quitting, and **A**rrange follow-up and support).

- The USPSTF statement emphasized counseling sessions and highlighted the goal of reaching at least four in-person sessions.
- Minimal contacts, lasting <3 minutes that include the 5As, are more successful in increasing cessation rates than interventions involving no contact.
- Motivational interviewing with standard care or brief cessation advice improves quit rates modestly.
- Counseling alone can be effective but is further augmented by the addition of pharmacotherapy

Cocaine, Methamphetamine, and MDMA Use

- Active monitoring and management of vital organ function are required for a positive outcome.

Pharmacologic Therapy

Nicotine Use Disorder

- First-line pharmacotherapies for smoking cessation include Nicotine Replacement Therapy (NRT), **bupropion sustained release**, and **varenicline**. Combinations of these should be considered if a single agent has failed. Second-line pharmacotherapies include **clonidine** and **nortriptyline** and should be considered if first-line therapy fails.

Nicotine Replacement Therapy

- Dosing and monitoring of pharmacotherapy for smoking cessation are shown in **Table 72-4**. Nicotine replacement therapy increases quit rates by 10%, with five products being available over the counter.
- The 2- and 4-mg gum and lozenge doses are recommended for those who experience time to first cigarette (TTFC) less than 30 minutes and greater than 30 minutes, respectively. The gum should be chewed slowly until a peppery or minty taste emerges and then parked between the cheek and gums to facilitate nicotine absorption. Generally, the gum should be used for up to 12 weeks at no more than 24 pieces per day and no more than 20 lozenges should be used in 1 day for up to 12 weeks. Patients should be given specific dosing and usage instructions for both the gum and lozenges to improve efficacy.
- The patch is available as nonprescription medication which has the highest rate of adherence. Patch use may be combined with as needed gum, lozenge, or nasal spray use. The initial patch dosage should be worn from 4 to 6 weeks, and then the dose should be tapered to the next strength every 2 weeks. A new patch should be placed on a relatively hairless location each morning.
- Nicotine nasal spray requires a prescription. It more than doubles long-term abstinence rates compared to placebo spray. Recommended duration of therapy is 3–6 months.
- Nicotine oral inhaler consists of a mouthpiece and plastic cartridge that is placed into the inhaler and delivers 4–10 mg of nicotine through vapor inhalation. Patients should actively puff on the inhaler for 5 minutes, adjusting use based on effect, as the cartridge can be used for up to 20 minutes of active puffing. The initial dosing is 6–16 cartridges/day for up to 12 weeks. A taper should be initiated after 6 weeks.
- NRT products have few side effects. Nausea and light-headedness may indicate nicotine overdose. Rotate the patch site to minimize skin irritation. Sleep disturbances are reported in 23% of patients using the patch. Eating or drinking anything except water should be avoided for 15 minutes before and during administration of the lozenge and gum. Long-term NRT may be needed in some patients.
- Electronic nicotine delivery systems (ENDS, or e-cigarettes) usage is controversial and continued research is needed to evaluate their efficacy and safety.

TABLE 72-4

First-Line Pharmacotherapy Treatment Options for Smoking Cessation

Drug	Dosing	Duration	Comments/Monitoring Parameters
Nicotine replacement therapies (NRTs)			
Nicotine patch	Based on cigarettes smoked per day: >10 cigs/day: Step 1: 21 mg/day: Weeks 1–6 Step 2: 14 mg/day: Weeks 7–8 Step 3: 7 mg/day: Weeks 9–10 <10 cigs/day: Step 2: 14 mg/day: 6 weeks Step 3: 7 mg/day: 2 weeks	10 weeks	Tapering dosing is considered optional after 6 weeks on a dose Patch can be worn for up to 24 hours per day If patient has sleep disturbances, remove patch at night and place one patch in morning (~16 hours per day) If waking up with cravings, patch should be worn for 24 hours Recommended to place patch on determined quit day Place a new patch on each day, hold patch on for 10 seconds to help adherence Rotate patches to avoid skin irritation
Nicotine gum	1st cigarette <30 minutes after waking: 4 mg 1st cigarette >30 minutes after waking: 2 mg Weeks 1–6: 1 piece of gum every 1–2 hours prn Weeks 7–9: 1 piece every 2–4 hours prn Weeks 10–12: 1 piece every 4–8 hours prn Then stop Do not exceed 24 pieces/day	12 weeks	Continuous use can lead to adverse effects (pyrosis, nausea, hiccups) 4 mg strength has shown to be more efficacious in heavy smokers over 6-week time period If patient uses with a cigarette, there is no major risk Counseling on proper use of gum: Repeat process until peppery sensation does not reoccur Use alternate sides of mouth when using chew and park method Park between cheek and gum after a peppery sensation becomes apparent Do not eat or drink 15 minutes before or during use of gum Chew each piece slowly
Lozenge available as Nicorette lozenge or Nicorette mini lozenge	1st cigarette <30 minutes after waking: 4 mg 1st cigarette >30 minutes after waking: 2 mg Weeks 1–6: 1 lozenge by mouth every 1–2 hours prn Weeks 7–9: 1 lozenge by mouth every 2–4 hours prn Weeks 10–12: 1 lozenge by mouth every 4–8 hours prn Then stop Do not exceed 20 lozenges/day	12 weeks	Counseling points: Do not eat or drink anything 15 minutes prior to or during lozenge use Allow the lozenge to dissolve slowly, approximately 20–30 minutes Nicotine release could create a tingling or warm sensation Do not chew or swallow the lozenge Periodically rotate the lozenge to different areas of the mouth
Nicotine oral inhaler + cartridge plus mouthpiece (Nicotrol®)	24–64 mg (6–16 cartridges) per day 1. Stop smoking completely before use 2. Use device by frequent continuous puffing (20 minutes) and use as needed (dosing is very individualized) based on nicotine needed 3. Recommended duration of treatment is 3 months	3–6 months	Patients should stop smoking prior to starting this product Most successful patients in trials; use ranged from 6 to 16 cartridges per day, 20 minutes continuous puffing Recommended duration of treatment: 3 months with subsequent weaning with gradual reduction over 6–12 weeks Treatment longer than 6 months has not been studied Precautions: patients with asthma, chronic pulmonary disease, history of recent myocardial infarction, serious arrhythmias, or

	4. Gradual daily dose taper over 6–12 weeks		worsening angina Pregnancy Category D
Nicotine metered nasal spray (Nicotrol NS®)	One spray (0.5 mg nicotine/spray) into each nostril one to two times each hour when craving cigarette Max. dose: 10 sprays per hour (max. of 80 sprays per day)	3 months	Two sprays is considered 1 dose Treatment duration is 3 months; safety beyond 6 months has not been studied Counseling: Breathe normally while administering spray, do not sniff or inhale deeply while administering spray For best results, use at least 16 sprays per day which has been found as the minimum effective dose
Non-nicotine replacement options			
Bupropion (Zyban)	150 mg by mouth daily × 3 days then 150 mg by mouth bid (dosing interval should be >8 hours)	3–6 months	Do not exceed 300 mg/day Recommend initiating therapy 1–2 weeks prior to set "quit" day Black box warning for neuropsychiatric warning and suicide warnings removed in 2016; downgraded to warning Pregnancy Category: C, excreted into breastmilk Monitor patients with renal/hepatic impairment Neuropsychiatric adverse events: black box warning removed in December 2016, warning remains Counseling points: might cause dry mouth, could cause insomnia
Varenicline (Chantix)	Start with dose titration: Days 1–3: 0.5 mg by mouth once daily Days 3–7: 0.5 mg by mouth twice daily Week 2 until end of treatment: 1 mg by mouth twice daily	3–6 months	Recommended to begin varenicline 1 week prior to quit day Maintenance up to 6 months of therapy is approved Renal impairment dosing for CrCl ≤30 mL/min (0.5 mL/sec) No dosing adjustment needed in hepatic impairment If patient has difficulty with cessation, recommend taper smoking by 50% each month with a goal of smoking abstinence in 12 weeks, continue varenicline for another 12 weeks for a full 24 week therapy Neuropsychiatric adverse events: black box warning removed in December 2016, warning remains Most common side effects: nausea, sleep problems, constipation, gas, vomiting Patients with intolerable insomnia might improve with lower doses

Bupropion and Varenicline

- Bupropion sustained release (SR) inhibits neuronal reuptake, and potentiates the effects of norepinephrine and dopamine. Its use is contraindicated in patients with current or past seizure disorder, current or prior diagnosis of bulimia or anorexia nervosa, and use of a monoamine oxidase inhibitor within the last 14 days. Concurrent use of medications that lower the seizure threshold is a concern.

  ✔ Side effects of bupropion may include neuropsychiatric symptoms (in adults and pediatric patients), including depression, anxiety, agitation, hostility, suicidal thoughts/behavior, and attempted suicide.

- **Varenicline** is a partial agonist that binds selectively to nicotinic acetylcholine receptors with a greater affinity than nicotine, producing a lesser response than nicotine. It is also FDA-approved for 6 months of maintenance therapy. It may result in a higher rate of cessation than bupropion and single forms of NRT. It may be equally effective with combination NRT.

  ✔ Side effects of varenicline may include suicidal thoughts and erratic and aggressive behavior. Screen patients for psychiatric illness or behavior change after starting varenicline. It may also be associated with a small increased risk of cardiovascular events.

Other Therapies

- **Clonidine** is an effective smoking-cessation treatment in doses varying from 0.15 to 0.75 mg/day orally and from 0.1 to 0.2 mg/day transdermally.

  ✔ The most common clonidine side effects include dry mouth, dizziness, hypotension, sedation, and constipation. Monitor blood pressure. Abrupt discontinuation may result in nervousness, agitation, headache, tremor, and elevation in blood pressure.

- **Nortriptyline** is initiated 10–28 days before the quit date. The dose is initiated at 25 mg/day, gradually increasing to 75–100 mg/day. In trials, treatment duration was commonly 12 weeks.

  ✔ Common side effects include sedation, dry mouth, blurred vision, urinary retention, tremor, and light-headedness.

Cocaine, Methamphetamine, and MDMA Use

Intoxication

- No antidotes or targeted therapies are available for these agents. When toxicology screens are desired, blood or urine should be collected immediately upon arrival for treatment.
- Treat pharmacologically only if the patient is agitated or psychotic. Injectable lorazepam 2–4 mg IM every 30 minutes to 6 hours can be used for agitation. Low-dose antipsychotics can be used short term for psychosis. Treat seizures supportively, but IV lorazepam or diazepam can be used for status epilepticus.

EVALUATION OF THERAPEUTIC OUTCOMES

Nicotine Use Disorder

- Tobacco cessation is a process that could take an extended period of time with extensive education and continual monitoring being vital to this process.
- The most effective treatment strategy for smoking cessation is a combination of behavioral and pharmacological treatment and frequent monitoring of both early on in the process is recommended.
- Patient counseling is vital to ensure maximum efficacy. Frequent reassessment should occur to evaluate breakthrough cravings, withdrawal symptoms, and relapses. Patients should be asked to immediately report any adverse effects to ensure adherence and prevent relapse.

Cocaine, Methamphetamine, and MDMA Use

- When considering therapeutic outcomes, each treatment must be evaluated to determine efficacy and safety. Ongoing psychosocial and educational support is important to maximize outcomes.

OTHER DRUGS OF ABUSE: PATHOPHYSIOLOGY

- **Catha edulis (Khat)** is a shrub native to the horn of Africa that when chewed produces stimulating effects. The psychoactive properties of this plant are due to several alkaloids including cathine and cathinone (thus the name cathinones). The pharmacology of the various cathinones and related drugs is not well studied. **Bath salts** (schedule I controlled substances) are synthetic, sympathomimetic, designer drugs that can cause

intoxication, dependence, and death. **Flakka** is a new very potent cathinone that has become very popular in some counties in Florida.

- **Marijuana** (known as reefer, pot, grass, and weed) is a commonly used drug. Federally this drug continues to be illegal, although many states have passed laws allowing use. The active compounds within marijuana include the principal psychoactive component **Δ^9-tetrahydrocannabinol (THC)** and **cannabidiol** (CBD), which does not have psychoactive effects. Marijuana is most commonly smoked, but it can be orally ingested. After inhalation, the pharmacologic effects can be seen in about 10 minutes. Both THC and CBD are poorly bioavailable; therefore, peak concentrations occur in about 2 hours after ingestion. The single use terminal half-life of 24 hours is significantly elongated with chronic use due to accumulation and redistribution from fatty tissues. In chronic users, THC is detectable on toxicologic screening for up to 4–5 weeks after cessation of use

- Over 100 compounds are cannabinoid receptor agonists called **synthetic marijuana** (spice, K2, dream, red X dawn, and others). The product is inert dry plant material sprayed with these compounds.

- **Lysergic acid diethylamide (LSD)** can cause either agonist or antagonist effects on 5-HT activity. It is sold as tablets, capsules, a liquid, and on squares of decorated paper.

- Organic solvents inhaled by abusers include **gasoline, glue, aerosols, amyl nitrite, butyl nitrite, typewriter correction fluid, lighter fluid, cleaning fluids, paint products, nail polish remover, waxes**, and **varnishes**. Chemicals in these products include **nitrous oxide, toluene, benzene, methanol, methylene chloride, acetone, methylethyl ketone, methylbutyl ketone, trichloroethylene**, and **trichloroethane**.

CLINICAL PRESENTATION

Synthetic Cathinones (Bath Salts) Use

- In addition to the stimulant effects of bath salts adverse effects include tachycardia, hypertension, diabetic ketoacidosis, paranoid psychosis, hyperthermia, agitation, headache, hyponatremia, and suicide.

Marijuana Use

- Initial effects of marijuana use include increased heart rate, dilated bronchial passages, and bloodshot eyes. Subsequent effects include euphoria, dry mouth, hunger, tremor, sleepiness, anxiety, fear, distrust, panic, incoordination, poor recall, amotivation, and toxic psychosis. Other physiologic effects include sedation, difficulty in performing complex tasks, and disinhibition. Endocrine effects include amenorrhea, decreased testosterone production, and inhibition of spermatogenesis. Recent findings suggest a neurotoxic effect on the adolescent brain.

- Cannabis use impairs driving performance, and is associated with increased risk of motor vehicle crashes.

- After abrupt discontinuation, heavy users may have a withdrawal syndrome characterized by irritability, anger, aggression, anxiety, depressed mood, restlessness, sleep difficulty, decreased appetite, or weight loss.

- Cannabinoid hyperemesis syndrome (CHS) is a syndrome of cyclical vomiting in habitual users that abates after discontinuation of cannabis.

Synthetic Cannabinoid Use

- Toxic symptoms are similar to the effects of marijuana plus sympathomimetic effects, including agitation, anxiety, tachycardia, hypertension, nausea and vomiting, muscle spasms, seizures, tremors, paranoid behavior, nonresponsiveness, diaphoresis, hallucinations, and suicidal thoughts and behaviors.

Lysergic Acid Diethylamide Use

- Signs and symptoms of LSD intoxication include mydriasis, tachycardia, diaphoresis, palpitations, blurred vision, tremor, incoordination, dizziness, weakness, and drowsiness; psychiatric signs and symptoms include perceptual intensification, depersonalization, derealization, illusions, psychosis, synesthesia, and flashbacks. It produces tolerance but is not addictive. There is no withdrawal syndrome.

Inhalant Use

- Physiologic effects include CNS depression, headache, nausea, anxiety, hallucinations, and delusions. With chronic use, the drugs are toxic to virtually all organ systems. Death may occur from arrhythmias or suffocation by plastic bags.

DIAGNOSIS

- See Diagnosis section in Chapter 69 for greater detail.

TREATMENT

- Goals of Treatment: The goals include cessation of use of the drug, termination of drug-seeking behaviors, and return to normal functioning.

Nonpharmacologic Therapy

- Treatment for all most often centers on psychosocial interventions and supportive care.
- For marijuana use, nonpharmacologic therapy includes cognitive behavioral therapy (CBT), motivational enhancement therapy (MET), or a combination, which is synergistic.

Pharmacologic Therapy

- Many patients with hallucinogen intoxication respond to reassurance.
- No antidotes or targeted therapies are available for these agents. When toxicology screens are desired, blood or urine should be collected immediately upon arrival for treatment.
- Treat pharmacologically only if the patient is agitated or psychotic. Injectable **lorazepam** 2–4 mg IM every 30 minutes to 6 hours can be used for agitation. Low-dose antipsychotics can be used short term for psychosis. Treat seizures supportively, but IV lorazepam or **diazepam** can be used for status epilepticus.

EVALUATION OF THERAPEUTIC OUTCOMES

- When considering therapeutic outcomes, each treatment must be evaluated to determine efficacy and safety. Ongoing psychosocial and educational support is important to maximize outcomes.

See Chapter 82, Substance-Related Disorders I: Overview and Depressants, Stimulants, and Hallucinogens and Chapter 83, Substance-Related Disorders II: Alcohol, Nicotine, and Caffeine, authored by Robin Moorman Li, Patrick Leffers, and Paul L. Doering, for a more detailed discussion of the topic.