Chapter 86: Substance Use Disorders II: Alcohol, Nicotine, and Caffeine

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 73, Substance Use Disorders, Non-Opioid.

KEY CONCEPTS

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1. Globally, more than 3 million people, predominantly males, died in 2016 from alcohol consumption, which represents 1 in 20 deaths.
2. Studies have identified genotypic and functional phenotypic variants that either serve to protect or predispose individuals toward developing an alcohol use disorder.
3. The metabolism of alcohol follows zero-order kinetics, except at very high and very low blood concentrations. This has important implications for the time course for the effects of alcohol.
4. Disulfiram, naltrexone, extended-release naltrexone, and acamprosate are FDA-approved for the treatment of alcohol use disorder. Their clinical utility to improve sustained abstinence and reduce heavy drinking remains controversial.
5. Tobacco is the most preventable cause of death in the United States.
6. Clinicians should ask all individuals about tobacco use, advise on how to stop using tobacco products, and provide pharmacotherapy and behavioral treatment options to aid in smoking cessation.
7. All forms of nicotine replacement therapy are effective in reducing the amount smoked and achieving abstinence.
8. Varenicline has similar efficacy to the nicotine patch and may be more efficacious than all other single nicotine replacement therapies (NRTs). It is approved for up to 6 months of maintenance therapy by the Food and Drug Administration (FDA).
9. As many as one in five adults consume doses of caffeine generally considered large enough to cause clinical symptoms.
10. Energy drinks continue to be popular, particularly among adolescents and emerging adults. Concerns have been raised regarding the safety of these products.

BEYOND THE BOOK

BEYOND THE BOOK

Alcohol Use Disorder

Watch this five-minute video titled “Brief intervention: Steve,” which provides an example of an outpatient clinician making an intervention on an individual with unhealthy alcohol use. This video enhances understanding of how the AUDIT tool can help collect information during an interview and how motivational interviewing can effectively help individuals realize their problem and develop a plan of action.

https://tinyurl.com/y5xvt3u3

1. The patient in the video scored in Zone 2 of the AUDIT questionnaire. Describe how you would interpret those results.
2. Motivational interviewing is a counseling approach where clinicians use a patient-centered stance in combination with techniques to help patients explore and resolve their own mixed feelings about changing unhealthy behaviors.

   The principles of motivational interviewing include:

   - Expressing empathy—building rapport and engaging the patient by seeking to understand his/her perspective
   - Developing discrepancy—determining the patient’s perception of how well current behaviors match desired behaviors
   - Rolling with resistance—letting the patient make the arguments for a change instead of the clinician arguing for change
   - Supporting self-efficacy—using reflective statements to restate the patient’s belief which he/she verbalized to be able to change a specific behavior

In the video, which principle(s) of motivational interviewing did the clinician utilize when interviewing the patient?

Smoking Cessation

1. Review the brief case provided.
2. Watch the 3-minute video titled, “The 5As in Practice: Role Play of a Brief Intervention,” which provides an example of the 5As in smoking cessation used in the clinic setting.

https://tinyurl.com/y437notb

3. List treatment recommendations that could be considered for this patient’s case. Further instructions provided with the table.

Case:

A 43-year-old patient presented to primary care 2 weeks ago for treatment for a chronic productive cough. During this visit, a smoking cessation discussion was captured (see video above), and it was determined they would begin the nicotine patches in 1 week. They are now returning 2 weeks later reporting an adverse reaction to the patch adhesive. They have called the quitline once but would like some other recommendations from you in regard to strategies for smoking cessation as well. What would you recommend?

PMH:

Asthma

Allergies:

PCN

Adhesive (just added today to medical record from experience from nicotine patches)

Completing the table below will help complete the Implement section of the PPCP

Goals of therapy		
	Recommendation #1	Recommendation #2
Medication(s)		
Name, dose, route, etc.		
Rationale for recommended action		
Pros		
Cons		
Possible adverse effects		
Other concerns		
Behavior intervention recommendations		

INTRODUCTION—ALCOHOL

1 Alcohol, nicotine, and caffeine are considered to be socially acceptable substances, yet they impose enormous social and economic costs on our society. The World Health Organization (WHO) estimates that in 2016, there were more than 3 million people worldwide who died from alcohol consumption with the majority being males. Long-term unhealthy alcohol use often leads to chronic disease, and a causal relationship has been established between unhealthy use and at least 200 types of chronic disease or injury worldwide (eg, cancers, liver disease, cardiovascular disease, seizures, homicide, HIV/AIDS, and motor vehicle accidents).[1] Nationally, alcohol contributes to approximately 18.5% of emergency department visits, and more than 95,000 people die annually from alcohol-related causes. This makes alcohol one of the leading causes of preventable death in the United States.[2]

EPIDEMIOLOGY

According to the National Survey on Drug Use and Health (NSDUH), 139.7 million Americans over age 12 reported current alcohol use, with 11.5% reporting heavy alcohol use. Additionally, 47.1% report binge alcohol use, defined as consuming five drinks or more on the same occasion on at least one day in the past 30 days for males and four drinks or more on the same occasion on at least one day in the past 30 days for females.[3] Furthermore, 1.2% reported heavy alcohol use, defined as binge drinking on 5 days or more in the past 30 days. It is estimated that 1 in 10 adolescents between the ages of 12 and 17 years are current alcohol users, which equates to 2.3 million young adults in one month.[3] Although, over the last 5 years, there has been an overall decline in alcohol use in this age group, within this specific age range, there are over 208,000 adolescents who are currently heavy alcohol users. In contrast, the estimates of heavy alcohol users in 2019 decreased to 2.8 million for individuals between the ages of 18 and 25, and 13 million for those 26 years and older.[3]

2 The disease concept of addiction, using alcoholism as a model, states that individuals who suffer from the disease do not choose to contract the disease any more than someone who suffers from heart disease or diabetes mellitus chooses to contract that illness. Alcohol use disorder (AUD) is a chronic disease characterized by problematic and uncontrolled drinking and is diagnosed based on DSM-5 criteria, which requires 2 of the 11 criteria to be met during a 12-month period. The DSM-5 criteria ask 11 questions about the amount of alcohol use, the effects of alcohol use both personally and professionally, and any presence of withdrawal symptoms in the past year. Severity is determined based on the number of criteria met and

subsequently classified as mild (2-3 symptoms), moderate (4-5 symptoms), or severe (6 or more symptoms).[4,5] See Chapter e84, "Introduction to Substance Use Disorders," for more information.

It has long been recognized that unhealthy alcohol use is heritable, as 50% of first-degree relatives of people with AUD become alcohol-dependent themselves.[6–8] Similarly, twin and adoption studies have had comparable results.[8] Additional research continues to identify common and rare genetic variations leading to not only variations in responses to alcohol but also the response to the pharmacological treatment of AUDs. Prospective data are lacking to determine the effects of genetic polymorphisms on individual responses of medications to treat AUD.[6,7] Large-scale pharmacoepidemiologic studies have further elucidated the environmental risk factors associated with either protective effects or predisposition toward unhealthy alcohol use (Table 86-1).[9]

TABLE 86-1

Genotypic, Phenotypic, and Environmental Factors That Increase Alcohol-Use Disorder Risk

Susceptibility Genes	Phenotype	Environment
Regions on chromosomes 1 and 4 that code for the following receptors: • $GABA_A$ • Serotonin 1B • DRD4 • Neuropeptide Y	Personality traits that include: • Novelty seeking • Impulsivity • Aggression • Depression • Early Exposure • Maximum number of alcoholic drinks consumed per day	• Religious background • Urban residence (vs rural) • History of sexual abuse • Being single • Having deceased parents
Gene that codes for: • ADH1B • ALDH2 • 5HTTLPR		

ADH1B, alcohol dehydrogenase 1B; ALDH2, aldehyde dehydrogenase 2; DRD4, type 4 dopamine receptor gene; GABA, γ-aminobutyric acid; 5HTTLPR, 5 hydroxytryptamine transporter.

Data from References 6,7,9.

ETIOLOGY

Alcohol is a central nervous system (CNS) depressant that acts in a dose-dependent fashion, producing sedation that progresses to sleep, unconsciousness, coma, and finally fatal respiratory depression potentially leading to cardiovascular collapse. Alcohol affects endogenous opiates and several neurotransmitter systems in the brain, including γ-aminobutyric acid (GABA), glutamate, serotonin, and dopamine. Alcohol is available in a variety of concentrations in various alcoholic beverages. There is approximately 14 g of alcohol in a 12-oz (355 mL) can of beer (approximately 5%), in 5 oz (148 mL) of nonfortified wine (approximately 12%), or in one shot (1.5 oz [44 mL]) of 80-proof whiskey (40%).[8,11] Full consumption of this amount will cause an increase in blood alcohol level of approximately 20 to 25 mg/dL (4.3 to 5.4 mmol/L) in a healthy 70-kg (154 lb) male, although this varies with the time frame of alcohol consumption, the type of alcoholic beverage, whether food is consumed co-currently, and many other patient-specific variables. The lethal dose of alcohol in humans is variable, but deaths generally occur when blood alcohol levels are greater than 400 to 500 mg/dL (87-109 mmol/L).[12]

PATHOPHYSIOLOGY

Approximately 20% of alcohol is absorbed through the stomach, with the remaining through the small intestine. Absorption begins in the stomach within 5 to 10 minutes of oral ingestion, with the onset of clinical effects following fairly rapidly. Peak serum concentrations of alcohol are usually achieved 30 to 90 minutes after finishing the last drink, although this depends on the type of alcoholic beverage, type and timing of food consumption, and other factors.[11,13]

More than 90% of alcohol in the plasma is metabolized in the liver by three enzyme systems that operate within the hepatocyte. The first system is metabolism to acetaldehyde by alcohol dehydrogenase (ADH) in the liver cell. In turn, acetaldehyde is metabolized to carbon dioxide and water by the enzyme aldehyde dehydrogenase (ALDH). A second pathway for oxidation of alcohol uses catalase, an enzyme located in the peroxisomes and microsomes. The third enzyme system, the microsomal alcohol oxidase system, has a role in the oxidation of alcohol to acetaldehyde. These last two mechanisms are of lesser importance than the alcohol dehydrogenase–aldehyde dehydrogenase system.[13,14] Beyond these, the remainder of alcohol is excreted by the lungs, and in urine and sweat.

3 The elimination of alcohol generally follows zero-order pharmacokinetics, where the concentration of alcohol in the blood decreases at a constant amount per unit of time. This can, in fact, be an oversimplification because at very high or very low concentrations elimination can follow first-order pharmacokinetics, where a constant percentage of alcohol is eliminated per unit of time. Blood alcohol concentration (BAC) measures the amount of alcohol present in the blood, and as BAC rises, the alcohol can result in different levels of impairment (Table 86-2) and the relationship between alcohol consumption and BAC is variable. On average, the BAC is lowered from 15 to 22.2 mg/dL (3.3-4.8 mmol/L) per hour in the nontolerant individual, assuming that the individual is in the post-absorptive state. In healthy males and females, alcohol has a volume of distribution of 0.7 and 0.6 L/kg, which corresponds closely with total body water.[15]

TABLE 86-2

Specific Effects of Alcohol Related to Blood Alcohol Concentration

BAC (%)* (mmol/L)	Type of Impairment	Effect(s)
0.0-0.05 (0-11)	Mild	Mild speech/memory/attention/coordination/balance impairment, relaxation, sleepiness
0.06-0.15 (12-34)	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

*Grams of ethyl alcohol per 100 mL of whole blood.

BAC, blood alcohol concentration.

Data from Reference 22.

CLINICAL PRESENTATION

Screening for Alcohol Use Disorder

The CAGE questionnaire is a mnemonic for four questions: (a) Have you ever felt the need to cut down on your drinking? (b) Have people *a*nnoyed you by criticizing your drinking? (c) Have you ever felt bad or *g*uilty about your drinking? (d) Have you ever had a drink the first thing in the morning to steady your nerves or get rid of a hangover ("eye opener")? This commonly used tool can be used for detecting individuals more likely to be misusing alcohol and therefore at greater risk for alcohol withdrawal. Each question is scored as 0 for a "no" answer and 1 for a "yes" answer. A positive response, a total of 2 or more to these four questions, suggests an increased likelihood of unhealthy alcohol use with an average sensitivity of 0.71 (71%) and an average specificity of 0.90 (90%).[17]

The Alcohol Use Disorders Identification Test (AUDIT) is a validated 10-question screening tool originally developed to screen for alcohol use disorder and the amount and frequency of alcohol consumption in adults in the primary care setting. This screening tool can be completed by the patient or can be completed via an interview with a healthcare provider. Each question is scored from 0 to 4. Out of a possible score of 40, scores greater than 8 indicate harmful or hazardous drinking. Scores higher than 13 for females and 15 for males necessitate further evaluation for alcohol use disorder.[18] The AUDIT tool, as well as a short version of AUDIT (AUDIT-C), has been used within a broad range of patient populations and is an appropriate first step in identifying those struggling with unhealthy alcohol use. However, a new adaptation of the AUDIT, the USAUDIT, was adapted to US standard drink size and hazardous drinking guidelines and has been developed to more accurately detect drinking in excess of recommended levels.[18]

Acute Effects of Alcohol

At lower serum concentrations, euphoria and disinhibition may be noted. Additionally, slurred speech, altered perception of the environment, impaired judgment, ataxia, incoordination, nystagmus, and hyperreflexia may occur. As plasma levels increase, combative and destructive behavior may occur. With higher levels still, somnolence and respiratory depression may ensue.[16] The typical effects of various BACs are shown in Table 86-3, although effects vary from individual to individual.

Alcohol Poisoning

Acute alcohol poisoning, also commonly referred to as alcohol overdose, usually occurs with the rapid consumption of large quantities of alcoholic beverages. With sustained drinking of moderate alcohol amounts, the user passes out before a toxic dose can be ingested, and/or the person vomits to rid the stomach of its toxic reservoir. With rapid drinking, the person may fall asleep or pass out without vomiting, allowing continued alcohol absorption from the gastrointestinal (GI) tract until fatal BACs are achieved.[16]

Laboratory Studies

In the emergency room, a BAC should be ordered in any patient in whom alcohol ingestion is suspected, regardless of the presenting complaint. For clinical purposes, most laboratories report BAC in units of mg/dL or mmol/L. In legal cases, results are reported in percentage (grams of ethyl alcohol per 100 mL of whole blood). Along with a BAC, a complete blood count should be ordered to assess for anemia and a complete metabolic panel plus serum magnesium should be ordered to assess electrolytes, glucose, and renal and liver function. If the diagnosis is unclear, if the intoxication seems atypical, or when there is suspicion of multiple substance ingestions, a complete toxicologic screen may be useful to rule out other substances.[19]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Alcohol Withdrawal

General

- Acute alcohol detoxification and withdrawal after chronic unhealthy alcohol use is a serious condition that can require hospitalization and adjunctive pharmacotherapy.
- At a very high BAC, death is possible.

Symptoms

- The intoxicated individual can present with slurred speech and ataxia. The patient can be sedated or unconscious.
- As BACs decrease rapidly, nausea, vomiting, tremors, and hallucinations can ensue. Delirium tremens (DT) and seizures are the most severe symptoms.
- An evaluation should be completed using the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar), a 10-item scale to document and score the patient's baseline symptoms (nausea and vomiting, tremors, paroxysmal sweats, anxiety, tactile/auditory/visual disturbances, headache, agitation, orientation and clouding of sensorium).

Signs

- The intoxicated individual can present with nystagmus.
- In withdrawal, the individual can present with tachycardia, diaphoresis, hypertension, and/or hyperthermia.

Laboratory Tests

- In the emergency department, a BAC should be ordered when alcohol ingestion is suspected. A whole blood alcohol level of 150 mg/dL (33 mmol/L) reported in the hospital corresponds to 0.15% BAC obtained by law enforcement.
- Order a complete blood count to assess for anemia, a complete metabolic panel to assess electrolytes, glucose, renal, and liver function, and serum magnesium.
- A complete toxicologic screen to rule out the presence of other substances can be useful.

Other Diagnostic Tests

- Differentiate acute alcohol intoxication from other medical illnesses (eg, head trauma).
- Order computed tomography (CT) on any patient with focal neurologic findings, failure to improve, new-onset seizures, or mental status out of proportion to the degree of intoxication.

TREATMENT

Desired Outcomes

While alcohol withdrawal most likely occurs in the face of alcohol use disorder, it is necessary to treat acute withdrawal symptoms (or prevent them from occurring) before other alcohol use disorder treatments are started. The goals for alcohol-dependent persons trying to decrease or discontinue alcohol intake include (a) the prevention and treatment of withdrawal symptoms (including withdrawal seizures and DT) and medical or psychiatric complications, (b) long-term abstinence after detoxification, and (c) entry into ongoing medical and unhealthy alcohol use treatment.[20]

Nonpharmacologic Therapy

Due to the severity of signs and symptoms and associated morbidity and mortality with alcohol withdrawal, nonpharmacologic therapy is not recommended. Patients with alcohol withdrawal require a coordinated approach in a monitored setting with the use of inpatient, outpatient, and rehabilitation services.[19]

Pharmacologic Therapy

A baseline assessment using a validated tool, such as the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar), should be completed.[21] Symptom-triggered treatment with a benzodiazepine is the current standard of care in alcohol detoxification to assess severity and avoid progression to more severe withdrawal stages. All benzodiazepines appear to be similarly efficacious in reducing the signs and symptoms of withdrawal. However, there are pharmacokinetic differences (ie, onset of action, duration, metabolism) between benzodiazepines, in addition to route of administration and cost, that guide pharmacotherapy decisions.[19,22,23]

Benzodiazepines are first-line treatment and the standard of care, given their documented efficacy in reducing the signs and symptoms of withdrawal.[23] Other agents with activity on the GABA system have been evaluated in the treatment of alcohol withdrawal. A Cochrane review[24] of the efficacy and safety of pharmacological options in treating alcohol withdrawal syndrome included a total of 7,333 patients. The medications evaluated included benzodiazepines, baclofen, antiseizure medications (ie, phenobarbital, valproic acid, carbamazepine, gabapentin, topiramate), and psychotropic analgesic nitrous oxide (PAN), along with gamma-hydroxybutyrate. Efficacy was determined based on the impact on alcohol withdrawal seizures. Benzodiazepines were more efficacious when compared to both placebo (RR 0.16; 95% CI 0.04-0.69) and antipsychotics (RR 0.24; 95% CI 0.07–0.88). Within the benzodiazepine class comparison, there was a trend toward better efficacy with chlordiazepoxide; however, no benzodiazepine was shown to be superior.[24] Phenobarbital, with a rapid onset of action and a long half-life, is the most commonly used alternative to benzodiazepines in alcohol withdrawal, demonstrating efficacy and safety with monitoring when used alone or in combination with benzodiazepines.[19,23]

Treatment Regimens

Front-Loading Therapy

One initial approach to managing alcohol withdrawal includes using an initial high dose of a long-acting benzodiazepine, such as diazepam 10 to 20 mg or chlordiazepoxide 100 mg, and administered in repeated doses every 1 to 2 hours until the patient is sedated. Adequate sedation is usually obtained after three doses. Front-loading therapy is recommended when the CIWA-Ar score is 19 or above. Patients must be closely monitored under clinical supervision for benzodiazepine toxicity, such as excessive sedation, respiratory depression, and delirium. This approach should be used with extreme caution in older patients or in those with liver disease since the elimination rate will be extended, leading to an increased risk of toxicity.[22,23]

Symptom-Triggered Therapy

With symptom-triggered therapy, medication is given only when the patient has symptoms and the CIWA-Ar score is 8 or above. Various benzodiazepines have been used in this therapy, including diazepam, chlordiazepoxide, oxazepam, and lorazepam. Agent choice depends on the patient's age, liver function, available dosage forms, the hospital's formulary, and cost. The patient is then reassessed hourly utilizing the CIWA-Ar. If the score remains above 8, they continue to receive a dose of the selected benzodiazepine. If the score is lower than 8 and the patient appears stable, the time frame for assessment and treatment can extend to 4 to 8 hours (Table 86-3). When used in the inpatient setting, this standard of care results in a shorter treatment duration and reduced risk for over-sedation, which allows the clinician to focus on specific therapy for alcohol use disorder. This approach is also appropriate for the outpatient setting if monitoring of signs and symptoms can be reliably performed by the patient or caregiver.[23,25]

TABLE 86-3

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

Agent/Route	Dosage Range Per Day (Unless Otherwise Noted)	Indication	Monitoring	Duration of Dosing	Level of Evidence for Efficacy*

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 for 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/hour	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 older individuals	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 older individuals	Autonomic tone rebound and hyperactivity	Shaking, tremor, sweating, blood pressure	1 week or less. One patch only	B3
Haloperidol oral/IV (Haldol)	2.5 to 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, second generation		Agitation unresponsive to benzodiazepines, hallucinations, or delusions in patients intolerant of first-generation antipsychotics	Subjective response plus rating scale (CIWA-AR or equivalent)	Individual doses as needed in addition to scheduled antipsychotic	C3
Quetiapine oral (Seroquel)	25-200 mg; dosage adjustment is necessary in hepatic impairment				
Aripiprazole oral (Abilify)	5-15 mg				
Benzodiazepines					
Lorazepam oral/IV/IM (Ativan)	0.5-8 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
Chlordiazepoxide oral (Librium)	25-300 mg				
Diazepam oral/IV/IM (Valium)	5-40 mg				

Oxazepam oral (Serax) oral	15-30 mg				
Dexmedetomidine IV (Precedex)	0.2 mcg/kg/hr, titrate based on response	Adjunct to BZD for autonomic hyperactivity, sympathetic symptom control	Tremor, blood pressure, heart rate	5 days or less	B2
Phenobarbital oral/IV (Luminal)	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/IV		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3

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

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.

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

Data from References 19,26,27.

Fixed-Dose Therapy

Although benzodiazepines given regularly at fixed dosing intervals and subsequently tapered off have been highly effective for alcohol withdrawal, additional medication may be needed for breakthrough withdrawal symptoms. With this approach, monitoring for excessive sedation and respiratory depression is still important. Due to the administration of medication regardless of symptoms, fixed-dose therapy could be preferred in patients with a history of seizures or DT, although there is a lack of evidence to determine superiority over symptom-triggered therapy.[19,23]

Treatment of Severe Alcohol Withdrawal

The progression of symptoms to include seizures and/or DT describes severe alcohol withdrawal, where patients are often refractory to benzodiazepines and require aggressive treatment in a closely monitored setting. For hospitalized patients, the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) can be used to assess the risk of developing severe or complicated alcohol withdrawal. The PAWSS tool is a questionnaire that incorporates patient responses and clinical evidence to assess severity, with a score of 4 or greater pointing toward a high risk of moderate to severe alcohol withdrawal. For patients with severe alcohol withdrawal (CIWA-Ar greater than 19), front-loading therapy with a benzodiazepine is recommended as a first-line treatment followed by phenobarbital. With close monitoring, phenobarbital can be utilized as either adjunctive therapy for patients not responding to high doses of benzodiazepines or alternative therapy if benzodiazepines are contraindicated.[19,25,26]

Alcohol withdrawal seizures do not require treatment with an antiseizure medication, such as phenytoin, unless they progress to status epilepticus or unless there is an underlying concomitant seizure disorder. In general, patients experiencing seizures, and/or experiencing resistant alcohol withdrawal, should be treated supportively under institutional/hospital-specific protocols. These patients should be closely monitored in an intensive care unit in case intubation and mechanical ventilation become necessary. For those requiring escalating doses of benzodiazepines, adjunctive therapy options to manage refractory withdrawal symptoms might include propofol with mechanical ventilation, dexmedetomidine, or ketamine.[19,25,26]

Treatment of Nutritional Deficits and Electrolyte Abnormalities

Supportive care is critical in the management of alcohol withdrawal. Fluid status, electrolyte, and vitamin abnormalities should be carefully assessed and corrected in all patients undergoing alcohol withdrawal. Hydration is necessary in patients with vomiting, diarrhea, increased body temperature, or severe agitation. Electrolyte imbalances, such as hypokalemia, hypomagnesemia, and hypophosphatemia, can often be seen because of inadequate nutrition and fluid volume related to antidiuretic hormone inhibition. Hypokalemia can be corrected with oral potassium supplementation as long as renal function is adequate. Thiamine (vitamin B1) is often depleted and can lead to decreased absorption of glucose. Thiamine deficiency should be addressed prior to glucose administration to prevent the development of Wernicke–Korsakoff syndrome (eg, mental confusion, eye movement disorders, and ataxia [poor motor coordination]). In practice, thiamine is usually given 100 mg once daily orally, IV, or intramuscularly for 3 to 5 days for prophylaxis; higher doses are utilized for acute treatment of Wernicke's encephalopathy. Additionally, patients also benefit from a daily multivitamin with folate due to poor nutritional status (see Table 86-4).[23,26]

Alcohol hypoglycemia was first described 60 years ago and usually occurs in the absence of overt liver disease. It is more likely to occur if the patient is fasting, exercising, or is sensitive to alcohol, and it is less likely if the patient is obese. Mechanistically, this occurs as alcohol directly interferes with hepatic gluconeogenesis, but not glycogenolysis. The energy required for alcohol metabolism is diverted away from the energy needed to take up lactate and pyruvate—substrates for gluconeogenesis. So, those who drink alcohol can become hypoglycemic once glycogen stores are depleted. Neurologic symptoms of hypoglycemia can be confused with alcohol intoxication, and in the inpatient setting, blood glucose should be monitored regularly.[28]

In general, alcohol withdrawal treatment can take place in hospitals, inpatient detoxification units, or outpatient settings. Only patients with mild-to-moderate symptoms should be considered for outpatient treatment, and it is a good idea to have a responsible, non-using person available to help the patient monitor symptoms and administer medications. Patients with a strong craving for alcohol, who concurrently use other substances, who have severe psychiatric problems (ie, suicidal ideations, psychosis), and/or who have a history of seizures or DT, are not good candidates for outpatient treatment. Pharmacologic agents used in the treatment of alcohol withdrawal are summarized in Table 86-4.[23,27,29]

TABLE 86-4

Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Unhealthy Alcohol Use

Medication	Dosage Range Per Day	Indication	Monitoring	Level of Evidence for Efficacy*
Disulfiram (Antabuse)	125-500 mg; use with caution in patients with hepatic disease or insufficiency	Deterrence	Facial flushing, liver enzymes	B2
Acamprosate (Campral)	999-1,998 mg and higher (333 mg tablets)	Craving	Patient-reported craving, renal function	A1
	Dosage adjustment necessary in renal impairment			
Naltrexone (ReVia)	50-100 mg; dosage adjustment may be needed in renal and liver impairment	Craving	Patient-reported craving, liver enzymes	A1
Naltrexone (Vivitrol)	380 mg intramuscularly once every 4 weeks	Craving	Patient-reported craving, liver enzymes, injection site reactions	B2
Antiseizure Medications (eg, topiramate [Topamax], carbamazepine [Tegretol], valproic acid [Depakote], gabapentin [Neurontin], oxcarbazepine [Trileptal])	Seizure disorder doses	Craving	Patient-reported craving, plasma medication levels	B2
Antidepressants (eg., fluoxetine [Prozac], amitriptyline [Elavil], citalopram [Celexa], sertraline [Zoloft])	Depression doses	Craving, depression, anxiety	Patient-reported craving	B2

*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.

Data from References 23,29,30.

Treatment of Alcohol Use Disorder

Nonpharmacologic Therapy

In alcohol use disorder, psychosocial interventions proven to be beneficial include motivational enhancement therapy, family therapies, cognitive behavioral therapy, behavioral approaches, and 12-step programs, such as Alcoholics Anonymous. The combination of a psychosocial intervention and pharmacologic therapy for alcohol use disorder can help reduce the frequency of drinking and the risk of binge drinking.[30]

Pharmacologic Therapy

4 In the United States, disulfiram, naltrexone, once-monthly injectable extended-release naltrexone, and acamprosate are the only four medications FDA approved for the treatment of alcohol use disorder. Disulfiram acts as a deterrent to the resumption of drinking, and naltrexone is a competitive opioid antagonist that has been shown to reduce cravings for alcohol. Acamprosate is a GABAergic agonist that modulates alcohol cravings (Table 86-4). Other medications, including nalmefene, baclofen, bupropion, various serotonergic agents (including selective serotonin reuptake inhibitors and serotonin-3 [5-HT3] receptor antagonists), topiramate, gabapentin, and varenicline, have also been used off-label in the United States or abroad for alcohol use disorder. A Cochrane review[31] of 25 trials with 2,641 patients evaluated a variety of antiseizure medications, including gabapentin, topiramate, oxcarbazepine, valproate, levetiracetam, pregabalin, zonisamide, and carbamazepine, to determine efficacy in the treatment of alcohol use disorder. Overall, these agents did perform better than placebo when comparing the number of drinks per day and average heavy drinking days, but there was insufficient evidence that these agents resulted in increased alcohol abstinence rates. The conclusion was there is insufficient evidence of efficacy to support the use of antiseizure medications in alcohol use disorder.[31] A recent meta-analysis of seven randomized controlled trials found that topiramate had moderate benefits on the number of abstinence days and frequency of heavy drinking. Of the antiseizure medications, topiramate appears to decrease alcohol consumption and is increasingly prescribed off-label as a treatment of AUD.[32]

For moderate-to-severe AUD, the American Psychiatric Association's (APA) practice guideline recommends (1) naltrexone or acamprosate to reduce alcohol consumption or achieve abstinence or (2) disulfiram for patients who have not responded to naltrexone and acamprosate and who understand the potential adverse effects with concurrent alcohol intake. Additionally, the APA also recommends gabapentin or topiramate in moderate-to-severe AUD, for patients who prefer one of these medications or who are intolerant of or who have not responded to the FDA-approved agents.[33]

Disulfiram

Disulfiram was the first FDA-approved medication for alcohol use disorder. It deters a patient from drinking by producing an aversive reaction if alcohol is consumed; otherwise, it has minimal effects. Pharmacologically, it inhibits aldehyde dehydrogenase in the biochemical pathway for alcohol metabolism, allowing acetaldehyde to accumulate. If a patient consumes alcohol within 12 to 24 hours of taking disulfiram, the resulting increase in acetaldehyde causes severe facial flushing, throbbing headache, nausea and vomiting, chest pain, palpitations, tachycardia, weakness, dizziness, blurred vision, confusion, and hypotension, referred to as a "disulfiram reaction." In severe (rare) cases, the reaction can lead to myocardial infarction, congestive heart failure, cardiac arrhythmia, respiratory depression, convulsions, and death, particularly in vulnerable individuals. When disulfiram is prescribed, abstinence from alcohol is a critical component of patient education and supervision is recommended to promote adherence.[20,33] Evidence in a meta-analysis of 22 randomized trials found that, in 17 open-labeled studies, disulfiram was associated with a higher abstinence benefit compared with controls; blinded studies did not demonstrate a benefit.[34]

Naltrexone

Naltrexone, a potent opiate antagonist, is available for the treatment of unhealthy opioid use as it blocks the effects of exogenous opioids (for more details, see Chapter 85, "Substance Use Disorders I: Opioids, Cannabis, and Stimulants"). It is also FDA approved for the treatment of unhealthy alcohol use, and it is thought to attenuate the reinforcing effects of alcohol. Those who consume alcohol while taking naltrexone report feeling less intoxicated and having fewer alcohol cravings.[4,29] Evidence suggests that genetics play a role in the clinical response to naltrexone, and its efficacy varies greatly among individuals. In previous preliminary studies, the Asn40Asp (118A>G, A355G, rs1799971) polymorphism in the μ-opioid receptor gene (*OPRM1*) demonstrated an increased response to naltrexone with lower rates of relapse to heavy drinking; however, a recent controlled clinical trial disputed these results,[35] and further studies are ongoing.

Naltrexone administration does not induce alcohol withdrawal; however, it should not be given to patients currently receiving opiates because it will block their therapeutic effects and can precipitate severe opioid withdrawal syndrome. Naltrexone should be used with caution in patients with moderate-to-severe renal impairment and baseline liver function tests (LFTs) are recommended. Current evidence supports the tolerability of naltrexone in high-risk patients with hepatitis C and human immunodeficiency virus (HIV). When initiating naltrexone, the patient should not be in acute alcohol withdrawal and should be involved in psychosocial treatment.[33,36] A review of 50 randomized controlled studies,[37] which included 7,793

patients, found that oral naltrexone decreased drinking days by 4% and decreased the risk of heavy drinking by 83% compared to placebo. The most common adverse effects were nausea and daytime sedation. The usual starting dose of oral naltrexone is 50 mg/day, but doses of 100 mg/day have been used.[37]

In April 2006, the FDA approved Vivitrol, a once-monthly intramuscular naltrexone formulation, given at a dose of 380 mg that can be administered in an outpatient setting.[36]

Extended-release formulations reduce the likelihood of forgetting or choosing not to take the medication, ensuring medication adherence for the next month. However, the cost is considerably higher than the oral formulation.[36]

The extended-release form of naltrexone may be more beneficial in reducing heavy drinking rather than abstinence. In a recent meta-analysis of seven randomized, double-blind trials, all requiring abstinence before treatment, extended-release naltrexone resulted in two fewer drinking days and one to two fewer heavy drinking days per month compared to placebo. Larger reductions in heavy drinking were reported in trials that did not require abstinence prior to study enrollment and that lasted longer than three months.[38]

Acamprosate

Acamprosate is a glutamate modulator at the *N*-methyl-D-aspartate receptor that reduces alcohol craving. Individuals treated with acamprosate are more successful in maintaining abstinence from alcohol versus placebo. Acamprosate is well tolerated, with GI adverse effects being the most common. It is not metabolized through the liver but is excreted through the kidneys and should be used with caution in individuals with severe renal dysfunction by making appropriate dose adjustments.[29,33]

A Cochrane review of 24 randomized controlled trials with 6,915 participants[39] found that acamprosate significantly reduced the risk of any drinking and significantly increased the cumulative abstinence duration (mean difference 10.94 days) compared to placebo. Diarrhea was the only adverse effect more frequently reported with acamprosate than placebo.

TABLE 86-5 includes the dosing information for acamprosate and other options used in treating alcohol use disorder.[20,29,30] When selecting a medication for an individual patient, factors such as ease of administration, available formulations, renal or hepatic disease, pregnancy, adverse effects, presence of co-occurring conditions, or specific symptoms of AUD should guide medication therapy decisions. Duration of treatment is dependent on several patient-specific factors, such as clinical response, tolerability, patient preference, history of relapses, and severity of the disorder.[23]

TABLE 86-5

Summary US Preventive Services Task Force (USPSTF) Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons

Population	Adults >18 Years Old (Nonpregnant)	Pregnant Persons >18 Years Old
Assessment	Screen for all tobacco Consider the following approaches: ○ 5As ○ Ask Assist Refer ○ Use smoking status as a vital sign	Screen for all tobacco Consider the following approaches: ○ 5As ○ Ask Assist Refer ○ Use smoking status as a vial sign ○ Consider using a multiple choice question approach during assessment to improve comfort level
Behavioral interventions	• In person behavioral support and counseling >4 sessions which each session averaging 90-300 minutes (group/individual option) ○ Efficacy improves with 8 sessions or more • Telephone counseling/mobile phone based interventions (>3 sessions)	• Counseling • Self help materials • Feedback • Health education • Incentives • Social support
Pharmacotherapy	• NRT • Bupropion SR • Varenicline • +/-Behavioral interventions • Combination of NRT (long acting + short acting NRT demonstrated higher efficacy vs. single NRT approach)	• Inadequate evidence due to lack of studies to determine benefit vs risk
Comments on benefits and harms	Conclusion from USPSTF; behavioral interventions and +/− pharmacotherapy interventions with FDA-approved pharmacotherapy agents for smoking cessation demonstrated substantial benefit	Conclusion from USPSTF; behavioral interventions demonstrated substantial benefit for perinatal outcome and improved smoking abstinence
Electronic nicotine delivery systems (electronic cigarettes)	Evidence on the use of ENDS for tobacco cessation is insufficient, benefit vs risk cannot be determined	Evidence on the use of ENDS for tobacco cessation is insufficient, benefit vs risk cannot be determined

ENDS, Electronic Nicotine Delivery Systems; FDA, Food and Drug Administration; NRT, Nicotine Replacement Therapy.

Data from Reference 10

EVALUATION OF THERAPEUTIC OUTCOMES

Considering the increasing rates of alcohol use and the variable effects of alcohol from individual to individual, screening tools such as the CAGE questionnaire and AUDIT are instrumental in detecting unhealthy alcohol use and identifying those at risk for alcohol withdrawal. Treating alcohol withdrawal takes precedence over the treatment of alcohol use disorder. The assessment of alcohol withdrawal begins with utilizing the CIWA-Ar to

assess withdrawal symptom severity before initiating pharmacologic therapy with benzodiazepines. Close monitoring is essential to avoid progression to severe withdrawal, which includes seizures and/or DT.

For alcohol use disorder, both psychosocial interventions and pharmacologic therapy can be beneficial to reduce drinking frequency. Four agents have FDA approval for the treatment of alcohol use disorder. Careful consideration of patient-specific factors needs to be done, as each agent works pharmacologically different to reduce cravings (acamprosate and extended-release naltrexone) or act as a deterrent to the resumption of drinking (disulfiram). Patient counseling on potential adverse effects followed by close monitoring and follow-up are necessary to assess response to therapy and promote adherence.

INTRODUCTION—NICOTINE

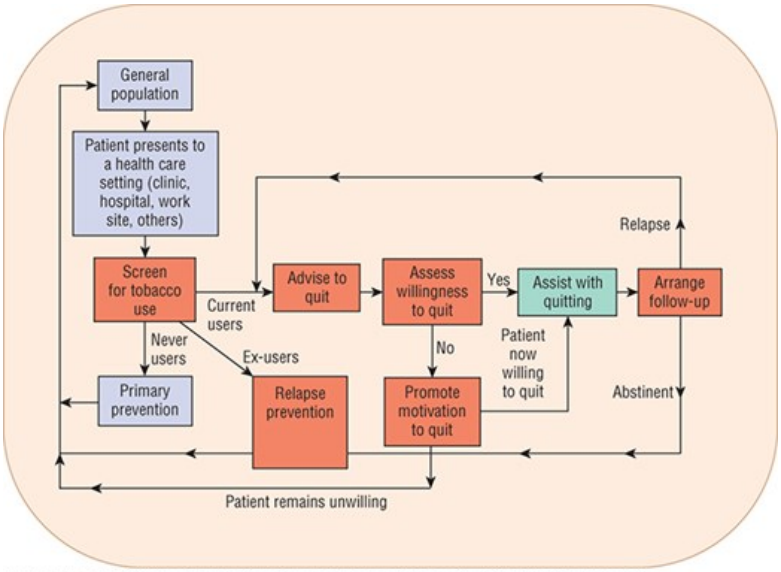
5 Annually, approximately 480,000 deaths in the United States are attributable to tobacco use, making smoking the leading cause of preventable death and disease in the United States.[40–42] Adverse health effects of tobacco use impact almost every organ in the body and can result in an increased risk of cancer, respiratory disease, and cardiovascular disease, as well as negatively impacting the immune system and reproductive health. Over 16 million Americans currently suffer from diseases directly related to smoking.[41,43]

The number of individuals who smoke cigarettes has continued to decline over the years. In 2019, the National Health Interview Survey reported 14% or 34.1 million of adults smoked cigarettes, which is reduced from the 42% reported in 1964, when the first Surgeon General's report on smoking was released.[44]

Although smoking cigarettes is still the most popular method of tobacco exposure,[10] a small percentage of individuals use alternative forms of nicotine products such as cigars (3.6%), pipes (1%), smokeless tobacco (2.4%), and e-cigarettes (4.5%).[44] It is important to recognize the downward trend in the percent of individuals who smoke cigarettes is not uniform across all populations in the United States. In order to reduce the disparities seen in tobacco use, continued education for healthcare providers is needed. Behavioral and pharmacotherapy interventions have proven effective and these are supported by the clinical guidelines for tobacco use and use disorder as outlined in Fig. 86-1.[10]

FIGURE 86-1

Model for treatment of tobacco use and use disorder.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

There have been numerous approaches to smoking cessation, including a focus on sales, marketing, and manufacturing of all tobacco products marketed in the United States thatare now regulated by the FDA. Federal tobacco excise taxes have increased, and states have also added cigarette

excise tax rates. Additionally, many states have enacted comprehensive smoke-free laws, and further opportunities for access to smoking cessation pharmacotherapy and counseling are available through the Affordable Care Act.[41,45]

National telephone quitlines, smoking cessation counseling services, and mass media campaigns have been utilized to improve smoking cessation rates. “Tips from Former Smokers” was a successful federally funded national mass media antismoking campaign,[46,47] and various internet and mobile phone text messaging programs have been developed over the years. The QuitGuide Mobile App is a free app released by Smokefree.gov, which provides resources to track craving patterns and motivation, and monitors progress as milestones are achieved.[48] Despite the proven effectiveness of pharmacological and counseling services to aid in sustained smoking cessation, cigarette smoking continues to be the leading cause of preventable morbidity and mortality in the United States.[41]

EPIDEMIOLOGY

The National Survey on Drug Use and Health (NSDUH) reported in 2017 that an estimated 58.1 million people (21.1%) had exposure to a tobacco product at least once in the month prior to being interviewed. Additionally, 45.9 million of the US population age 12 and older currently smoke cigarettes, defined as smoking at least a part of the cigarette. Of these, 58.4% were daily smokers (26.8 million) and 40.5% (10.8 million) reported smoking a pack or more of cigarettes per day.[3] In addition, 11.7 million smoked cigars, 8.5 million used smokeless tobacco, and 1.9 million smoked pipe tobacco.[3] Comparing age groups, data from 2019 demonstrated adults 26 years and older have the highest rate of daily cigarette use (62.5%). In contrast, adolescents 12 to 17 years of age reported the lowest daily cigarette use in the month (13.2%). This data from 2019 shows that each age group has reported lower percentages of daily cigarette use compared to the early 2000s, although the percentages in recent years have been fairly similar. The downward trend over the last two decades is encouraging but continued tobacco cessation education is needed. Importantly, this report has not included vaping of nicotine products; however, tracking of trends in the use of nicotine vaping products is ongoing.[3]

Additional data has been provided in the Population Assessment of Tobacco and Health (PATH) Study launched in 2011. This household-based longitudinal cohort study is a collaboration between the FDA Center for Tobacco Products, the National Institute on Drug Abuse (NIDA) and the National Institutes of Health (NIH), which include youths age 12 to 17 years old and adults. Overall 45,000 current tobacco users and nonusers in the United States were included to help evaluate tobacco use and its effects on overall health.[49,50] The PATH study differs from NSDUH since the assessment includes biomarker collection, a detailed assessment of tobacco-use behaviors, and further detailed examination of specific tobacco products to distinguish between them and ensure clarity in usage patterns.[51] The goals of this study are to determine what products are commonly used including the use of e-cigarettes; factors associated with susceptibility of use; evaluate patterns of use; review the overall health impacts associated with smoking, smoking cessation, and relapse; and identifying any racial/ethnic, gender, and age differences in use.[51]

The Wave 1 data, collected from September 2013 through December 2014, indicated that more than 25% of adults used one type of tobacco product during this time period. Approximately 9% of youth used a tobacco product in the last 30 days, and 1.6% of these were daily users of tobacco. Forty percent of the respondents indicated they were using multiple tobacco products at the same time, with the most common combination being cigarettes and e-cigarettes together. The PATH Study also found that in adults, tobacco use is higher in males, members of racial minority groups, and individuals who have lower household incomes or lower education levels.[51]

However, tobacco-related health disparities (TRHD) have been identified in many patient populations.[52] In addition to those reported in in the PATH study, individuals with mental health conditions, and substance use disorders also have higher rates of tobacco use.[10] Additionally, certain geographic locations in the United States have been identified as having a higher prevalence of cigarette smoking, including the Midwest and South compared to the Northeast and West. The prevalence of cigarette smoking is higher the lesbian, gay, bisexual, transgender, and queer (LGBTQ+) population in both adults and youth. Further study on tobacco-related health disparities is needed to continue to develop guidelines and policies on how to effectively identify and reduce disparities, inequities, and inequalities to improve overall care and continue to improve the tobacco cessation rates.[41]

Economic Impact of Smoking

The yearly direct healthcare expenditures associated with smoking for adults is estimated at nearly $170 billion for direct medical care and $156 billion in indirect costs, such as lost productivity.[43,53] Included in these costs are the estimated $39 billion annually for Medicaid patients. This number is

significant, as this small subset of the population has higher smoking rates compared to privately insured patients.[54]

Health Risks of Smoking

Cigarette smoking greatly increases the risk of (a) cardiovascular diseases such as stroke, sudden death, and heart attack; (b) nonmalignant respiratory diseases including emphysema, asthma, chronic bronchitis, and chronic obstructive pulmonary disease; (c) lung cancer and other cancers, (d) diabetes, and (e) harmful effects to reproductive health, including erectile dysfunction.[40,43] Exposure to environmental tobacco smoke (*passive exposure and secondhand smoke*) has been cited as the cause of lung cancer, stroke, and coronary heart disease in adults.[55] Children who are exposed to environmental smoke have a higher risk of heart disease, respiratory infections, asthma, and ear infections than those not exposed.[55] Sudden infant death syndrome (SIDS) occurs more often in infants whose mothers smoked during pregnancy compared to offspring of nonsmoking mothers. Studies continue to determine how environmental smoke can increase the risk of SIDS. Additionally, long-term adverse negative cardiovascular consequences have been identified in children exposed to environmental smoke leading to an increased risk of cardiovascular complications later in life.[56]

PATHOPHYSIOLOGY

Nicotine is an agonist at nicotinic acetylcholine receptors (nAchRs) with pharmacologic effects highly dependent on dose. These effects include central and peripheral nervous system stimulation and depression, respiratory stimulation, skeletal muscle relaxation, catecholamine release by the adrenal medulla, peripheral vasoconstriction, and increased blood pressure, heart rate, cardiac output, and oxygen consumption. Cigarette smoking or low doses of nicotine produce an increased alertness and increased cognitive functioning by stimulating the cerebral cortex. At higher doses, nicotine stimulates dopamine within the “reward” center in the brain’s limbic system.[57] When nicotine is ingested, a feeling of pleasure and relaxation can occur. Repetitive exposure to nicotine leads to neuroadaptation, which builds tolerance to the initial effects. An accumulation of nicotine in the body leads to a more substantial withdrawal reaction if cessation is attempted. Common symptoms experienced during withdrawal can include anxiety, difficulty concentrating, irritability, and strong cravings for tobacco.[58] Onset of these withdrawal symptoms usually occurs within 24 hours and can last for days, weeks, or longer. Additionally, some might experience a state of malaise or inability to experience pleasure during this nicotine withdrawal period. These types of reactions have been termed “hedonic dysregulation” and can be rapidly reversed with nicotine readministration.[59] This powerful force of nicotine effects leading to physical dependence is one reason smokers attempting smoking cessation have a high rate of relapse, and only 3% remain abstinent 6 months following the quit date.[60]

The genetics associated with nicotine addiction is very complex and continues to be studied with great interest. Progress continues to be made in understanding the human genome and identifying more specific markers for various diseases. Many phenotypes and corresponding genes have been identified as markers, which include the genetic markers, nicotinic cholinergic receptor alpha5 subunit (CHRNA5) and cytochrome P450 2A6 (CYP2A6), and the metabolic marker, nicotine metabolism ratio (NMR). All three of these have been found to have a relationship with smoking behavior, including nicotine physical dependence and cigarettes per day. Additionally, the CHRNA5-CHRNA3-CHRNB4 locus has been found to predict lung cancer, chronic obstructive pulmonary disease (COPD), coronary artery disease, and mortality.[61,62] Having the ability to identify patients at higher risk can improve chances of diagnosing cancer earlier in the disease process so treatment can begin sooner and improve prognosis.[61]

Studies continue to evaluate the effects of polymorphisms on various genes and the effect this has on the efficacy of pharmacotherapy treatment options in order to offer options for more personalized treatment in the future.[62] Genetic variability in nicotine metabolism continues to be evaluated since variations in CYP2A6 lead to different rates of nicotine physical dependence and responses to NRT.[61] Further understanding of these variations will continue to prove helpful in creating a personalized pharmacotherapy plan to improve smoking cessation rates.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Nicotine Withdrawal

General

- The patient may experience anxiety, but may not be in acute distress. Symptoms can wax and wane over time.

Symptoms

- The patient may complain of cravings, difficulty concentrating, frustration, irritability, and impatience. Hostility, insomnia, and restlessness can also occur.
- Increased skin temperature can be present.

TREATMENT

Desired Outcomes

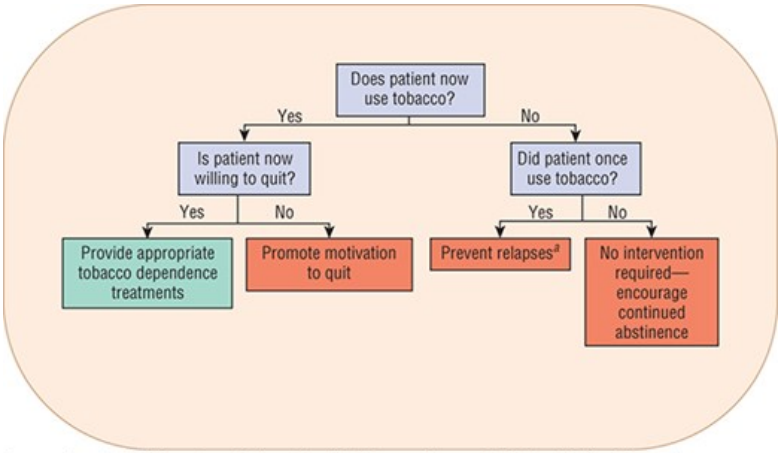
Ideally, the desired outcome is for all tobacco users to quit, and that young people never take up the habit. Unfortunately, this is unlikely to happen. The Healthy People 2030 target has set a goal prevalence of tobacco use at less than or equal to 16.2% in adults 18 years and older. This is a realistic and believed to be an achievable goal since the National Health Interview Survey 2018 figures have reported at 20.1% of adults use any tobacco product, as well as continued declines in the percent of the adult population who smoke cigarettes.[44,63]

Nicotine physical dependence: Recognition of Behavior

6 The United States Preventive Services Task Force (USPSTF) released the "Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons in 2021."[10] This recommendation stresses that all healthcare providers should ask each adult about tobacco use, advise any adult using tobacco to stop using, and provide behavioral inventions and pharmacotherapy options to aid in smoking cessation (Fig. 86-2). These recommendations also included pregnant individuals and are summarized in Table 86-5. Additional information regarding the challenges of pharmacotherapy treatment options for smoking cessation in pregnant persons is also available.[10]

FIGURE 86-2

Algorithm for treating tobacco use.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

A well-established method of assessing an individual's smoking status utilizes the 5As as follows:[10]

1. Ask about tobacco use
2. Advise the person to quit through clear individualized messages
3. Assess the person's willingness to quit
4. Assist in quitting
5. Arrange follow-up and support

Other approaches recommend using the "Ask, Advise, Refer" approach or recording the patient's smoking status as a vital sign during each appointment. The USPSTF statement expanded on the 5As and recommended that for pregnant individuals a higher comfort level was demonstrated if these questions were asked in a multiple-choice format instead of open-ended questions.[10] Additionally, another approach includes the "Ask, Advise, Refer," which can be used to assist individuals in obtaining access to smoking cessation services.

The Fagerström test for nicotine physical dependence can be used to help identify how much someone is smoking, the compulsion to use, and the level of physical dependence. This instrument includes questions that can be answered as either yes or no. Each question answered as yes is worth 1 point. The scoring is 0 to 10; the higher the score, the higher the individual's physical dependency to nicotine.[64] When assessing for tobacco use and approaching tobacco cessation counseling, there might be times when someone is not ready to consider an attempt tobacco cessation. A motivational intervention to consider is the 5R's.[65]

- Relevance: Discuss possible reasons why tobacco cessation is personally relevant.
- Risks: Explore the individual's views of potential risks and negative consequences of tobacco use.
- Rewards: Explore what positive benefits could result in tobacco cessation
- Roadblocks: Encourage the individual to identify and voice potential benefits of tobacco cessation.
- Repetition: Commit to address tobacco cessation during each interaction and continue to encourage those who have previously failed attempts.

Nonpharmacologic Therapy

The USPSTF statement emphasized the importance of counseling sessions and highlighted the goal of reaching at least four in-person sessions, with a total contact time ranging from 90 to 300 minutes.[10] A Cochrane analysis reviewed 65 trials, which included approximately 23,000 patients, who received a combination of pharmacotherapy treatment and behavioral support either in person or through telephone interaction. This review determined that the addition of behavioral support improves the smoking cessation efforts by 10% to 20%.[66] Although comprehensive behavioral interventions have been shown to be more effective in helping people quit smoking and remain abstinent, less intensive treatments may be beneficial as well. Even minimal contacts lasting less than 3 minutes, which include the 5As, are more successful in increasing cessation rates than an intervention involving no contact.[41]

Motivational interviewing is a collaborative approach to help patients identify barriers for making a behavior change. A meta-analysis of 37 studies, including over 15,000 smokers undergoing motivational interviewing (MI) compared the efficacy of both intensive MI and less intensive MI to no treatment, other smoking cessation treatments, and other types of smoking cessation treatments. Overall, MI is moderately effective in increasing the chances of long-term smoking cessation when utilized with other smoking cessation treatment approaches and when compared to other treatment approaches without the MI approach. However, there was insufficient evidence to determine if MI improves smoking cessation when compared with no treatment. Further research is needed to continue to evaluate the efficacy of MI.[67]

Additionally, other forms of interventions are effective in improving smoking cessation rates. Telephone-based quitlines, which are operated by the National Cancer Institute and offered in all 50 states, the District of Columbia, Puerto Rico, and Guam via 1-800-QUIT-NOW, provide various options, such as recorded messages, counseling services, mailed materials, counselor follow-up services, and access to pharmacotherapy options for smoking cessation.[68] Along with continued support and monitoring of state quitlines, the Centers for Disease Control and Prevention (CDC) has now

established the National Quitline Data Warehouse (NQDW) for continual evaluation and support of services.[69] The use of technology to further enhance counseling opportunities has also increased over the years, including websites, text messaging, social networking, and smartphone applications. A systematic review and meta-analysis evaluated 26 manuscripts that included over 33,000 smokers who received text messages for smoking cessation. Overall patients receiving the text messages were much more likely to achieve smoking cessation by 50% to 60%.[70]

Furthermore, while counseling alone can be effective, its efficacy is further augmented by the addition of pharmacotherapy, with NRT also being effective independent of counseling services.[10] The combination of pharmacotherapy and behavioral interventions were evaluated in different subpopulations, including ethnic minorities and patients suffering from mental health conditions. No evidence was found suggesting there was a difference in risk or benefit of this treatment approach within these populations.[41]

Pharmacologic Therapy

Pharmacologic therapy helps facilitate the process of tobacco cessation by the following mechanisms:[71]

1. “Reducing nicotine withdrawal symptoms”

2. “Reducing the rewarding effects of nicotine from smoking by blocking or desensitizing nicotine receptors”

3. “Providing an alternative source of nicotine with the desired pharmacologic effect previously provided by nicotine from cigarettes””

All patients attempting to quit should be encouraged to use effective pharmacotherapy agents for smoking cessation except in the presence of special circumstances or contraindications. For pregnant individuals, the USPSTF statement recommends that clinicians weigh the benefits and the harms associated with pharmacotherapy interventions and treat each patient on an individual basis.[10] Current recommendations list seven first-line agents including the NRT medications, sustained release bupropion hydrochloride, and varenicline tartrate as treatment options.[10,41] First-line therapy options in smoking cessation are summarized in Table 86-6.[41,72–79]

TABLE 86-6

First-Line Pharmacotherapy Treatment Options for Smoking Cessation

Medication	Dosing (For individuals 18 years or older. For those <18 years, discuss with a prescriber before use)	Duration	Comments/Monitoring Parameters
Nicotine Replacement Therapies (NRTs)			

Nicotine patch	Based on cigarettes smoked per day:
	>10 cigs/day:
	Step 1: 21mg/day: Weeks 1-6
	Step 2: 14mg/day: Weeks 7-8
	Step 3: 7mg/day: Weeks 9-10
	
	<10 cigs/day:
	Step 2: 14mg/day: 6 weeks
	Step 3: 7mg/day: 2 weeks
		8-10 weeks	• 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 stop day. However, if patient smokes with patch on, there is no major risk
			• Place a new patch on each day, hold patch on for 10 seconds to help adherence
			• Rotate patches to avoid skin irritation
			• Do not cut patches, do not wear patches for greater than 24 hours, do not use more than one patch at a time

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:
			  ○ Do not eat or drink 15 minutes before or during use of gum
			  ○ Chew each piece slowly
			  ○ Park between cheek and gum after a peppery sensation becomes apparent
			  ○ Repeat process until peppery sensation does not reoccur (approximately 30 minutes)
			  ○ Use alternate sides of mouth when using chew and park method
			  ○ Use at least 9 pieces of gum per day for first 6 weeks to improve cessation

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 5 lozenges in 6 hours or 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
			  ○ Use at least 9 lozenges per day for first 6 weeks to improve cessation.

Nicotine oral inhaler + cartridge plus mouthpiece (Nicotrol®)	10 mg nicotine/cartridge; supplies 80 puffs
	1. Stop smoking completely before use.
	2. Initial dose: 1 cartridge every 1-2 hours
	3. Begin gradual reduction of device after 3 months of use
	4. Gradual dose taper over 6-12 weeks
		6 months	• Patients should stop smoking prior to starting this product
			• Most successful patients in trials; use ranged from 6-16 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 worsening angina
			• Counseling:
			  ○ Insert cartridge into mouthpiece and inhale medication quickly by puffing on mouthpiece for continuously for 20 minutes or four 5 minute sessions
			  ○ Deep inhalation is not necessary when using this product

			○ Change cartridge when nicotine taste is no longer detected ○ Dosing is individualized; initially it is recommended to use at least 6 cartridges per day for 3-6 weeks. Do not exceed 16 cartridges per day.
Nicotine metered nasal spray (Nicotrol NS)	Availed in 10mg/ml bottle 1 spray (0.5mg nicotine/spray) into each nostril 1-2 times each hour when craving cigarette Max dose: 10 sprays per hour (max of 80 sprays per day)	3-6 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 ○ Wait at least 2-3 minutes before blowing nose after using product ○ For best results, use at least 16 sprays per day which has been found as the minimum effective dose ○ Pregnancy Category D
Non-Nicotine Replacement Options			
Bupropion (Zyban)	150 mg by mouth daily × 3 days then 150 mg by mouth twice daily (dosing interval should be > 8 hours)	3-6 months	• Do not exceed 300mg/day • Recommend initiating therapy 1-2 weeks prior to set “quit” day • Tapering is not needed with discontinuing agent • 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 • Counseling points: ○ May cause dry mouth ○ May cause insomnia, avoid bedtime dosing ○ May help with post-cessation weight gain ○ Recommended dosing interval: more than 8 hours when taking twice daily
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	12 weeks; an additional 12 week course may be used in select patients	• Take with food and a full glass of water • Quit day can be flexible with 4 options: ○ Start varenicline 1 week after quit day ○ Start varenicline and establish quit day between days 8 and 35 ○ Start varenicline and gradually reduce smoking with goal of cessation by week 12 of therapy • If patient has difficulty with cessation, 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 • Maintenance up to 6 months therapy is approved

			• Renal impairment dosing for CrCl ≤ 30mL/min (0.5 mL/s)
			• No dosing adjustment needed in hepatic impairment
			• Neuropsychiatric adverse events: black box warning removed in December 2016, warning remains
			• Counseling Points:
			  ○ Varenicline works in two ways by reliving symptoms of nicotine withdrawal and blocking rewards of smoking
			  ○ Most common adverse medication effects: nausea, sleep problems, constipation, gas, vomiting
			  ○ Consider dose reduction if experiencing insomnia

Data from References 41,72–79.

Nicotine Replacement Therapy

Nicotine replacement therapy provides lower peak levels and lower levels of nicotine concentrations compared to cigarettes, leading to reductions in the reinforcing effects of smoking. Another benefit of NRT includes the decrease and eventual elimination of exposure to the harmful substances included in cigarettes.[80] Individuals have easy access to many of these products since five of these are available over-the-counter, with only the nasal inhaler and the nasal spray currently being prescription products. A recent review showed that all the commercially available forms of NRT (eg, chewing gum, transdermal patches, nasal spray, lozenge, inhalers, and tablets) were effective for smoking cessation, increased the quit rate by 50% to 60%, and were tolerated with very limited reports of serious adverse events.[81] Combinations of these agents have been demonstrated in multiple studies and meta-analyses to improve abstinence rates in comparison to monotherapy.[10,82]

In some smoking cessation protocols, it is suggested that NRT use begins on the patient's defined quit day. However, other recommendations have suggested patients utilize the preloading approach with NRT in which patients start NRT prior to setting the quit date. It is thought the use of NRT with smoking will reduce the satisfaction associated with smoking and break the reward pattern associated with smoking. This approach can allow the patient to set the quit date when comfortable. A recent Cochrane review for 9 studies with over 4,000 patients demonstrated there is moderate evidence to support this approach in improving quit rates (RR 1.25, 95%, CI 1.08-1.44).[82]

Nicotine Gum

Nicotine gum offers a rapid onset and short duration of effect that can be very beneficial since the amount of nicotine and the timing can be controlled by the patient. The recommended dosing is based on the "time to first cigarette" (TTFC), which indicates the response to the nicotine deprivation.[83] The FDA has approved the nicotine starting doses of 4 mg for patients who experience TTFC less than 30 minutes and 2 mg for patients who experience the TTFC greater than 30 minutes.[84] Recent studies have demonstrated utilization of the 4-mg dose will increase the chances of achieving smoking cessation compared to the use of the 2-mg gum in highly dependent smokers.[82] 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 through the oral mucosa. Acidic beverages (eg, coffee, juices, or soft drinks) interfere with the buccal absorption of nicotine, so eating and drinking anything except water should be avoided for 15 minutes before and during chewing. Instructions to chew the gum on a fixed schedule (at least one piece every 1-2 hours) for at least 1 to 3 months can be more beneficial than ad libitum use.[78] Generally, the gum should be used for up to 12 weeks with no more than 24 pieces chewed per day.[78]

Nicotine Lozenge

The nicotine lozenge is available as a 2-mg or 4-mg dose, with the lower amount recommended for patients who normally smoke their first cigarette later than 30 minutes after awakening, and the higher dose being reserved for smokers who smoke within 30 minutes of waking. It is recommended that no more than 20 lozenges should be used in one day, for up to 12 weeks. The most common adverse effect of the lozenge is nausea. As with the

nicotine gum, acidic beverages (eg, coffee, juices, or soft drinks) interfere with the buccal absorption of nicotine, so eating and drinking anything except water should be avoided for 15 minutes before and during use of the lozenge.[75]

Nicotine Patch

The nicotine patch is available as a nonprescription medication and is the NRT option with the highest rate of adherence.[71] This nicotine product provides a steady amount of transdermal nicotine for 16 to 24 hours based on the selected product. The patch is available in three strengths and package labeling suggests individuals who smoke more than 10 cigarettes per day start with the 21 mg patch and those who smoke less than 10 cigarettes per day start with the 14-mg patch. This initial regimen will be worn for 4 to 6 weeks and then a tapering regimen will begin which includes reducing the patch strength approximately every 2 weeks.[41,77] The patch can be used up to 8 to 10 weeks per the labeling guidelines. Patients who experience sleep disruption should remove the 24-hour patch prior to bedtime or use the 16-hour patch. The patient should place a new patch on a relatively hairless location, typically between the neck and waist. The site of application should be changed daily to diminish any skin irritation from the patch adhesive. There are no restrictions on activity while using the patch.[41,77]

The patient should be told that using the patch results in less desire to smoke and provides an opportunity for a new nonsmoker to reduce their hand-mouth habit without being burdened by craving. The patient should understand that with smoking, there are naturally peaks and valleys in the amount of nicotine in the bloodstream. However, with the patch, there is a steady gradual rise in the blood nicotine concentration that levels off and remains constant for much of the day, and then gradually decreases while the person is asleep.[41] A recent Cochrane review concluded that in individuals who smoke more than 15 cigarettes per day, the 21 mg nicotine patches resulted in a higher quit rate compared to the lower 14 mg nicotine patches.[81] Combining the nicotine patch with an oral formulation, such as the nicotine gum which allows ad libitum nicotine delivery, can improve overall cessation without significant increased risk for harm.[41] In fact, various studies have evaluated combination NRTs and based on high certainty evidence, the use of a nicotine patch can be used with the nicotine gum, lozenge, or nasal spray on an as needed basis to improve the long-term quit rate compared to NRT monotherapy.[82] However, it is important to also incorporate behavioral strategies with pharmacotherapy as recommended by current guidelines.[41,79,85]

Nicotine Nasal Spray

Nicotine nasal spray is available exclusively as a prescription medication and differs from the other short-acting NRTs due to the higher peak and trough concentrations, as it is more rapidly absorbed and eliminated than other forms.[85] A dose of nicotine nasal spray consists of one 0.5 mg delivery to each nostril (1 mg total). Initial dosing should be one to two doses per hour, increasing as needed for symptom relief. The minimum recommended treatment is 8 doses per day, with a maximum limit of 40 doses per day (five doses per hour). Recommended duration of therapy is 3 months. Individuals should not sniff, swallow, or inhale through the nose while administering doses because this increases irritating adverse effects.[74]

Nicotine Oral Inhaler

The nicotine oral inhaler consists of a mouthpiece and a plastic cartridge placed into the inhaler, which delivers 4 mg or 10 mg of nicotine, through vapor inhalation. Approximately 2 mg is systemically absorbed mainly in the throat and upper airway.[71,72] It is suggested that the individual actively puff on the inhaler for 5 minutes at a time and adjust use based on effect, as the cartridge can be used for up to 20 minutes of active puffing. The recommended initial dosing is 6 to 16 cartridges per day for up to 12 weeks of therapy. Tapering of the product should start 6 weeks after initiation.[72] As the inhaler resembles a cigarette, it also provides the sensory stimulation to help decrease some of the cue-induced cravings by alleviating the hand-mouth habit.[41,71,85] However, there are some concerns this inhaler may do the opposite and possibly reinforce smoking habits.[85]

Instructing Patients in the Use of NRT

Compliance with NRT improves when individuals are presented a clear rationale for its use and realistic expectations about response. It should be explained that nicotine is responsible for physical dependence and that discontinuation causes cigarette craving, tension, irritability, sadness, problems with sleep, and difficulty concentrating. The NRT products help reduce these physical symptoms so individuals can modify behavioral and psychological aspects associated with smoking.[71] The products have relatively few adverse effects; however, nausea and light-headedness are possible

symptoms of nicotine overdose that warrant a dose reduction.[10,82]

Duration

Initially, when NRT products were approved by the FDA, they were approved for 8 to 12 weeks of therapy. However more recent practice is to inform those who commit to quitting smoking than using NRT for up to 3 months is common. Additionally, some individuals will experience severe withdrawal even beyond this time period, and thus long-term use of NRT might be indicated. The long-term use of NRT 6 months or longer has not been linked to any safety concerns,[41,71] although there is still insufficient efficacy data based on a meta-analysis and further research is needed.[41,86]

Electronic Nicotine Delivery Systems

Electronic nicotine delivery systems (ENDS) (also known as e-cigarettes or electronic cigarettes, or vaping devices) are designed to deliver a propylene glycol or glycerin product with a combination of nicotine, flavorings, and/or other chemicals through an aerosol. The device usually includes a battery, a heating coil, an atomizer, a cartridge, which contains the e-liquid (also called “juice”), and a mouthpiece. The range of nicotine delivered to the user can vary according to the product type and brand, and is available in first-, second-, third-, and fourth-generation models, with some products not containing any nicotine at all.[87] The first-generation devices are disposable and resemble a cigarette, and the second-generation products are tank devices that can be recharged. Pod/pod mods are the third-generation products that allow for high levels of nicotine and are refillable, and the fourth-generation products are vape pens that are battery operated and can be refilled.[88] It has been suggested that using the ENDS products instead of smoking traditional cigarettes can eliminate the exposure to most of the toxins commonly seen in traditional cigarettes. However, no e-cigarette has been approved by the FDA as a cessation aid. A Cochrane review of 56 studies with over 12,000 currently smoking adults evaluated the use of quit rates with e-cigarette use compared to the quit rates of e-cigarettes without nicotine or traditional smoking cessation pharmacotherapy options including NRT, varenicline, and behavioral support. Overall there is moderate evidence supporting e-cigarettes as effective in achieving smoking cessation for 6 months or longer. There is some data to indicate e-cigarettes could be more effective than traditional smoking cessation treatments.[89] Adverse effects associated with e-cigarettes were limited and included coughing, throat and mouth irritation, and headache; all of which resolved with continuous exposure to the e-cigarettes. However, it was emphasized that more studies are needed since the overall evidence is low and concern over long-term health effects of e-cigarettes continues.[89] Thus, although ENDS may offer a possible benefit during the smoking cessation process, their use is controversial as the potential harms associated with their use are still being evaluated and studied.[41,71] E-cigarette use for smoking cessation has also been evaluated for use in pregnant individuals.[10] Although it has been well established that the exposure to toxins is much lower when using an e-cigarette compared to cigarette smoke, there are no long-term safety studies in humans to determine if e-cigarettes are safer than traditional cigarettes.[41,90]

In the fall of 2019, a severe lung illness related to use of e-cigarettes and vaping, referred to as “E-cigarette or Vaping use-Associated Lung Injury” (EVALI) was reported. By February 2020, over 2,800 patients were hospitalized, and 68 patients died. Most cases were linked to THC-containing products (82%), but some cases were linked to nicotine-only products. The EVALI outbreak was linked to an additive, vitamin E acetate, in predominately THC-containing products. A public awareness campaign was launched to educate the public on the risk associated with vaping THC or using THC-containing e-cigarettes. Additionally, vitamin E acetate was removed from products and law enforcement worked to remove illicit products from the market. Although these actions have decreased the number of EVALI cases reported, the CDC has stressed that there is insufficient evidence to rule out other chemicals as the cause of EVALI and further research is needed.[91]

The e-cigarettes have proven to be very appealing children, adolescents, and young adults due to the variety of devices, high concentration of nicotine, flavor-based products, and wide promotion of these products on social media.[41] Based on the data from the 2020 National Youth Tobacco Survey (NYTS), e-cigarettes use among middle school and high school students steadily increased from 2011 to an epidemic level peak in 2019, where 10.5% (1.24 million) of middle students and 27.5% (4.11 million) of high school students reported e-cigarette use.[92] Data from 2020 demonstrated a decrease in use among both age groups, where 4.7% of middle students (555,000) and 19.6% of high school students (3.02 million) reported current use of electronic cigarettes.[92] To improve regulation of these products, the Deeming Rule expanded the FDA’s regulatory authority to include manufacture, import, packaging, labeling, advertising, promotion, sale, and distribution of all tobacco products, including ENDS. This prohibited the sale of ENDS products to youth under 18 years of age, banning their sale in most vending machines (only allowed in adult-only facilities), or providing free samples. Manufacturers now have to receive marketing authorization from the FDA, and health warnings on ENDS and other tobacco products are now

required.[93] Furthermore, vape shops that mix e-liquid must comply with the same legal requirements as tobacco manufacturers. In December 2019, the Federal Food, Drug, and Cosmetic Act was amended via the Tobacco 21 legislation to raise the federal minimum age of sale of tobacco products, including e-cigarettes, from the age of 18 to 21.[93] All 50 states and territories have now also restricted the sale of e-cigarettes to individuals 21 years of age and older.[94] The FDA additionally issued an enforcement policy focusing on the flavor-based e-cigarette products that appeal to adolescents.[93] Despite changes in regulations, these products are still very popular in the United States. The FDA continues to promote education campaigns, such as "The Real Cost" Youth E-Cigarette Prevention Campaign, which is aimed at youth who have experience with using ENDS or are considering trying these devices. Regardless, work continues in an effort to reduce the toxicity of the tobacco products, find ways to make products less appealing and less addictive, and improve the child-resistant packaging.[95]

The level of harm and/or risk associated with secondary passive exposure to ENDS aerosol is an ongoing debate, as passive exposure to the vapor emitted from the ENDS user could be hazardous based on a systematic review of 16 studies.[96] Data show e-cigarette vapor could expose bystanders to chemicals, including nicotine, glycine, formaldehyde, acetaldehyde, and propylene glycol, leading to an impact on indoor air quality. This risk, however, was noted to be lower than that associated with passive exposure from conventional cigarettes.[96] To limit second-hand exposure, many states have extended indoor smoking bans to include ENDS, although the laws for each state vary considerably.[94] The level of carcinogen and toxicant delivered to the user of the ENDS has been raised as a safety concern and due to the large variations in delivery devices and fluctuations in the amount of product a user will receive, it is difficult to study. While additional concerns have been raised regarding ENDS and toxic substances, the toxic levels of ENDS are estimated to be 1/4th to 1/95th the levels of the traditional cigarette.[97] Continued research is needed to evaluate the efficacy of e-cigarette use in regards to its role in helping with smoking cessation, youth exposure, and overall safety of this delivery system. Based on the current available evidence, USPSTF continues to recommend behavioral counseling and pharmacotherapy in nonpregnant adults and utilization of only behavioral counseling in pregnant individuals.[10]

Non-Nicotine Options

Bupropion (Zyban)

Pharmacologically, bupropion inhibits neuronal reuptake of norepinephrine and dopamine and potentiates their effects. Although its precise mechanism in smoking cessation is not well understood, bupropion's dopaminergic effects help reduce nicotine craving as dopamine neurotransmission is key to the brain's reward system.[71]

Bupropion SR is marked under the brand name Zyban and has been shown to be an effective treatment option for smoking cessation, although the brand product Wellbutrin contains the same pharmacological product.[76] A recent meta-analysis involving 155 trials showed that bupropion significantly increased the incidence of long-term cessation when used as a sole agent in 45 separate trials.[98]Other trials using bupropion as an add-on agent with NRT did not show bupropion had an additional benefit in improving cessation rates.[98] For smoking cessation, the manufacturer recommends a dosage of 150 mg once daily for 3 days and then twice daily (dosing should be at least 8 hours apart) for 7 to 12 weeks or longer, with or without NRT. Patients are instructed to initiate bupropion one week prior to the scheduled quit date and are encouraged to use counseling and support services along with the medication.[41] For maintenance therapy, consider bupropion SR 150 mg twice daily for up to 6 months.[71]

Contraindications to bupropion use include current or past seizure disorders, a history of monoamine oxidase inhibitor use over the last 14 days, and a history of anorexia nervosa or bulimia. Along with multiple other precautions listed in the product labeling, current alcohol use and use of medications that lower seizure threshold (eg, antidepressants and antipsychotics) are possible concerns when using this medication.[76] In 2009, the FDA required bupropion manufacturers to add new boxed warnings and to develop a medication guide highlighting the risk of serious neuropsychiatric symptoms in patients using this product. Possible symptoms include depressed mood, agitation, anxiety, hostility, changes in behavior, suicidal thoughts and behavior, and attempted suicide. However, in 2016 following a FDA-requested clinical trial review, the FDA announced the removal of the Black Box Warning and the Risk Evaluation and Mitigation Strategies (REMS) requirement for bupropion although continued to caution that the risk of mental health adverse effects are still possible, particularly in patients with a past history of mental health disorders or currently being treated for anxiety, depression, or schizophrenia.[41,99] The risk of adverse effects is higher with bupropion compared to placebo, including a higher rate of psychiatric adverse effects compared to placebo, leading to a higher number of discontinuation of treatment compared to placebo.[98]

Varenicline (Chantix)

Pharmacologically, varenicline is a partial agonist that binds selectively to α_4-β_2-nicotinic acetylcholine receptors (nAChRs) with a greater affinity than nicotine. When bound to the receptor, the medication blocks nicotine binding and also evokes a response, but to a lesser degree than nicotine.[73] Clinically, varenicline acts at sites in the nicotine-affected brain in two ways: by providing nicotine effects to ease withdrawal symptoms and by blocking the effects of nicotine from cigarettes if smoking is resumed. Additionally, varenicline has been found to have full agonist, although less potent, activity at α_7 and α_4-β_2 nAChRs and a full agonist at serotonin 3 receptor (5-HT_3).[100] A systematic review of 39 trials showed a two- to three-fold increased likelihood of long-term smoking cessation with varenicline compared with no NRT treatment (placebo).[101] Data from the trials included in this review also suggested that varenicline could have a role in relapse prevention and that it demonstrated better results compared to bupropion and NRT. These results were also seen in the largest randomized controlled trial for smoking cessation to date, the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial, which showed that varenicline is more efficacious than all other single NRTs, except for similar efficacy to the nicotine patch.[102]

The recommended dosage for varenicline is 0.5 mg daily for 3 days, increased to 0.5 mg twice daily for 3 days, and then increased to 1 mg twice daily for a standard 12-week treatment. It is suggested the quit date should be set for 1 week after initiating varenicline, but studies have shown allowing a flexible quit date is efficacious and safe. If abstinence has not been achieved after the 12-week treatment, then a second 12-week treatment may be prescribed.[103] Preloading varenicline for four weeks prior to the designated stop date has also demonstrated some higher response rates and can be considered as a treatment option.[104,105] Additionally, continuing varenicline as maintenance therapy for 6 months has been shown to decrease the risk of relapse.[41]

Common adverse effects associated with varenicline are nausea, vomiting, and insomnia. Over the years there have been concerns of neuropsychiatric adverse effects including suicidal thoughts, depression, and psychosis, leading to the black box warning. The previously mentioned EAGLES trial[102] also included a composite measure of neuropsychiatric symptoms as a primary safety endpoint and indicated there was no evidence of a significant increase in neuropsychiatric adverse effects which could be attributed to varenicline or bupropion. Specifically, in the individuals with psychiatric histories, moderate-to-severe neuropsychiatric symptoms were reported for varenicline (6.5%), bupropion (6.7%), nicotine patch (5.2%), and placebo (4.9%). In comparison, for patients without psychiatric histories, moderate-to-severe neuropsychiatric symptoms were reported as 1.3% to 2.5% of those enrolled in the trial. Overall, the risk differences reported for varenicline and bupropion versus placebo or the nicotine patch were nonsignificant. Following review of the trial results, the FDA announced the removal of the black box warning for varenicline and bupropion. In addition, a statement was included confirming bupropion, varenicline, and nicotine replacement patches are all more efficacious in smoking cessation compared to placebo regardless of mental illness history.[102] The most recent FDA Drug Safety communication indicates that although the risks of direct adverse effects from varenicline are lower than previously thought, the risk is still possible, especially in patients diagnosed with a mental illnesses, including schizophrenia, depression, or anxiety.[99] Cardiovascular safety concerns have also been raised regarding varenicline over the years and, to date, the results of various studies are still conflicting. In 2012, the FDA released a safety review update on the risk of cardiovascular adverse events indicating there is a higher risk of cardiovascular risks associated with varenicline.[106] However, results from the EAGLES extension trial, which was specifically designed to evaluate cardiovascular safety data, concluded there was no evidence of any cardiovascular adverse effects associated with these medications.[107]

Combination Therapy

Strong evidence exists for NRT combination therapy utilizing a short-acting form of NRT in combination with a nicotine patch based on a meta-analysis (RR 1.34; 95% CI: 1.18-1.48).[82] Additionally, a small systematic review and meta-analysis of 3 randomized controlled trials with 904 patients found that combining varenicline with NRT is more effective than varenicline alone. Individuals treated with both the nicotine patch and varenicline had similar adverse events to monotherapy except for skin reactions from the nicotine patch. Although the results for this study were positive for the combination, there were limited numbers of studies included in this analysis, so larger controlled clinical trials are needed.[108] Utilizing bupropion plus NRT has been shown to be more effective than bupropion monotherapy.[109] A meta-analysis evaluating the effectiveness of combining varenicline and bupropion in heavy smokers has demonstrated efficacy at 6 months but sustained cessation was not observed at 12 months. Increased reports of adverse effects including insomnia and anxiety were reported with the combination compared to varenicline monotherapy.[110]

Second-Line Medications

Second-line medications are therapeutic options for treating tobacco use, but have a more limited role than first-line medications because (a) the FDA has not approved them for smoking cessation and (b) there are more concerns about potential adverse medication effects than with first-line medications.[41] Although these second line medications have shown some efficacy for smoking cessation, they should only be considered for use on a case-by-case basis after first-line treatments have been used or considered.

Clonidine

Results from a meta-analysis of six trials showed that clonidine increased smoking cessation rates by 9%.[111] The main significant adverse effect reported with its use is hypotension, particularly postural hypotension; thus, blood pressure should be monitored.[111] Additional adverse effects include dry mouth, drowsiness, dizziness, and sedation. Overall, clonidine can be considered a second-line, off label, agent for smoking cessation.

Nortriptyline

Nortriptyline is also considered to be efficacious as a second-line agent for smoking cessation. When used for this indication, therapy is initiated 10 to 28 days before the quit date to allow for steady state to be reached at the target dose. Trials have initiated treatment at a dose of 25 mg/day, increasing gradually to a target dose of 75 to 100 mg/day.[111] Treatment duration used in smoking cessation trials have been approximately 12 weeks. A meta-analysis of 6 trials with 975 patients showed that nortriptyline as a sole agent is efficacious for smoking cessation when compared to placebo but is less efficacious when compared to varenicline.[98,112] Adding nortriptyline as an adjuvant to NRT did not prove to be an additional benefit in 4 trials which included over 1600 patients.[112] Most commonly reported adverse effects included sedation, dry mouth, blurred vision, urinary retention, light-headedness, and tremor.[113]

EVALUATION OF THERAPEUTIC OUTCOMES

Assisting a patient for 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. There are seven pharmacological treatment options and agent selection will be determined by a variety of factors. Patient counseling on selected pharmacotherapy options and common adverse effects is vital to ensure proper use and maximum efficacy. Frequent reassessment should occur to monitor overall treatment efficacy and to evaluate breakthrough cravings, withdrawal symptoms, and relapses. Dose adjustments should be made accordingly and individuals should be monitored closely and asked to immediately report any adverse effects to ensure proper adherence and prevent relapse.

INTRODUCTION—CAFFEINE

Caffeine is the most widely used psychoactive substance in the world, with approximately 90% of adults in the United States regularly consuming behaviorally active doses,[114] which result in psychoactive or stimulating responses including an increased sense of well-being, concentration, energy, alertness, and sociability. Caffeine is generally recognized as safe by the FDA for use in cola-type beverages as long as levels do not exceed 0.02% (200 parts per million),which is 30 to 40 mg of caffeine in a 12-oz (355 mL) serving.[115] A systematic review of data regarding potential adverse effects associated with caffeine found up to 400 mg caffeine per day in healthy adults was not associated with cardiovascular, behavioral, reproductive, or developmental adverse effects.[116] The FDA has cited that 400 mg per day, which is approximately four to five cups of coffee, is generally considered safe for adults.[114] However, in the United States, children consume an average 37.3 mg of caffeine per day.[117] Doses of 100 to 400 mg of caffeine have been reported to result in stimulant-related effects, such as jitteriness in children and adolescents. The American Academy of Pediatrics discourages children and adolescents consuming stimulants or caffeine due to the possible negative impact on sleep and blood pressure.[118] There is limited knowledge of caffeine effects on cognitive development and further study is necessary to determine the proper levels of safe consumption for this patient population.[115,117] Although, in general, caffeine consumption in reasonable amounts has been considered fairly safe, there are situations in which problems arise. Caffeinism has been associated with a daily caffeine intake of 1,000 to 1,500 mg. This term was coined to describe the clinical

syndrome produced by acute or chronic unhealthy use of caffeine, which is usually characterized by central nervous system and peripheral manifestations, most notably, anxiety, psychomotor alterations, sleep disturbances, mood changes, and psychophysiological complaints.[119]

Pharmacologically, the risk of developing meaningful clinical manifestations from caffeine becomes high when intake exceeds 500 mg/day.[120] It could be assumed this level of caffeine might not be reached when traditionally drinking coffee. This helps explain why, up until recently, deaths from acute ingestions of caffeine were virtually nonexistent. However, pure caffeine powder and liquid formulations are available via the internet and just small doses could be toxic. One teaspoonful of highly concentrated powder is estimated to be equivalent to 28 cups of coffee (approximately 3,200 mg caffeine) and just one half cup of highly concentrated liquid is equivalent to approximately 20 cups of coffee (approximately 2,000 mg caffeine).[121] A 200 mg caffeine dose of pure caffeine powder is considered 1/16 teaspoon, where the caffeine liquid is 2.5 teaspoonfulls.[122] Due to the concerns of safety and reported deaths associated with concentrated caffeine products, the FDA has provided guidance documents to companies manufacturing, marketing, and distributing these products. Subsequent warning letters have been sent to all identified and who continue to sell illegal caffeine products.[122]

Caffeine in general has been proposed as a model of substance use despite the fact that its sale is largely unrestricted and that heavy consumption of caffeine-containing beverages is not considered to be problematic. The following information represents a broad overview of physical dependence, withdrawal, and tolerance. Interested readers are encourage to consult Meredith et al. and Sweeny et al. for further information.[123,124]

EPIDEMIOLOGY

Recently, data from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 was evaluated regarding caffeine consumption through caffeinated beverages, foods, and energy drinks in adults 19 years of age and older. Approximately 90% of individuals in the United States consume caffeine daily, predominantly through caffeinated beverages (98%). The most common being coffee (64%), with tea and soft drinks being less popular (16% and 18%, respectively). Caffeine intake averaged 169 mg/day and mostly was consumed in the morning hours. Older adults, ages 75 to 79, consumed a greater amount of caffeine (153 mg/day) compared to younger adults ages 20 to 24 who averaged 107 mg/day. Caffeine intake varied with ethnicity, where non-Hispanic black individuals averaged the lowest caffeine consumption (80 mg/day) and non-Hispanic white individuals had the highest consumption averaging 194 mg/day.[114] Intake among children, adolescents, and young adults is prevalent from foods and beverages based on the 2011-2012 NHANES data. The average caffeine intake increased with age where 4- to 8-year-olds averaged 15 mg/day, 9- to 13-year-olds averaged 26 mg/day, and 14- to 19-year-olds averaged 61 mg/day.[125]

10 Energy drinks containing caffeine also include a variety of other products, such as taurine, vitamins, minerals, electrolytes, and sugar. These products are sold under brand names such as Red Bull, Monster Energy, Rockstar, and Bang Energy and are promoted to increase energy, enhance alertness, and physical performance. They continue to gain popularity among adolescents and emerging adults. Data from the 2003-2016 NHANES demonstrated an increase in consumption of energy drinks among a wide range of individuals, including adolescents (12-19 years old), young adults (20-39 years old), and middle-aged adults (40-59 years old). However, further analysis of the data did indicate that there could be a small decline in use patterns within the younger age groups, including adolescents and young adults, and an upward trend for middle-aged adults.[126] It is reported, aside from multivitamins, that these products are the most popular dietary supplement for young adults.[127] There are two types of products on the market based on volume. One product is similar to a soft drink, for example, Red Bull (8.4 oz [250 mL]) which contains 80 mg of caffeine, although other products can contain higher amounts of caffeine depending on the size of the container. The second product is a smaller volume product referred to as an “energy shot,” which provides a range of 200 to 300 mg of caffeine in a 2- to 3-ounce product. Additionally, these products also commonly contain other products such as B vitamins, creatine, and CoQ10.[128]

Over the years, there have been many questions regarding the safety of these products and emergency room visits attributed to these energy drinks doubled from 2007 to 2011, with 58% of visits involving energy drinks alone and 42% including energy drinks with other substances including alcohol, marijuana, and/or stimulants.[129] Each year, the most common age group seen in the emergency room due to energy drink consumption included patients ages 18-25. However, energy drink related emergency visits in patients older than 40 year of age, has increased over 279%.[129] A recent study evaluated adverse event reports associated with energy drinks alone and in combination with other substances from 2008 to 2015. During this time period, a total of 13,179 reports were received on single product energy drinks and 1,084 reports on energy drinks combined with other substances.[130] A variety of health complications have been associated with their use in the adolescent population, including insomnia, arrhythmias, high blood

pressure, agitation, anxiety and migraines.[131] Energy drink consumption has also been associated with a higher rate of unhealthy alcohol and substance use.[132]

PATHOPHYSIOLOGY

Caffeine is rapidly and completely absorbed from the GI tract, reaching a peak blood level within 30 to 60 minutes after oral ingestion. It easily crosses the blood–brain barrier, and levels achieved in the brain are proportional to the dose administered.[133] Caffeine is metabolized by cytochrome P450 1A2 (CYP1A2) and has a half-life of approximately 4 to 5 hours in healthy nonsmoking adults. Fast metabolizers of CYP1A2 include heavy caffeine users, children less than 12 years old, and individuals who smoke cigarettes. Individuals in later stages of pregnancy are slower metabolizers of caffeine, as are those with liver dysfunction.[119,133], Overdoses of caffeine are now more common due to the wide availability of energy drinks. Caffeine increases the heart rate and force of cardiac contractions, and also has a strong diuretic effect. Due to the stimulating properties of caffeine, nervousness, agitation, and insomnia may occur with more serious reactions including cardiac arrhythmias, hypotension, and seizures.[116,119] The key factor promoting caffeine use and dosage increases can be the substance's reinforcing effect on pleasure and reward centers of the brain. Caffeine's pharmacologic actions appear comparable (although less potent) to those of other stimulants, such as amphetamines and cocaine.[134]

CLINICAL PRESENTATION

The *DSM-5* has four caffeine-related diagnoses, including caffeine intoxication, caffeine withdrawal, other caffeine-induced disorders, which include both caffeine-induced sleep and anxiety disorders, and unspecified caffeine-related disorder. Each of these diagnoses could include symptoms which might be attributed to caffeine use, but do not fit in any other category. The *DSM-5* does not currently list a diagnosis of caffeine use disorder, but it has been identified as an area that needs further research to determine if it should become an official diagnosis.[5]

The diagnostic criteria for caffeine intoxication includes recent consumption of caffeine normally exceeding 250 mg and five or more symptoms during, or shortly after, consumption of caffeine. The symptoms of caffeine intoxication will usually decrease over 24 hours as the caffeine is eliminated from the body; however, consumption of very high doses of caffeine could be dangerous and require immediate medical attention.[5]

Caffeine withdrawal is a DSM-5 diagnosis, which occurs after the abrupt cessation of chronic caffeine use and can occur even with low doses of caffeine. The diagnosis of caffeine withdrawal requires three of the five listed symptoms, including headache (most common), marked fatigue or drowsiness, altered mood (depressed, irritable, and dysphoric), difficulty concentrating, or flu-like symptoms, including nausea, vomiting, and muscle pain/stiffness. The extent and severity of withdrawal can vary individually but normally will be more severe with higher chronic doses of caffeine (Table 86-7).[5]

TABLE 86-7

***DSM-5* Diagnostic Criteria for Caffeine Withdrawal**

Criteria
Prolonged daily use of caffeine Abrupt cessation or decrease use in caffeine leading to at least three of the following symptoms after 24 hours of cessation • Concentration problems • Mood changes: dysphoric mood, depressed mood, irritability • Dramatic fatigue or drowsiness • Headache • Flu-like symptoms • Nausea • Vomiting • Muscle pain/stiffness Symptoms negatively impact areas of functioning such as social or occupational aspects of life. The symptoms experienced cannot be explained by other concurrent medical conditions.

Data from References 5.

CLINICAL PRESENTATION: Caffeine Intoxication

General

- The individual may not be in acute distress.

Symptoms

- The individual may complain of nausea, vomiting, diarrhea, and psychomotor agitation, and can appear restless, nervous, and excited.

Signs

- The individual can present with facial flushing, diuresis, and muscle twitching.
- Tachycardia or cardiac arrhythmias can also occur.

Laboratory Tests

- Caffeine serum concentrations are rarely used clinically.

Effect on Sleep

Caffeine is commonly used to improve alertness and improve performance during times of sleep deprivation at doses of 75 to 150 mg. Sleep disruption can occur with caffeine consumptions ranging from 200 to 600 mg.[119] Caffeine's disruptive effects following a fixed dose of 400 mg provided 0, 3, and 6 hours prior to the usual bedtime has been associated with sleep disruption at all administration time periods.[135] However, any sleep disruption is likely to resolve 8 hours after caffeine consumption.[119]

Caffeine During Pregnancy

Over the years, there has been much discussion regarding the safety of caffeine intake during pregnancy and possible risks to the developing fetus. A systematic review of 380 studies published in 2017 evaluated data from 2001 through June 2015 and determined daily consumption of up to 300 mg of caffeine per day in a healthy pregnant individuals was not associated with any adverse health outcomes or developmental effects.[116] A narrative review which evaluated 42 original observational studies and 14 meta-analysis evaluating maternal consumption of caffeine during pregnancy reported increased negative outcomes during pregnancy including miscarriage, stillbirth, low birthweight/small gestational age. Additionally, increased risk of childhood leukemia as well as childhood overweight/obesity were identified in these studies.[136] Safe levels of caffeine consumption were recommended in this review; however, the author recommended based on this evidence, pregnant individuals should consider avoiding all caffeine consumption.[136] Currently, American College of Gynecology suggests limiting caffeine consumption to less than 200 mg per day and reports this level of caffeine intake has not been identified as a major contributing factor to miscarriage and preterm birth. Further information on the effect of caffeine intake on intrauterine growth was undetermined.[137] The March of Dimes also advises pregnant individuals to limit their caffeine intake to less than 200 mg/day.[138] Data will continued to be collected and evaluated to determine safe levels of caffeine consumption in pregnancy.

CLINICAL PRESENTATION: Caffeine Withdrawal

General

- The individual may not be in acute distress.

Symptoms

- Complaints of headache, nausea, vomiting, drowsiness, poor concentration, and depressed mood may be seen which are adversely affecting overall social/occupational functioning and/or leading to distress.

Laboratory Tests

- Caffeine serum concentrations are rarely used clinically.

TREATMENT

Desired Outcomes

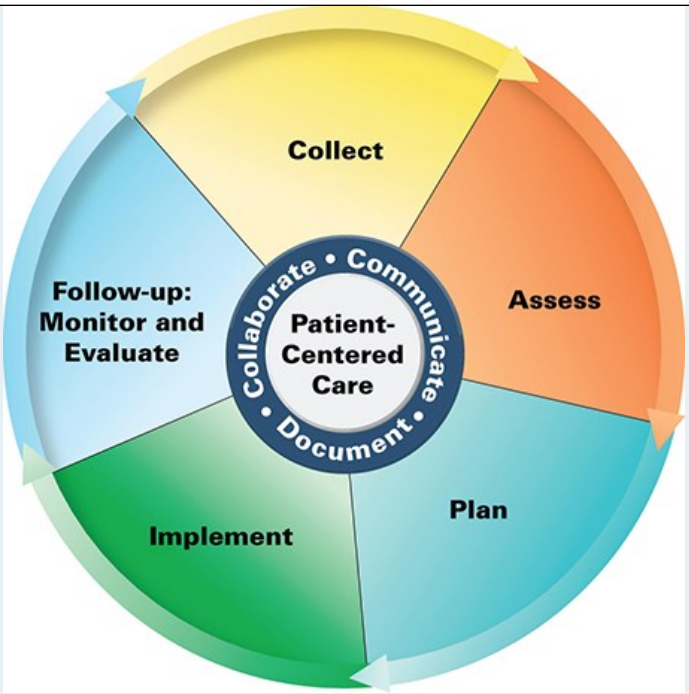
Many people drink coffee, tea, and other caffeinated beverages without problems. When adverse health effects occur (eg, insomnia, headaches, anxiety, and palpitations), it may be necessary to cut down on the amount of caffeine ingested or to eliminate it altogether to achieve elimination of these symptoms.

Nonpharmacologic Therapy

The primary treatment of caffeinism is reducing or discontinuing the use of the substance. For some it may be necessary to wean off the substance gradually because a rapid reduction in consumption can lead to adverse reactions, such as irritability, headaches, fatigue, flu-like symptoms, difficulty concentrating, and reduction in alertness.[123,124] The gradual reduction in caffeine intake over multiple days can reduce the risk of common withdrawal reactions.[139] For cases of extreme caffeine toxicity and withdrawal, necessary supportive measures should be instituted to prevent short- and or long-term sequelae.[118]

PATIENT CARE PROCESS

Patient Care Process for Alcohol Use Disorder



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (eg, tobacco/alcohol use) and dietary habits
- Utilize CAGE questionnaire or Alcohol Use Disorders Identification Test (AUDIT) to assess for alcohol use disorder
- Current medications including prescription, over-the-counter (OTC), herbal products, dietary supplements
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including serum creatinine (SCr), liver function tests (LFTs)

Assess

- Hemodynamic instability (eg, systolic BP <90 mm Hg, HR >110 bpm, O_2-sat <90% (0.90), RR >20) to assess for signs of acute alcohol withdrawal
- Utilize motivational interviewing to assess the individual's readiness to quit
- Ability/willingness to pay for pharmacotherapy options for Alcohol Use Disorder (AUD), and abstain from alcohol with disulfiram and avoid opiates with naltrexone
- Ability/willingness to obtain laboratory monitoring tests (eg, SCr [eg, naltrexone, acamprosate], LFTs [ie, disulfiram])
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Pharmacotherapy regimen including specific AUD agent, dose, route, frequency, and duration (see Table 86-5)

- Monitoring parameters including efficacy (eg, decrease in craving, adherence) and safety (eg, adverse effects specific to selected agent, SCr, LFTs); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, medication-specific information, importance of adherence)
- Self-monitoring for adverse effects from pharmacotherapy treatment
- Referrals to other providers when appropriate (eg, behavioral health; highly recommended but not required for pharmacotherapy treatment)

Implement*

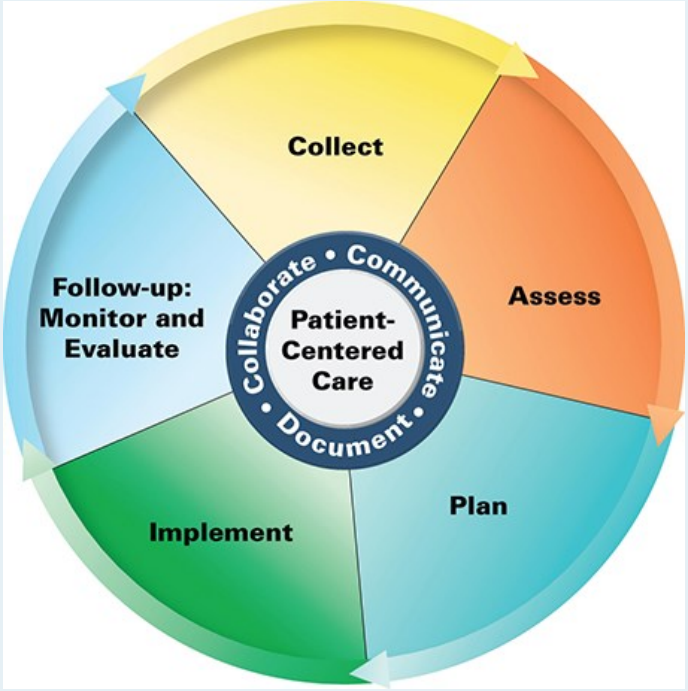
- Provide patient education regarding all elements of treatment plan
- Utilize motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, adherence assessment, SCr [eg, naltrexone, acamprosate], LFTs [eg, disulfiram])

Follow-up: Monitor and Evaluate

- Presence of adverse effects (eg, medication specific)
- Individual adherence to treatment plan using multiple sources of information
- Reevaluate duration of therapy initially with frequent follow-up and then lengthen follow-up to every 1 to 2 months

**Collaborate with patient, caregivers, and other healthcare professionals.*

Patient Care Process for Smoking Cessation



Collect

- Patient characteristics (eg, age, sex, pregnant)

- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use) and dietary habits
- Smoking history (eg, current triggers, last cessation attempt, pharmacotherapy trials used in cessation, individual's level of interest for cessation at this time)
- Current medications including prescription, OTC use, herbal products, dietary supplements
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including serum creatinine (SCr), liver function tests (LFTs)

Assess

- Hemodynamic stability (eg, systolic BP >90 mm Hg, HR <110 bpm, O_2-sat >90% (0.90), RR >20)
- Utilize motivational interviewing to assess readiness to quit
- Ability/willingness to pay for pharmacotherapy options and/or behavioral treatment for smoking cessation
- Ability/willingness to obtain laboratory monitoring tests (eg, LFTs [ie, bupropion], SCr [ie, varenicline])
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Medication therapy regimen including specific nicotine replacement therapy (NRT), non-NRT, dose, route, frequency, and duration; (see Table 86-5 and Table 86-7)
- Monitoring parameters including efficacy (eg, decreases in craving, smoking) and safety (eg, adverse medication effects specific to selected agent); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, lifestyle modification, medication-specific information, medication administration technique; see Table 86-7)
- Self-monitoring for adverse medication effects from pharmacotherapy treatment
- Referrals to other providers when appropriate (eg, behavioral health; highly recommended but not required for pharmacotherapy treatment)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Set quit date if appropriate for this patient at this time (if appropriate)
- Schedule follow-up (eg, adherence assessment)

Follow-up: Monitor and Evaluate*

- Quit date set
- Presence of adverse effects (eg, medication specific)

- Individual adherence to treatment plan using multiple sources of information
- Reevaluate duration of therapy initially with frequent follow-up and then lengthen follow up to every 1 to 2 months

Collaborate with patient, caregivers, and other healthcare professionals.

EVALUATION OF THERAPEUTIC OUTCOMES

Identifying the treatment goals associated with the individual's current caffeine consumption and addressing these goals will be the primary focus in evaluating therapeutic outcomes. When an individual is working to reduce or discontinue caffeine, frequent reassessment should occur to monitor the individual for symptoms of caffeine withdrawal and educate on possible effects of withdrawal. If effects of withdrawal are experienced, appropriate adjustments should be made to improve reaching treatment goals.

CONCLUSION

Alcohol, nicotine, and caffeine are considered by most to be socially acceptable substances, yet they impose an enormous social and economic cost on our society. It is vital that all healthcare professionals continue to educate individuals on the healthcare risks of each of these substances to decrease the negative impact that can occur with their chronic use.

ABBREVIATIONS

ADH	alcohol dehydrogenase
ALDH	aldehyde dehydrogenase
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test—Consumption questions
BAC	blood alcohol concentration
BP	blood pressure
CHRNA5	cholinergic receptor alpha5 subunit
CIWA-Ar	Clinical Institute Withdrawal Assessment for Alcohol, revised
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CUD	caffeine use disorder
CYP	cytochrome P450

DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
DT	delirium tremens
EAGLES	Evaluating Adverse Events in a Global Smoking Cessation Study
ENDS	electronic nicotine delivery systems
EVALI	e-cigarette or vaping use-associated lung injury
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GI	gastrointestinal
5-HT_3	serotonin-3 receptor
HIV	human immunodeficiency virus
HR	heart rate
IM	intramuscular
IV	intravenous
LFTs	liver function tests
LGBTQ+	lesbian, gay, bisexual, transgender, queer (or sometimes questioning), and others
MI	motivational interviewing
nAChRs	α4-β2-nicotinic acetylcholine receptors
NHANES	National Health and Nutrition Examination Survey
NIH	National Institute of Health
NIDA	National Institute on Drug Abuse
NMR	nicotine metabolic ratio
NQDW	National Quitline Data Warehouse
NRT	nicotine replacement therapy
NSDUH	National Survey on Drug Use and Health
NYTS	National Youth Tobacco Survey
O2	oxygen

OPRM1	μ-opioid receptor gene
OTC	over the counter
PAN	psychotropic analgesic nitrous oxide
PATH	Population Assessment of Tobacco and Health
PAWSS	Prediction of Alcohol Withdrawal Severity Scale
REMS	risk evaluation and mitigation strategies
RR	respiratory rate
SCr	serum creatinine
SIDS	sudden infant death syndrome
SR	sustained release
THC	tetrahydrocannabinol
TRHD	tobacco-related health disparities
TTFC	time to first cigarette
USAUDIT	United States Alcohol Use Disorders Identification Test
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

REFERENCES

1. World Health Organization Department of Mental Health and Substance Abuse. *Global Status Report on Alcohol and Health 2018.* Geneva: World Health Organization; 2018. License: CC BY-NC-SA 3.0IGO. http://www.who.int/substance_abuse/publications/global_alcohol_report/en/.

2. NIAAA. Alcohol facts and statistics. 2021. https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics. Accessed July 9, 2021.

3. Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53).* Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2018. Accessed September 28, 2018. https://www.samhsa.gov/data. Accessed September 28, 2018

4. NIDA. Drug Abuse and Addiction: One ofAmerica's Most Challenging Public Health Problems. National Institute on DrugAbuse website. https://archives.drugabuse.gov/publications/drug-abuse-addiction-one-americas-most-challenging-public-health-problems. June 1, 2005. Accessed July 22, 2021.

5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed, DSM-5.* Arlington, VA: American Psychiatric Association; 2013.

6. Enoch M. Genetic influences on the development of alcoholism. *Curr Psychiatry Resp.* 2013;15(11):412. doi: 10.1007/s11920-013-0412-1.

7. Edenberg HJ, Foroud T Genetics and alcoholism. *Nat Rev Gastroenterol Hepatol* 2013;10(8):487–94. 10.1038/nrgastro.2013.86 [PubMed: 23712313] .

8. Verhulst B, Neale M, Kendler K. The heritability of alcohol use disorders: A meta-analysis of twin and adoption studies. *Psychologic Med.* 2015;54:1061–1072.

9. Agrawal A, Verweij KJ, Gillespie NA, et al. The genetics of addiction—a translational perspective. *Transl Psychiatry.* 2012;2:e140. doi: 10.1038/tp.2012.54.

10. Krist AH, Davidson KW, Mangione CM, et al. Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons: US Preventive Services Task Force Recommendation Statement. *JAMA* 2021;325(3):265–279. 10.1001/jama.2020.25019 [PubMed: 33464343] .

11. Chan L, Anderson G. Pharmacokinetic and pharmacodynamics drug interactions with ethanol (alcohol). *Clin Pharmacokinet.* 2014;53:1115–1136. [PubMed: 25267448]

12. Perry PJ, Doroudgar S, Van Dyke P. Ethanol forensic toxicology. *J Am Acad Psychiatry Law*. 2017;45:429–38. [PubMed: 29282233]

13. Cedarbaum AI. Alcohol metabolism. *Clin Liver Dis.* 2012;16:667–685. [PubMed: 23101976]

14. Nassir F, Ibdah J. Role of mitochondria in alcoholic liver disease. *World J Gastroenterol.* 2014;20(9):2136–2142. [PubMed: 24605012]

15. Jones AW. Pharmacokinetics of ethanol—Issues of forensic importance. *Forensic*. *Sci Rev.* 2011;23:91–136.

16. Understanding the dangers of alcohol overdose. National Institute on Alcohol Abuse and Alcoholism. Updated May 2021. https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/understanding-dangers-of-alcohol-overdose. Accessed July 30, 2021.

17. Dhalla S, Kopec JA. The CAGE questionnaire for alcohol misuse: A review of reliability and validity studies. *Clin Invest Med.* 2007;30:33–41. [PubMed: 17716538]

18. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. *AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care*. 2nd ed. Geneva: World Health Organization; 2001.

19. Wolf C, Curry A, Nacht J, et al. Management of Alcohol Withdrawal in the Emergency Department: Current Perspectives. *Open Access Emerg Med* 2020;12:53–65. 10.2147/OAEM.S235288 [PubMed: 32256131] .

20. Holt SR, Tobin DG. Pharmacotherapy of alcohol use disorder. *Med Clin N Am.* 2018;102:653–666.

21. Sulivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict.* 1989;84:1353–1357. [PubMed: 2597811]

22. Carlson RW, Kumar NN, Wong-McKinstry E, et al. Alcohol withdrawal syndrome. *Crit Care Clin.* 2012;28:549–585. [PubMed: 22998991]

23. Lindsay DL, Freedman K, Jarvis M, et al. Executive Summary of the American Society of Addiction Medicine (ASAM) Clinical Practice Guideline on Alcohol Withdrawal Management. *J Addict Med* 2020;14(5):376–392. 10.1097/ADM.0000000000000732

[PubMed: 32909985] .

24. Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. *Cochrane Database Syst Rev.* 2011;(6):CD008537. doi: 10.1002/14651858.CD008537.pub2.

25. Mirijello A, D'Angelo C, Ferruli A, et al. Identification and management of alcohol withdrawal syndrome. *Drugs*. 2015;75:353–365. [PubMed: 25666543]

26. Schmidt KJ, Doshi MR, Holzhausen JM, et al. Treatment of severe alcohol withdrawal. *Ann Pharmacother.* 2016;50:389–401. [PubMed: 26861990]

27. Muncie HL, Yasinian Y, Oge' L. Outpatient management of alcohol withdrawal syndrome. *Am Fam Physician*. 2013;88(9):589–595. [PubMed: 24364635]

28. Marks V, Teale JD. Drug-induced hypoglycemia. *Endocrinol Metab Clin North Am.* 1999;28:555–577. [PubMed: 10500931]

29. Fairbanks J, Umbreit A, Kolla BP, et al. Evidence-Based Pharmacotherapies for Alcohol Use Disorder: Clinical Pearls. *Mayo Clin Proc* 2020;95(9):1964–1977. 10.1016/j.mayocp.2020.01.030
[PubMed: 32446635] .

30. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: A review. *JAMA.* 2018:320:815–824. [PubMed: 30167705]

31. Pani PP, Trogu E, Pacini M, Maremmani I. Anticonvulsants for alcohol dependence. *Cochrane Database Syst Rev.* 2014;(2):CD008544. doi: 10.1002/14651858.CD008544.pub2.

32. Blodgett JC, Del Re AC, Maisel NC, et al. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcohol Clin Exp Res.* 2014;38:1481–1488. [PubMed: 24796492]

33. Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *Am J Psychiatry*. 2018;175:86–90. [PubMed: 29301420]

34. Skinner MD, Lahmek P, Pham H, et al. Disulfiram efficacy in the treatment of alcohol dependence: A meta-analysis. *PLoS One*. 2014;9(2):e87366. [PubMed: 24520330]

35. Oslin D, Leong S, Lynch K, et al. Naltrexone vs. Placebo for the treatment of alcohol dependence. *JAMA Psychiatry*. 2015;72(5):430–437. [PubMed: 25760804]

36. Sudakin D. Naltrexone: not just for opioids anymore. *J Med Toxicol.* 2016;12:71–75. [PubMed: 26546222]

37. Rosner S, Hackl-Herwerth A, Leucht S, et al. Opioid antagonists for alcohol dependence. *Cochrane Reviews*. 2010;(12):CD001867. doi: 10.1002/14651858.

38. Murphy CE 4th, Wang RC, Montoy JC, Whittaker E, Raven M, et al. Effect of extended-release naltrexone on alcohol consumption: a systematic review and meta-analysis. *Addiction* 2021 10.1111/add.15572
[PubMed: 34033183] .

39. Rösner S, Hackl-Herrwerth A, Leucht S, et al. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev.* 2010;(9):CD004332.

40. US Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. https://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf. Accessed October 21, 2018. [PubMed:] [[XSLOpenURL/]]

41. U.S. Department of Health and Human Services. Smoking cessation: a report of the Surgeon General. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. https://www.cdc.gov/tobacco/data_statistics/sgr/2020-smoking-cessation/index.html#full-report. Updated January 23, 2020. Accessed May 10, 2021.

42. Cornelius ME, Wang TW, Jamal A, et al. Tobacco Product Use Among Adults - United States, 2019. *MMWR Morb Mortal Wkly Rep* 2020;69(46):1736–1742. 10.15585/mmwr.mm6946a4
[PubMed: 33211681]

43. CDC: Smoking &tobacco statistics: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm. Accessed May 10, 2021.

44. National Center for Health Statistics. Survey description, National Health Interview Survey, 2019. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2020.
ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2019/srvydesc-508.pdfpdf icon. Accessed May 10, 2021

45. Young-Wolff KC, Klebaner D, Campbell CI, et al. Association of the Affordable Care Act With Smoking and Tobacco Treatment Utilization Among Adults Newly Enrolled in Health Care. *Med Care* 2017;55(5):535–541. 10.1097/MLR.0000000000000712
[PubMed: 28288073] .

46. Murphy-Hoefer R, Davis KC, Beistle D, King BA, Duke J, Rodes R, et al. Impact of the Tips From Former Smokers Campaign on Population-Level Smoking Cessation, 2012–2015. *Prev Chronic Dis.* 2018;15:180051. http://dx.doi.org/10.5888/pcd15.180051.

47. Shrestha SS, Davis K, Mann N, et al. Cost Effectiveness of the Tips From Former Smokers® Campaign-U.S., 2012-2018. *Am J Prev Med* 2021;60(3):406–410. 10.1016/j.amepre.2020.10.009
[PubMed: 33455819] .

48. CDC Tips From Former Smokers. FREE QuitGuide Mobile App. Available at: https://www.cdc.gov/tobacco/campaign/tips/quit-smoking/mobile-quit-guide/index.html?s_cid=OSH_tips_D9405. Accessed November 2, 2018.

49. Hyland A, Kasza KA, Borek N, et al. Overview of tobacco use transitions for population health. *Tob Control* 2020;29(Suppl 3):s134–s138. 10.1136/tobaccocontrol-2019-055367
[PubMed: 32321846]

50. Stanton CA, Sharma E, Seaman EL, et al. Initiation of any tobacco and five tobacco products across 3 years among youth, young adults and adults in the USA: findings from the PATH Study Waves 1-3 (2013-2016). *Tob Control* 2020;29(Suppl 3):s178–s190. 10.1136/tobaccocontrol-2019-055573
[PubMed: 32321852] .

51. Kasza K, Ambrose B, Conway K, et al. Tobacco-Product use by Adults and Youths in the United States in 2013 and 2014. *NEJM.* 2017;376(4):342–353.

52. U.S. National Cancer Institute. A Socioecological Approach to Addressing Tobacco Related Health Disparities. National Cancer Institute Tobacco Control Monograph 22. NIH Publication No. 17-CA-8035A. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2017.

53. Xu X, Bishop EE, Kennedy SM, Simpson SA, Pechacek TF. Annual healthcare spending at-tributable to cigarette smoking: an update. *Am J Prev Med.* 2015;48(3):326–333. Epub 2014/12/17. pmid:25498551; PubMed Central PMCID: PMCPmc4603661. [PubMed: 25498551]

54. DiGiulio A, Jump Z, Yu A, et al. State Medicaid Coverage for Tobacco Cessation Treatments and Barriers to Accessing Treatments — United States, 2015-2017. *Morbidity and Mortality Weekly Report*. 2018;67(13):390–395. [PubMed: 29621205]

55. Saccone N, Baurley J, Bergen A, et al. The Value of Biosamples in Smoking Cessation Trials: A Review of Genetic, Metabolomic, and Epigenetic Findings. Nicotine & Tobacco. *Nicotine Tob Res.* 2018;20(4):403–413.
[PubMed: 30521502] .

56. Raghuveer G, White DA, Hayman LL, Woo JG, Villafane J, Celermajer D, Ward KD, de Ferranti SD, Zachariah J Cardiovascular Consequences of Childhood Secondhand Tobacco Smoke Exposure: Prevailing Evidence, Burden, and Racial and Socioeconomic Disparities: A Scientific Statement From the American Heart Association. *Circulation* 2016;134(16):e336–e359. 10.1161/CIR.0000000000000443
[PubMed: 27619923] .

57. Balfour DJ Neuroplasticity within the mesoaccumbens dopamine system and its role in tobacco dependence. *Curr Drug Targets CNS Neurol Disord* 2002;1(4):413–21. 10.2174/1568007023339076
[PubMed: 12769613] .

58. Benowitz N. Nicotine Addiction *NEJM.* 2010;362:2295–2303.

59. Benowitz NL. Clinical pharmacology of nicotine implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther.* 2008;83:531–541. [PubMed: 18305452]

60. Benowitz N. Pharmacology of nicotine: Addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol.* 2009;49:57–71.
[PubMed: 18834313]

61. Chen LS, Horton A, Bierut L. Pathways to precision medicine in smoking cessation treatments. *Neuroscience Letters*. 2018;669:83–92. [PubMed: 27208830]

62. Icick R, Forget B, Cloëz-Tayarani I, et al. Genetic susceptibility to nicotine addiction: Advances and shortcomings in our understanding of the CHRNA5/A3/B4 gene cluster contribution. *Neuropharmacology* 2020;177:108234–108234. 10.1016/j.neuropharm.2020.108234
[PubMed: 32738310] .

63. U.S. Department of Health and Human Services Healthy People 2030. https://health.gov/healthypeople/objectives-and-data/browse-objectives/tobacco-use/reduce-current-tobacco-use-adults-tu-01/data. Accessed May 20, 2021.

64. NIDA CTN Common Data Elements: Instrument: Fagerstrom Test for Nicotine Dependence (FTND). https://cde.drugabuse.gov/instrument/d7c0b0f5-b865-e4de-e040-bb89ad43202b. Accessed May 20, 2021.

65. Patients Not Ready To Make A Quit Attempt Now (The “5 R’s”). Content last reviewed December 2012. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/prevention/guidelines/tobacco/5rs.html. Accessed May 10, 2021.

66. Hartmann-Boyce J, Hong B, Livingstone-Banks J, et al. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev* 2019;6:CD009670–CD009670. 10.1002/14651858.CD009670.pub4
[PubMed: 31166007] .

67. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev.* 2015;(3):CD006936.

68. Centers for Disease Control and Prevention. Frequency Asked Questions about 1-800-QUIT-NOW and National Network of Tobacco Cessation Quitlines. (n.d.). Available at: https://www.cdc.gov/tobacco/quit_smoking/cessation/pdfs/1800quitnow_faq.pdf. Accessed October 2, 2018.

69. Centers for Disease Control and Prevention. Smoking and Tobacco Use. https://www.cdc.gov/tobacco/quit_smoking/cessation/faq-about-1-800-quit-now/. Accessed May 20, 2021.

70. Whittaker R, McRobbie H, Bullen C, et al. Mobile phone text messaging and app-based interventions for smoking cessation. *Cochrane Database Syst Rev* 2019;10:CD006611–CD006611. 10.1002/14651858.CD006611.pub5

[PubMed: 31638271] .

71. Prochaska JJ, Benowitz NL Current advances in research in treatment and recovery: Nicotine addiction. *Sci Adv* 2019;5(10):eaay9763–eaay9763. 10.1126/sciadv.aay9763
[PubMed: 31663029] .

72. Nicotrol Inhaler package insert. Pfizer. Last revised December 2008. Available at: https://www.pfizer.com/files/products/uspi_nicotrol_inhaler.pdf. Accessed October 11, 2018.

73. Varenicline Package insert. Pfizer. Last revised June 2018. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=557. Accessed October 11, 2018.

74. Nicotrol Nasal Spray package insert. *Pfizer*. Last revised January 2010. Available at: https://www.pfizer.com/files/products/uspi_nicotrol.pdf. Accessed October 11, 2018.

75. Nicorette Lozenge labeling information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022360Orig1s007lbl.pdf. Accessed October 11, 2018.

76. Bupropion package insert. Last revised May 2017. GlaxoSmithKline. Available at: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Zyban/pdf/ZYBAN-PI-MG.PDF. Accessed October 11, 2018.

77. Nicoderm CQ Nicotine patch extended release package insert. Last revised May 2016. GlaxoSmithKline. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=93b2d1b9-83c1-40b5-b6af-90c38c8d6cef. Accessed October 11, 2018.

78. Nicorette Gum labeling information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022360Orig1s007lbl.pdf. Accessed October 11, 2018.

79. Barua RS, Rigotti NA, Benowitz NL, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2018;72(25):3332–3365. 10.1016/j.jacc.2018.10.027
[PubMed: 30527452] .

80. Prochaska J, Benowitz N. The Past, Present, and Future of Nicotine Addiction Therapy. *Annu Rev Med.* 2016;67:467–468. [PubMed: 26332005]

81. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database of Systematic Reviews*. 2018;(5):CD000146. doi: 10.1002/14651858.CD000146.pub5.

82. Lindson N, Chepkin SC, Ye W, et al. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2019;4:CD013308–CD013308. 10.1002/14651858.CD013308
[PubMed: 30997928] .

83. Branstetter SA, Muscat JE, ercincavage M M Time to First Cigarette: A Potential Clinical Screening Tool for Nicotine Dependence. *J Addict Med* 2020;14(5):409–414. 10.1097/ADM.0000000000000610
[PubMed: 31972768] .

84. Shiffman S, Sembower M, Rohay J, et al. Assigning dose of nicotine gum by time to first cigarette. *Nicotine & Tobacco Research*. 2013; 15(2):407–412.

85. Hsia S, Myers M, Chen T Combinations nicotine replacement therapy: strategies for initiation and tapering. *Preventative Medicine*. 2017;97:45–49.

86. Livingstone-Banks J, Norris E, Hartmann-Boyce J, et al. Relapse prevention interventions for smoking cessation. *Cochrane Database Syst Rev*

2019;2:CD003999–CD003999. 10.1002/14651858.CD003999.pub5
[PubMed: 30758045] .

87. Williams M, Talbot P Design Features in Multiple Generations of Electronic Cigarette Atomizers. *Int J Environ Res Public Health* 2019;16(16 10.3390/ijerph16162904
[PubMed: 31416115] .

88. Substance Abuse and Mental Health Services Administration (SAMHSA): Reducing Vaping Among Youth and Young Adults. SAMHSA Publication No. PEP20-06-01-003. Rockville, MD: National Mental Health and Substance Use Policy Laboratory, Substance Abuse and Mental Health Services Administration, 2020. https://doi.org/10.4135/9781452240121.n378

89. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews*. 2016;(9):CD010216. doi: 10.1002/14651858.CD010216.pub3.

90. Gotts JE, Jordt SE, McConnell R, et al. What are the respiratory effects of e-cigarettes? *BMJ* 2019;366:l5275–l5275. 10.1136/bmj.l5275
[PubMed: 31570493] .

91. CDC Smoking & Tobacco Use. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed May 23, 2021.

92. Wang TW, Neff LJ, Park-Lee E, et al. E-cigarette Use Among Middle and High School Students - United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69(37):1310–1312. 10.15585/mmwr.mm6937e1
[PubMed: 32941408] .

93. U.S. Food and Drug Administration Vaporizers, E-Cigarettes, and other Electronic Nicotine Delivery Systems (ENDS). https://www.fda.gov/tobacco-products/products-ingredients-components/vaporizers-e-cigarettes-and-other-electronic-nicotine-delivery-systems-ends. Accessed May 23, 2021.

94. CDC State Tobacco Activities Tracking and Evaluation (STATE) System. STATE System E-Cigarette Fact Sheet. https://www.cdc.gov/statesystem/factsheets/ecigarette/ECigarette.html#. Accessed May 23, 2021.

95. FDA. The Real Cost Campaign. https://www.fda.gov/tobacco-products/public-health-education/real-cost-campaign. Accessed May 23, 2021.

96. Hess IM, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapor. *Public Health Res Pract.* 2016;26(2):e2621617. doi: 10.17061/phrp2621617.

97. Glasser A, Collins L, Pearson J. Overview of electronic delivery systems: a systematic review. *Am J Prev Med.* 2017;52(2):e33–e66. [PubMed: 27914771]

98. Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N, et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2020;4:CD000031–CD000031. 10.1002/14651858.CD000031.pub5
[PubMed: 32319681] .

99. FDA Drug Safety Communication: Accessed May 23, 2001. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed May 23, 2021.FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings

100. Gomez-Coronado N, Walker A, Berk M, et al. Current and emerging pharmacotherapies for cessation of tobacco smoking. *Pharmacotherapy*. 2018;38(2):235–258. [PubMed: 29250815]

101. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews*. 2016;(5):CD006103. doi: 10.1002/14651858.CD006103.pub7.

102. Anthenelli R, Benowitz N, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomized, placebo-controlled clinical trial. *The Lancet*. 2016;387:2507-25–20.

103. Rennard S, Hughes J, Cinciripini P, et al. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quite dates. *Nicotine Tob Res.* 2012;14(3):343–350. [PubMed: 22080588]

104. Hajek P, McRobbie HJ, Myers KE, et al. Use of varenicline for 4 weeks before quitting smoking: decrease in ad lib smoking and increase in smoking cessation rates. *Arch Intern Med* 2011;171(8):770–7. 10.1001/archinternmed.2011.138 [PubMed: 21518946] .

105. Tonstad S, Arons C, Rollema H, et al. Varenicline: mode of action, efficacy, safety and accumulated experience salient for clinical populations. *Curr Med Res Opin* 2020;36(5):713–730. 10.1080/03007995.2020.1729708 [PubMed: 32050807] .

106. FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of cardiovascular adverse events. Available at: #professionals findings https://www.fda.gov/Drugs/DrugSafety/ucm330367.htm #professionals findings https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm. Accessed May 23, 2021.

107. Benowitz N, Pipe A, West R, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers a randomized clinical trial. *JAMA Intern Med.* 2018;178(5):622–631. [PubMed: 29630702]

108. Chang P, Chiang C, Ho W, et al. Combination therapy of varenicline with nicotine replacement therapy is better than varenicline alone: A systematic review and meta-analysis of randomized controlled trials. *BMC Public Health*. 2015;15:689. doi: 10.1186/s12889-015-2055-0.

109. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2012;(11):CD000146.

110. Zhong Z, Zhao S, Zhao Y, et al. Combination therapy of varenicline and bupropion in smoking cessation: A meta-analysis of the randomized controlled trials. *Compr Psychiatry* 2019;95:152125–152125. 10.1016/j.comppsych.2019.152125 [PubMed: 31669972] .

111. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: An overview and network meta-analysis. *Cochrane Database of Systematic Reviews*. 2013;(5):CD009329. doi: 10.1002/14651858.CD009329.pub2.

112. Hughes JR, Stead LF. Antidepressants for smoking cessation. *Cochrane Database Syst Rev.* 2014;(1):CD000031.

113. Pamelor Package Insert Mallinckrodt. Last revised May 2007. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/018013s58lbl.pdf. Accessed May 25, 2021.

114. Lieberman HR, Agarwal S, Fulgoni VL 3rd Daily Patterns of Caffeine Intake and the Association of Intake with Multiple Sociodemographic and Lifestyle Factors in US Adults Based on the NHANES 2007-2012 Surveys. *J Acad Nutr Diet* 2019;119(1):106–114. 10.1016/j.jand.2018.08.152 [PubMed: 30446428] .

115. Spilling the beans: How much caffeine is too much. Food and Drug Administration. https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much. Accessed May 25, 2021.

116. Wikoff D, Welsh B, Henderson R, Brorby G, et al. Systematic review of the potential adverse effects of caffeine consumption in health adults, pregnant women, adolescents, and children. *Food and Chemical Toxicology*. 2017;109:585–648. [PubMed: 28438661]

117. Zhang H, Lee ZX, Qiu A Caffeine intake and cognitive functions in children. *Psychopharmacology (Berl)* 2020;237(10):3109–3116. 10.1007/s00213-020-05596-8

[PubMed: 32601990] .

118. Sojar SH, Shrier LA, Ziemnik RE, et al. Symptoms Attributed to Consumption of Caffeinated Beverages in Adolescents. *J Caffeine Res* 2015;5(4):187–191. 10.1089/jcr.2015.0006
[PubMed: 26649254] .

119. Doepker C, Lieberman H, Smith AP, et al. Caffeine: Friend or Foe? *Annu Rev Food Sci Tech-nol.* 2016;7:117–137.

120. Willson C The clinical toxicology of caffeine: A review and case study. *Toxicol Rep* 2018;5:1140–1152. 10.1016/j.toxrep.2018.11.002
[PubMed: 30505695] .

121. FDA Pure and Highly Concentrated Caffeine. https://www.fda.gov/food/dietary-supplement-products-ingredients/pure-and-highly-concentrated-caffeine. Accessed June 3, 2021.

122. FDA warns companies to stop selling dangerous and illegal pure and highly concentrated caffeine products. https://www.fda.gov/news-events/press-announcements/fda-warns-companies-stop-selling-dangerous-and-illegal-pure-and-highly-concentrated-caffeine. Accessed June 3, 2021.

123. Meredith SE, Juliano LM, Hughes JR, et al. 2013 Caffeine Use Disorder: A Comprehensive Review and Research Agenda., J Caffeine Res, 3, 114-130, 10.1089/jcr.2013.0016

124. Sweeney MM, Weaver DC, Vincent KB, et al. Prevalence and Correlates of Caffeine Use Disorder Symptoms Among a United States Sample. *J Caffeine Adenosine Res* 2020;10(1):4–11. 10.1089/caff.2019.0020
[PubMed: 32181442] .

125. Drewnowski A, Rehm CD Sources of Caffeine in Diets of US Children and Adults: Trends by Beverage Type and Purchase Location. *Nutrients* 2016;8(3):154–154. 10.3390/nu8030154
[PubMed: 26978391] .

126. Vercammen KA, Koma JW, Bleich SN Trends in Energy Drink Consumption Among U.S. Adolescents and Adults, 2003-2016. *Am J Prev Med* 2019;56(6):827–833. 10.1016/j.amepre.2018.12.007
[PubMed: 31005465] .

127. NIH National Center for Complementary and Integrative Health: Energy Drinks. Available at: https://nccih.nih.gov/health/energy-drinks. Accessed September 23, 2018.

128. Caffeine informer Top Selling Energy Drink Brands. https://www.caffeineinformer.com/the-15-top-energy-drink-brands. Accessed June 4, 2021.

129. Mattson ME. Update on Emergency Department Visits Involving Energy Drinks: A Continuing Public Health Concern. January 10, 2013. In: The CBHSQ Report. Rockville (MD): Substance Abuse and Mental Health Services Administration (US). Available at: https://www.ncbi.nlm.nih.gov/books/NBK384664/. Accessed October 2, 20018.

130. Markon AO, Jones OE, Punzalan CM, et al. Caffeinated energy drinks: adverse event reports to the US Food and Drug Administration and the National Poison Data System, 2008 to 2015. *Public Health Nutr* 2019;22(14):2531–2542. 10.1017/S1368980019001605
[PubMed: 31317857] .

131. De Sanctis V, Soliman N, Soliman AT, et al. Caffeinated energy drink consumption among adolescents and potential health consequences associated with their use: a significant public health hazard. *Acta Biomed* 2017;88(2):222–231. 10.23750/abm.v88i2.6664
[PubMed: 28845841] .

132. Chrysant SG, Chrysant GS Cardiovascular complications from consumption of high energy drinks: recent evidence. *J Hum Hypertens*

2015;29(2):71–6. 10.1038/jhh.2014.47
[PubMed: 24943288] .

133. Benowitz N. Clinical pharmacology of caffeine. *Ann Rev Med.* 1990;41:277–288.

134. Ferré S Mechanisms of the psychostimulant effects of caffeine: implications for substance use disorders. *Psychopharmacology (Berl)* 2016;233(10):1963–79. 10.1007/s00213-016-4212-2
[PubMed: 26786412] .

135. Drake C, Roehrs T, Shambroom J, et al. Caffeine effects on sleep taken 0, 3, or 6 hours before going to bed. *J Clin Sleep Med* 2013;9(11):1195–200. 10.5664/jcsm.3170
[PubMed: 24235903] .

136. James JE Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be. *BMJ Evid Based Med* 2021;26(3):114–115. 10.1136/bmjebm-2020-111432
[PubMed: 32843532] .

137. ACOG CommitteeOpinion No. 462: Moderate caffeine consumption during pregnancy. *Obstet Gynecol* 2010;116(2 Pt 1):467–468. 10.1097/AOG.0b013e3181eeb2a1
[PubMed: 20664420] .

138. March of Dimes. Caffeine in pregnancy. https://www.marchofdimes.org/pregnancy/caffeine-in-pregnancy.aspx. Accessed June 3, 2021.

139. van Dam RM, Hu FB, Willett WC Coffee, Caffeine, and Health. *N Engl J Med* 2020;383(4):369–378. 10.1056/NEJMra1816604
[PubMed: 32706535] .

SELF-ASSESSMENT QUESTIONS

1. Based on the *DSM -5* criteria, an individual must meet _____ of the 11 criteria during a 12-month period to reach the diagnosis of alcohol use disorder (AUD).

   A. one

   B. two

   C. three

   D. four

2. The lethal dose of alcohol is associated with blood levels greater or equal to _____.

   A. 100mg/dL (22 mmol/L)

   B. 200mg/dL (43 mmol/L)

   C. 300mg/dL (65 mmol/L)

   D. 400mg/dL (87 mmol/L)

3. Which of the following laboratory studies should be ordered in an individual suspected of alcohol ingestion?

   A. Blood alcohol concentration (BAC)

B. CBC (complete blood count)

C. CMP (complete metabolic panel)

D. All of the above

4. Which of the following assessment tools can be used when evaluating a patient in acute alcohol withdrawal?

A. CAGE Questionnaire

B. Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar)

C. Alcohol Use Disorders Identification Test (AUDIT)

D. Fast Alcohol Screening Test (FAST)

5. The preferred class of medications used in treatment of alcohol withdrawal is:

A. barbiturates.

B. antidepressants.

C. benzodiazepines.

D. antiseizure medications.

6. Which of the following treatment options will help prevent the development of Wernicke–Korsakoff syndrome?

A. Thiamine

B. Riboflavin

C. Magnesium

D. Biotin

7. There are four medications currently approved for pharmacological management of alcohol use disorder in the United States. Which of these approved agents is a GABAergic agonist that modulates alcohol cravings?

A. Disulfiram

B. Acamprosate

C. Intramuscular naltrexone

D. Oral naltrexone

8. Which of the following medications approved for the pharmacological management of alcohol use disorder would NOT be an appropriate choice for a patient with a recent history of a myocardial infarction?

A. Disulfiram

B. Oral naltrexone

C. Intermuscular naltrexone

D. Acamprosate

9. Which of the following NRTs would be appropriate for a 45-year-old individual who smokes 35 cigarettes per day? Upon further discussion, you discover they smoke their first cigarette about 10 minutes after waking up each morning. Past medical history includes hypertension, asthma, and seizure disorder. Medication allergies include angiotensin converting enzyme (ACE) Inhibitors and adhesive.

    A. Bupropion 150 mg PO daily for 3 days then increase to twice daily

    B. Nicotine gum 2 mg: chew and park gum as directed every 1 to 2 hours as needed

    C. Nicotine gum 4 mg: chew and park gum as directed every 1 to 2 hours as needed

    D. Nicotine patch 21 mg/day: apply 1 patch to skin daily; rotate application sites

10. Based on the USPSTF taskforce recommendations, which of the following statements is false?

    A. In nonpregnant adults, utilization of behavioral interventions along with FDA-approved pharmacotherapy agents for smoking cessation achieved a substantial benefit.

    B. For pregnant individuals, utilization of behavioral interventions demonstrated substantial benefit for both perinatal outcomes and improved smoking abstinence.

    C. For pregnant individuals, the only FDA-approved NRT agent suggested by the USPSTF was the Nicotrol inhaler.

    D. For both pregnant and nonpregnant adults, there evidence on use of ENDS is insufficient at this time so benefit vs. risk cannot be determined.

11. Which of the following agents is considered second-line therapy for smoking cessation treatment?

    A. Nicotine lozenge

    B. Bupropion

    C. Varenicline

    D. Nortriptyline

12. Which of the following statements is true regarding the Nicotine Patch?

    A. The patient must be told he should never smoke while wearing the patch

    B. If the patient has sleep disturbances, it is due to nicotine withdrawal and the patient should wear the patch through the night to decrease the sleep disturbances

    C. To improve adherence of the patch, after placing the patch on, hold the patch in place for 10 seconds.

    D. It is important to have a nicotine-free period, so it is important to take the patch off every night before going to bed

13. Per labeling, which of the following smoking cessation aids recommend smoking must stop before using this agent?

    A. Nicotine gum

    B. Nicotine lozenge

    C. Nicotrol inhaler

    D. Varenicline

14. Which statement is true regarding ENDS (electronic nicotine delivery systems)?

    A. Studies have now proved using ENDS is safer than traditional cigarettes and eliminates all exposure to toxins that are commonly seen in

traditional cigarettes.

B. There is strong evidence that use of ENDS has now increased the odds of patients achieving full success with smoking cessation

C. Use of ENDS has dramatically increased among the middle school and high school age population and is now the most common tobacco product used in this age group.

D. Use of e-cigarettes is currently approved as a first-line therapy option based on smoking cessation treatment options.

15. A patient who is suffering from "Caffeinism" usually will have a daily intake of approximately _____mg of caffeine and commonly will demonstrate what typical common symptoms?

A. 500–600 mg: drowsiness/sedation/difficulties concentrating

B. 500,600 mg: anxiety/mood changes/psychomotor alterations

C. 1,000–1,500 mg: drowsiness/sedation/difficulties concentrating

D. 1,000–1,500 mg: anxiety/mood changes/psychomotor alterations

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Two of the 11 *DSM -5* criteria must be met during a 12-month period to diagnose AUD. For more information, see "Epidemiology" for the Alcohol section in the chapter.

2. **D.** The lethal dose of alcohol occurs when blood alcohol levels are greater than 400 mg/dL (87 mmol/L). For more information, see the "Etiology" for Alcohol section in the chapter.

3. **D.** Laboratory studies that should be ordered for suspected alcohol ingestion would include a blood alcohol concentration, a complete blood count, and a complete metabolic panel. For more information, see the "Clinical Presentation: Alcohol Withdrawal" section in the chapter.

4. **B.** The Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) is utilized to evaluate patients in acute alcohol withdrawal. For more information, see the "Clinical Presentation: Alcohol Withdrawal" section in the chapter.

5. **C.** Benzodiazepines are the class of medications that are the standard of care in alcohol detoxification. For more information, see the "Treatment of Alcohol Withdrawal Pharmacologic Therapy" section in the chapter.

6. **A.** Thiamine administration is important prior to the administration of glucose to prevent Wernicke–Korsakoff syndrome. See the "Treatment of Nutritional Deficits and Electrolyte Abnormalities" section in the chapter for more information.

7. **B.** Acamprosate is a GABAergic agonist that modulates alcohol cravings. For more information, see the "Pharmacologic Therapy for Alcohol" section in the chapter.

8. **A.** Disulfiram would not be an appropriate choice with a history of a myocardial infarction. If a patient consumes alcohol while taking disulfiram, the resulting disulfiram reaction can lead to myocardial infarction in severe cases. For more information, see the "Pharmacologic Therapy for Alcohol" section in the chapter.

9. **C.** Nicotine 4 mg based on TTFC (time to first cigarette), which is less than 30 minutes from arising. For more information, see the "Treatment" within the Nicotine section.

10. **C.** Nicotrol is Pregnancy Category D and the USPSTF has also highlighted there is inadequate evidence to suggest pharmacotherapy due to lack of studies to determine benefit vs risk at this time. See Table 86-7.

11. **D.** Nortriptyline is considered second-line therapy. All other options are considered first-line. For more information, see the "Second-Line Medications" section in the chapter.

12. **C.** Holding the patch on for 10 seconds when applying can improve adherence to the skin. See Table 86-7.

13. **C.** By label, it specifically states the patient should be counseled to stop smoking completely before using the Nicotrol inhaler. All other agents do state if patient continues to smoke, the patient will not be at risk. See Table 86-7.

14. **C.** The use of e-cigarettes in this age population has increased dramatically and so has the concern due to the exposure to nicotine. The FDA is working on this by working on education campaigns and also working to decrease the availability of these products to this demographic. For more information, see the "Electronic Nicotine Delivery Systems" section of the chapter.

15. **D.** This term has been associated with a daily intake of caffeine of 1,000 to 1,500 mg used to describe the clinical syndrome produced by acute or chronic overuse of caffeine which can be characterized by CNS and peripheral manifestations. For more information, see the "Introduction—Caffeine" section of the chapter.