On April 14, 1994, a House subcommittee met to discuss the health concerns of tobacco use. Before the committee were seven corporate executive officers of large U.S.-based tobacco companies. In his opening remarks, the subcommittee chair reviewed the risks of tobacco use: high mortality rate, cancer, heart disease, and lung disease. Then Rep. Ron Wyden...
In Chapter 6, we considered the most powerful psychostimulants: amphetamines, cathinones, and cocaine. The current chapter covers two less powerful but more often used psychostimulant drugs: nicotine and caffeine.

Nicotine: Key Psychoactive Ingredient in Tobacco

**Nicotine** is the central psychoactive ingredient in tobacco. Tobacco consists of leaves from plants in the genus *Nicotiana* of which the primary nicotine-containing species grow in South and North America ([Figure 7.1](#)). The most popular plant used commercially is *Nicotiana tabacum*, leading to the name “tobacco.” This plant species produces greater amounts of nicotine than other *Nicotiana* species (Saitoh, Noma, & Kawashima, 1985). Traditional forms of tobacco consisted of rolled tobacco leaves, and modern versions consist of cigars and cigarettes. When tobacco is chewed or smoked, small nicotine-containing tobacco particles called *tar* and other tobacco chemicals enter the body.

Cigarettes are the most commonly used tobacco product. A **cigarette** is composed of a tobacco blend rolled in a thin sheet of paper. Many cigarettes contain a filter of cellulose acetate that reduces the amount of tobacco tar inhaled. The tobacco portion of a regular cigarette is approximately 60 mm (2.25 in.) in length, and filtered cigarettes have a 25 mm (~1 in.) filter and usually shorter length of tobacco. Depending on the size and blend, a cigarette contains 1–2 mg of nicotine. Some brands of cigarettes have a flavoring added, the most popular of which is menthol. Menthol cigarettes, in particular, are almost exclusively used by African Americans, and more women tend to use menthol cigarettes than men (Muscat, Richie, & Stellman, 2002).

**Cigars** consist of tightly rolled bundles of dried tobacco leaves wrapped in a leaf. Cigars vary widely in diameter, length, and nicotine content. For example, a Winchester Little Cigar is 8 mm (~⅜ in.) in diameter and 60 mm (2⅓ in.) long, whereas a Cuesta-Rey No. 1 is 20 mm (~¾ in.) in diameter and 211 mm (8⅝ in.) in length. A Winchester Little Cigar contains 5.9 mg of nicotine, and a Cuesta-Rey No. 1 cigar contains 335.2 mg of nicotine (Henningfield, Fant, Radzius, & Frost, 1999).
Pipe smoking consists of inhaling smoke from a tobacco blend. Water pipes consist of inhaling smoke that has passed through a container of water. Hookah water pipe smoking is increasingly prevalent among younger Western adults, although it has been a common method of smoking in the Middle East for centuries (Neergaard, Singh, Job, & Montgomery, 2007) (Figure 7.2). A typical hookah is an ornately shaped and decorated water pipe assembly consisting of a charcoal-heated tobacco-holding chamber pipe connected through the water jar mouth and into the water; smokers inhale tobacco smoke from a hose projecting from the top of the jar. Inhaled tobacco smoke first passes through a bowl of water. Many users believe that this method reduces the harmful effects of tobacco, although studies of water-pipe tobacco exposure state otherwise (Ahmed, Jacob, Allen, & Benowitz, 2011; Jacob et al., 2011).

Smokeless tobacco products consist of any tobacco form intended for absorption in the mouth. Products called chew, snuff, and dipping tobacco consist of a tobacco blend that a user either chews or pockets in his or her cheek. When the product is spent, users spit the tobacco out. Dissolvable tobacco is another type of smokeless tobacco. These products come in the form of sweetened strips, sticks, or pellets that dissolve in the mouth. Dissolvable tobacco products contain amounts of nicotine similar to those found in cigarettes. For example, a strip contains 0.6 mg of nicotine, and a stick contains 3.1 mg of nicotine. The resemblance of these products to candy recently led to redesigning the appearance of these products (Connolly et al., 2010).
Finally, **e-cigarettes** (or **electronic nicotine delivery systems**), electronic nicotine vaporizers often shaped like a cigarettes, have emerged as another popular form of nicotine delivery. Modern e-cigarettes contain a battery that powers a heater attached to an *atomizer*, a component that reduces liquid into a fine spray. A liquid cartridge containing nicotine and propylene glycol plugs into the atomizer, which vaporizes the liquid when a sensor detects airflow passage or the user presses a button (Trtchounian, Williams, & Talbot, 2010) (Figure 7.3). Thus, a user inhales a nicotine vapor solution through an e-cigarette.

E-cigarettes once were used as a cigarette cessation approach—that is, they somewhat had the feel of a cigarette, but the user inhaled vaporized nicotine rather than tar particles from tobacco. These first-generation e-cigarettes closely resembled traditional cigarettes. Thus, we could describe those e-cigarette users as “smokers” who...
were attempting to quit smoking traditional cigarettes. Today, many e-cigarette liquid cartridges also include flavorings, such as fruit and candy flavors, and users can assemble their e-cigarettes using customized components (or “mods”). For example, a user can add a mod to adjust the level of power to the heater, with greater heat leading to more e-liquid vaporized, and vice versa (Farsalinos et al., 2014). The amount of nicotine found in most e-cigarette liquid cartridges varies from 20 to 40 mg/ml (Davis, Dang, Kim, & Talbot, 2015). These second-generation e-cigarettes seldom resemble actual cigarettes; instead they have metallic, sleek-looking designs (Farsalinos et al., 2014). These devices tend to be referred to as personal vaporizers, “vape pens,” or similar names. Further, users of these devices may not be current or former tobacco smokers, leading us to identify them as “vapers” rather than smokers. Thus, a person using a nicotine vaporizer is “vaping” rather than smoking (Fagerstrom, Etter, & Unger, 2015).

Tobacco use is widespread. In 2009, 70 million Americans ages 12 and older—a little less than 25 percent of the U.S. population—had used tobacco products within the preceding month. However, tobacco use is declining in the United States. Cigarette use in the United States peaked during the 1960s and has steadily decreased since (Figure 7.4).

According to the World Health Organization, tobacco use is high in many parts of Europe and Asia and throughout Central and South America (Figure 7.5).
Asia includes the highest rates. More than 60 percent of males in the Russian Federation and China use tobacco products. Males generally use tobacco products more than females, but these differences vary across countries. For example, equal smoking rates occur among males and females in Norway and Sweden, whereas less than 10 percent of females smoke in the Russian Federation and China (Mackay & Eriksen, 2002).

Vaping e-cigarette products is still a relatively new practice at the time of writing this book, but there are a number of trends suggesting increased use of these products and a likelihood of later using traditional tobacco products. The percentage of a large sample of U.S. adults who ever used an e-cigarette rose from 3.3 percent in 2010 to 8.5 percent in 2013; among a large sample of chronic smokers, reported recent e-cigarette use had risen from 1.1 percent in 2010 to 18.4 percent in 2013 (King, Patel, Nguyen, & Dube, 2014; Rigotti et al., 2015). 6.1 percent of middle and high school students had reported ever using e-cigarettes between the years 2011 and 2013 (Bunnell et al. 2015).
Tobacco use has serious health effects. The three primary causes of tobacco-related death each year are cancer, pulmonary disease, and cardiovascular disease. According to the U.S. Centers for Disease Control and Prevention, 443,000 tobacco-related deaths occurred each year between 2000 and 2004. Of those deaths, more than 75 percent resulted from at least one of these three conditions, with lung cancer being the leading cause of tobacco-related deaths (Figure 7.6). African Americans have greater mortality rates from smoking, despite smoking less than European Americans, because of greater incidents of these smoking-related diseases (Fiore et al., 1989).

Evidence of adverse effects from e-cigarette use varies across scientific studies. The most consistent finding is that most e-cigarette vapors contain volatile organic compounds, including toluene and xylene. Otherwise, conflicting studies have been shown for a variety of potential health effects, including presence of organic compounds.
Lung cancer, chronic obstructive pulmonary disease such as emphysema, and heart disease are the greatest causes of death associated with tobacco use.

About 443,000 U.S. Deaths Attributable Each Year to Cigarette Smoking*

- **Lung cancer**: 128,900
- **Ischemic heart disease**: 126,000
- **Other cancers**: 35,300
- **Stroke**: 15,900
- **Other diagnoses**: 44,000
- **Chronic obstructive pulmonary disease**: 92,900

* Average annual number of deaths, 2000–2004.


(e.g., formaldehyde, acetaldehyde) and particulate matter in e-cigarette vapor and the potential of vapor exposure to cause cytotoxicity (i.e., damage to cells). In a comprehensive review of studies that evaluated potential negative health effects from e-cigarette use, Pisinger and Døssing (2014) concluded that inconsistent results across studies and lack of long-term data preclude making firm conclusions about e-cigarette use, except that using them appears safer than smoking cigarettes.

Secondhand smoke exposure also increases one's risk to negative health effects. **Secondhand smoke** consists of smoke exhaled from a smoker or smoke released from a burning tobacco product (i.e., a lit cigarette or cigar). In 2005, this form of tobacco exposure accounted for 3,000 deaths from lung cancer and 46,000 deaths related to coronary heart disease. Secondhand smoke exposure also accounted for 430 sudden infant death syndrome incidents in that same year (CDC, 2008). We also link secondhand smoke to health effects in children, where we find greater incidents of asthma, bronchitis, pneumonia, and ear infections (U.S. Department of Health and Human Services, 2006).

A nonsmoker may also be exposed to thirdhand smoke. **Thirdhand smoke** consists of remnants from tobacco smoking gathered on material in the smoker's local environment after smoking has finished (Winickoff et al., 2009). A nonsmoker may be exposed to tobacco products that cling to hair, skin, or clothing, and these products can remain on fabrics for months after smoking ceases (Bahl et al., 2016). Tobacco products from smoke gather on walls, flooring, and various objects in the setting, making these other sources of exposure for nonsmokers. Young children, in particular, may ingest this material from...
playing on the floor or putting objects on their mouths. Thirdhand smoke effects is a relatively new area of research, and potential health effects from this exposure have yet to be found. So far, researchers have found cytotoxic chemicals deposited from thirdhand smoke as well as chemicals that inhibit cell proliferation (Bahl et al., 2016). These findings suggest that a risk of adverse effects occur from exposure to thirdhand smoke.

### Discovery of Tobacco

The discovery of fossilized leaves of *Nicotiana tabacum* in Peru suggests that tobacco existed at least 2.5 million years ago. Indigenous peoples in the Americas, including the Mayas, Incans, Toltecs, and Aztecs, smoked tobacco as part of their religious practices. In religious ceremonies, tobacco was smoked to achieve a trancelike state ([Figure 7.7](#figure7.7)).

![Tobacco was smoked by ancient Mayan priests for ceremonial purposes.](source: Shutterstock/Jef Thompson)
Religious practices remained the primary use of tobacco until Europeans discovered tobacco during Columbus’s 1492 expedition. After Columbus landed in the Bahamas, the native Arawak gave dried tobacco leaves as a gift to the explorer. Not realizing the significance of the tobacco leaves to the Arawak, Columbus simply discarded them. A few days later, however, Columbus noted that the leaves had “high value among [the Arawak]” (Brecher, 1972; Gately, 2001).

Rodrigo de Jerez, a member of Columbus’s expedition, participated in the native practice of rolling tobacco leaves and smoking them. Thus, Jerez became the first European to smoke tobacco. In fact, he became a habitual user and brought back a large personal tobacco supply to Spain. Yet the frightening sight of tobacco smoke coming from his mouth and nose brought him to judgment by the holy inquisitors, who imprisoned him for 7 years (Gately, 2001).

Use of tobacco in Europe soon grew. By the mid-16th century, tobacco was a widely traded commodity. Complaints against tobacco also grew. The first medical concern against using tobacco was published in the early 17th century, which compared the deleterious health effects of chimney sweeps to those of tobacco smokers. In 1610, Sir Francis Bacon noted the difficulty in quitting tobacco use. In 1634, Russian Tsar Michael I decreed that a first offense for tobacco use was punishment by whipping and transport to Siberia; the second offense was death (Brecher, 1972).

In 1612 Jamestown, John Rolfe raised the first European tobacco crop for commercial use, marking the beginning of a thriving American industry that remains active today. Nearly 200 years later, in 1809, Louis Nicolas Vanquelin isolated nicotine as a key ingredient in tobacco.

The beginning of the 20th century marked a renewed study of tobacco’s health effects. Early in this century, scientists studied the effects of tobacco and cancer in animals, and biologist Davis Jordan publicly stated, “The boy who smokes cigarettes need not be anxious about his future—he has none.” In 1938, a study by Raymond Pearl reported that heavy smokers lived a shorter life than nonsmokers (Gately, 2001).

By the 1990s, the health risks of tobacco were well characterized and widely publicized. As presented at the beginning of this chapter, the 1994 tobacco hearings included the testimony of seven tobacco company CEOs who denied any knowledge of tobacco’s adverse effects. Today, tobacco products must include special health warning labels, but the product is still sold legally throughout the world.

STOP & CHECK

1. What is the key psychoactive ingredient in tobacco?
2. Among the many forms of tobacco, which product remains the most used?
3. What is the greatest cause of death from smoking?
4. In which American colony was the first tobacco crop grown?

Chapter 7 • Nicotine and Caffeine

Tobacco Use and Pharmacokinetic Properties

Tobacco Use and Nicotine Absorption

Tobacco use consists of inhaling or chewing tobacco blends or other products. Smoked tobacco was seldom inhaled into the lungs prior to common practice of flue-curing tobacco blends in cigarettes in the early 1900s. **Flue curing** consists of venting heat through a metal flue onto tobacco leaves. The process reduces the pH of smoke toward neutral (i.e., closer to pH = 7.0) by converting starches to sugars, making the smoke less harsh and irritating to inhale. Cigars instead use air-dried tobacco leaves, retaining an alkaline pH and having less sugars. As a result, cigar smokers may be less likely to inhale tobacco smoke into their lungs than cigarette smokers. Cigarette smokers who also smoke cigars, however, do tend to fully inhale cigar smoke into their lungs (Turner, Sillett, McNicol, 1977).

Nicotine Absorption Through Lung and Oral Tissues

A typical cigarette user consumes 13 cigarettes per day, although smokers who repeatedly attempt to quit smoking tend to smoke between 20 and 40 cigarettes per day (Shiffman, 1989). In general, though cigarette smokers tend to inhale smoke into their lungs more often than cigar smokers do, cigar smokers absorb more nicotine than cigarette smokers. Greater nicotine absorption from cigars likely occurs from nicotine absorption through mucous membranes in the mouth (Turner, Sillett, & McNicol, 1977). For e-cigarettes, Farsalinos and colleagues (2014) found that newer devices lead to 70 percent greater nicotine levels in plasma than first-generation devices, and that nicotine absorbed from new-generation devices reaches levels similar to traditional cigarettes.

When smoking tobacco, **tar**, the particulate matter produced from burning tobacco, adheres to tissues in the mouth, nose, throat, and, if fully inhaled, the lungs. When exhaled, tar also adheres to the skin. Nicotine and many other chemicals leach from the tar and onto tissue the tar makes contact with. All tissue sites provide a means of absorption. Given the large surface area of the lungs, inhaled tobacco smoke provides the most effective route of nicotine administration.

The freebase form of nicotine is lipid soluble, allowing for absorption through mucous membranes in the mouth. The greatest amount of freebase nicotine that can be absorbed is 50 percent, which occurs at a pH of 8.02. As pH levels deviate from 8.02, the percentage of freebase nicotine decreases. Many smokeless and dissolvable tobacco products offer pH values close to 8.02, as shown for dissolvable nicotine products in **Table 7.1** (Djordjevic, Hoffman, Glynn, & Connolly, 1995; Henningfield, Radzius, & Cone, 1995; Rainey, Conder, & Goodpaster, 2011). The majority of e-cigarette liquids have pH values between 7.0 to 9.0, leading to greater than 50 percent of freebase nicotine for many of these products (Lisko, Tran, Stanfill, Blount, & Watson, 2014).

When inhaling tobacco smoke, the acidity of smoke from a cigarette reduces saliva to a pH less than 6.0, reducing the amount of freebase nicotine available for absorption in the mouth (Armitage & Turner, 1970). However, tobacco companies do add ammonia-forming compounds to tobacco blends, which increases the amount of freebase nicotine (Pankow et al., 1997). Smoke from cigars tends to have pH levels closer to 7.0, although the pH levels vary considerably, depending on the size of the
cigar and part of the cigar smoked (Henningfield et al., 1999). The pH levels for cigars therefore favor greater nicotine absorption in the mouth. This can mean significant nicotine absorption for many cigar smokers who do not fully inhale tobacco smoke, as noted earlier.

Most tobacco products result in blood nicotine concentrations of 12 to 16 nanograms$^1$ per milliliter, although absorption times vary. Peak absorption for nicotine from cigarettes occurs after approximately 7 minutes. Nicotine absorption times through oral mucous membranes tend to peak between 20 and 30 minutes after introduction (Vansickel et al. 2010; Henningfield & Keenan, 1993). Peak nicotine absorption from e-cigarettes, from either first- or new-generation devices, occurs after 30 minutes, suggesting that most nicotine absorption occurs through mucous membranes in the mouth, rather than the lungs (Farsalinos et al. 2014).

In addition to the speed of nicotine delivery, tobacco smoking or vaping provides users the ability to adjust the amount of nicotine absorbed. A smoker accomplishes these adjustments by varying the number of inhalations, duration of an inhalation, completeness of inhalation, and the number of cigarettes smoked (Frederiksen, Martin, & Webster, 1979). Vapers also can adjust a nicotine vaporizer’s heating level to alter the amount of nicotine inhaled.

**Distribution and Biotransformation of Nicotine**

Once absorbed, nicotine readily passes through the blood–brain barrier. In the liver, CYP-2A6 enzymes metabolize 80 percent to 90 percent of nicotine, producing the active metabolite **cotinine**, which exhibits pharmacological actions similar to nicotine. Slower metabolism occurs for mentholated versus non-mentholated cigarettes (Benowitz, Herrera, & Jacob, 2004).

Genetic polymorphisms influence CYP-2A6 activity levels. CYP-2A6*4, *7 and *9 polymorphisms exhibit reduced CYP-2A6 activity, causing slower metabolism of nicotine to cotinine. In other words, nicotine levels remain higher in the body because of

---

$^1$ A nanogram is one billionth, or $10^{-9}$, of a gram.
reduced metabolism. These polymorphisms are prevalent within Asian populations. Individuals who exhibit homogenous mutant forms of these gene polymorphisms or heterogeneous mutant forms that have a combination of the *4, *7, or *9 polymorphisms, tend to be light smokers and have a lower risk of tobacco-related health effects (Ariyoshi et al., 2002; Minematsu et al., 2006; Yusof & Gan, 2009). African Americans exhibit a slower metabolism of nicotine, engendering a longer period of time for intact nicotine to exert pharmacological effects (Pérez-Stable, Herrera, Jacob, & Benowitz, 1998). This may be due to a preference by African American smokers for using mentholated cigarettes.

**Elimination of Nicotine**

The half-life for nicotine is approximately 2 hours, but this clearance time depends on a smoker’s status. Chronic smokers have a 30-percent faster elimination rate of nicotine than nonsmokers. These findings suggest that chronic tobacco use sensitizes pharmacokinetic processes for nicotine (Perkins et al., 1994). The half-life for cotinine is approximately 17 hours (Pérez-Stable et al., 1998). Both nicotine and cotinine are primarily eliminated from the body through urine, and so a simple urine analysis for cotinine can reveal tobacco use more than a day later.

**STOP & CHECK**

1. Why is inhalation the most effective route for absorbing nicotine from tobacco tar?
2. What factors influence nicotine’s ability to be absorbed in the mouth?
3. What is the active metabolite for nicotine?

**Nicotine and Nervous System Functioning**

Nicotine functions as an agonist for cholinergic nicotinic receptors (Figure 7.8). Cotinine, the active metabolite of nicotine, serves as a weak agonist for nicotine receptors. When a nicotinic receptor agonist binds to these receptors, a conformational change takes place, opening a channel for positively charged ions, such as Ca\(^{2+}\), Na\(^{+}\), and K\(^{-}\). Some ions pass more readily through nicotinic receptor channels than others. For examples, \(\alpha_7\) receptors are most permeable for Ca\(^{2+}\) ions (Séguéla, Wadiche, Dineley-Miller, Dani, & Patrick, 1993).
Review! Nicotinic receptors are ionotropic and comprise \( \alpha \) and \( \beta \) subunits. Nicotinic receptors can include other subunit types as well, which are denoted by different Greek symbols. The configuration of these subunits defines each receptor’s name. (Chapter 3.)

A short time after nicotine (or another agonist) activates a nicotinic receptor, the receptor enters a desensitized state, which limits the duration of action for nicotine’s acute pharmacological effects (Figure 7.9) (Hsu, Amin, Weiss, & Wecker, 1995; Fenster, Rains, Noerager, Quick, & Lester, 1997). During the desensitized state, the channels close and the receptors cannot be activated. These receptors enter this desensitized state even when the receptors remain bound by an agonist. After a period of time, the desensitized state ends and the receptors can again be activated by an agonist.

Because of desensitization, agonists cause nicotinic-receptor channels to remain closed longer than they are open. In this way, nicotinic-receptor agonists also produce functional antagonism, meaning that nicotine causes these receptors to have a longer inactivated state than an activated state. Thinking of nicotine as a functional antagonist is useful for understanding changes in nicotinic receptors during chronic nicotine administration. During such administration, the brain compensates for the repeated closing of nicotinic-receptor channels by upregulating nicotinic receptors (Schwartz & Kellar, 1985; Wonnacott, 1990). Upregulation refers to an increased production of proteins.
Both the central and peripheral nervous systems contain nicotinic receptors. Peripherally, nicotinic receptors are located postsynaptically on neuromuscular junctions in the somatic nervous system. Within neuromuscular junctions, the activation of \( \alpha_1 \beta_1 \delta \gamma \) nicotinic receptors on muscle fibers causes muscles to contract.

Nicotinic receptors are located in ganglia of the autonomic system, including both the sympathetic and the parasympathetic nervous systems. Of these two systems, the activation of nicotinic receptors primarily increases sympathetic nervous system activity (Li, LaCroix, & Freeling, 2009). Different subtypes of nicotinic receptors are likely involved in the sympathetic and parasympathetic systems. For cardiovascular effects, Li and colleagues (2009) discovered that \( \alpha_7 \) receptors activate the parasympathetic nervous system, whereas \( \alpha_4 \beta_2 \) receptors activate the sympathetic nervous system.

**Review!** The autonomic nervous system includes the sympathetic nervous system, which increases physiological activity, and the parasympathetic nervous system, which decreases physiological activity. (Chapter 2.)

Nicotinic receptors are found throughout the central nervous system and play an important role in many nervous system processes. The cerebral cortex and hippocampus, two brain areas important for cognitive functioning, highly express both \( \alpha_4 \beta_2 \) and...
α, nicotinic receptors. High amounts of α4β2 nicotinic receptors are also found in the basal ganglia, an area important for regulating movement, and the substantia nigra, the source of dopamine neurons that terminate in the basal ganglia. In the dopamine reward pathway, the ventral tegmental area contains αβ2 and α6β2 receptors, and the nucleus accumbens also contains α4β2 receptors (Brunzell, 2012; Yang et al., 2011; Zhao-Shea et al., 2011).

The activation of nicotinic receptors in either the ventral tegmental area or the nucleus accumbens increases dopamine release in the nucleus accumbens. Researchers discovered these effects using microdialysis techniques in animals (see Box 3.1). For example, Nisell and colleagues (1994) infused nicotine into either the ventral tegmental area or the nucleus accumbens in rats. Microdialysis probes in these structures collected cerebrospinal fluid samples for dopamine analysis. The infusion of nicotine in the ventral tegmental area produced a large, sustained increase in dopamine levels in the nucleus accumbens. When infused into the nucleus accumbens, nicotine produced a much shorter increase in dopamine levels in the nucleus accumbens (Figure 7.10). Based on these findings, nicotine acts in both areas to elevate dopamine levels in the nucleus accumbens, but nicotine’s actions in the ventral tegmental area are especially effective for inducing dopamine release in the nucleus accumbens.

In addition to enhancing the release of dopamine in the brain, the activation of nicotinic receptors influences many other neurotransmitters in the brain, including acetylcholine, glutamate, GABA, norepinephrine, serotonin, and the hormone vasopressin. These widespread interactions preclude identifying highly specific roles.
that nicotinic receptors have on behavior. Clearly, by acting on nicotinic receptors, nicotine and other nicotinic-receptor agonists have diverse effects on the central nervous system.

Beyond nicotine, other compounds in tobacco may act in the nervous system, possibly enhancing nicotine’s effects. In particular, many chemicals in tobacco inhibit MAO\textsubscript{A} and MAO\textsubscript{B} activities, including the compounds 2,3,6-trimethyl-1,4-naphthoquinone, 2-naphthylamine, harman, and norharman (Hauptmann & Shih, 2001; Herraiz & Chaparro, 2005; Khalil, Steyn, & Castagnoli, 2000).

These actions may explain why long-term smokers exhibit a decreased activity of MAO\textsubscript{A} and MAO\textsubscript{B} enzymes (Fowler et al., 1996a, 1996b). MAO inhibition also enhances the effects of nicotine on dopamine levels in the nucleus accumbens. In a microdialysis study conducted by Lotfipour and colleagues (2011), rats treated with both nicotine and tranylcypromine, an MAO\textsubscript{A/B} reuptake inhibitor, exhibited a substantially greater increase in nucleus accumbens dopamine levels than rats treated with either drug alone (Figure 7.11).

**Review!** Monoamine oxidase (MAO) is an enzyme that breaks down, or catabolizes, dopamine, norepinephrine, and serotonin. (Chapter 3.)

---

**FIGURE 7.11** Rats treated with both nicotine and tranylcypromine, an MAO reuptake inhibitor, exhibited a substantially greater increase in nucleus accumbens dopamine levels than rats treated with either drug alone.

SOURCE: Data from Lotfipour et al., 2011.
STOP & CHECK

1. At nicotinic cholinergic receptors, nicotine functions as an _________________.
2. Nicotine causes an increase in dopamine release in the nucleus accumbens by acting on nicotinic receptors in the nucleus accumbens and the _________________.
3. What is another compound in tobacco that may facilitate nicotine’s effects?

Nicotine’s Potent Pharmacological Effects

Nicotine produces physiological, behavioral, and subjective effects, and tobacco, the main source of nicotine, produces a host of adverse effects. When characterizing the pharmacological effects of nicotine, researchers understand that the length of nicotine use is important. Because upregulation of nicotinic receptors occurs during repeated administration, the acute effects of nicotine can differ from the chronic effects of nicotine. Thus, the effects of nicotine on a first-time smoker can differ greatly from the effects of nicotine on a long-time smoker.

Nicotine’s Effects on Cardiovascular Function and Appetite

Nicotine produces widespread physiological effects. The two most notable are on the cardiovascular system and appetite. In both smokers and nonsmokers, nicotine produces cardiovascular effects consisting of increases in heart rate and blood pressure. Because these effects are observed in smokers, a tolerance to these effects does not occur during chronic nicotine administration.

Acute tolerance occurs for a number of nicotine physiological effects. Acute tolerance refers to a decreased responsiveness to a drug’s effects after single administration of drug. Acute tolerance to nicotine’s effects on heart rate and blood pressure happens when nicotine is administered soon after the previous administration (Perkins et al., 1994) (Figure 7.12). Acute tolerance occurs partly because the subsequent nicotine administration occurs while many nicotinic receptors remain in a desensitized state.

Most smokers experience acute tolerance every morning. Nicotine delivered from the first cigarette of the day causes an increase in heart rate and blood pressure. The next cigarette exhibits weaker effects on heart rate and blood pressure. Because of acute tolerance, heart rate and blood pressure soon return to normal levels.

Nicotine reduces appetite in both non-tobacco users and long-term smokers. In a study by Perkins and colleagues (1991) nicotine was administered to either non-tobacco users or smokers who had not smoked since the night before. In both groups, nicotine reduced self-reported hunger and the number of snack foods consumed during the testing sessions (Figure 7.13). The appetite-suppressing effects of nicotine
Smokers exhibit acute tolerance to nicotine’s increase in heart rate. When smokers are given nicotine placebo prior to nicotine administration, an increase in heart rates occurs. However, after several administrations of nicotine, a subsequent administration of nicotine leads to weaker effect on heart rate.

**FIGURE 7.12**

SOURCE: Data from Perkins et al., 1994.

contribute to weight loss in many tobacco users, and tobacco users often cite potential weight gain as a reason not to quit.

**Nicotine Affects Movement and Cognitive Functioning**

Nicotine’s behavioral effects include alterations in movement and cognitive function. These effects differ between naïve and chronic tobacco users. Nicotine produces effects on motor stability, which are particularly noticeable in the hands. Hand tremor and reduced hand steadiness occur after nicotine administration to non-tobacco users. Tolerance occurs with these effects in tobacco users (Perkins et al., 1994).

Nicotine’s effects on psychomotor function also differ between acute and chronic administration. Acute administration of nicotine in nicotine-naïve users causes a decrease in psychomotor activity. However, sensitization to these effects occurs during chronic administration. Thus, in chronic tobacco users, nicotine increases psychomotor function. For example, Perkins and colleagues (1994) reported that nicotine administration increases the rate of finger tapping in chronic smokers, but decreases the rate of finger tapping in nonsmokers.

Animal studies also find differences between acute and chronic nicotine administration. For example, Pehrson and colleagues (2008) studied locomotor activity in rats during 14 days of nicotine administration using an open field-apparatus.
After test subjects fasted overnight, administration of nicotine significantly reduced feelings of hunger in both smokers and nonsmokers compared to baseline (i.e., before nicotine administration).

**FIGURE 7.13**

![Graph showing hunger levels](image)

(Source: Data from Perkins et al., 1991.

(Figure 7.14). An open-field apparatus, when used for rodents, consists of a box constructed from plastic or metal with walls high enough to prevent escape and an open top to allow for observation; open fields typically have grid lines drawn on the bottom. The grid lines allow researchers to count line-crosses an animal makes as an index of overall movement. In place of grid lines, many open fields can emit photo beams instead; that is, researchers count photo beam breaks rather than line crosses.

On the first day of treatment, nicotine suppressed locomotor activity as indicated by fewer photo beam breaks in an open-field apparatus. However, on the 7th and 14th days of treatment, nicotine enhanced locomotor activity.

Although public attitudes toward nicotine are generally negative, nicotine may show some benefits for cognitive functioning. Studies show that nicotine improves attention, particularly when reorienting attention toward another stimulus (Thiel, Zilles, & Fink, 2005), and improves information processing (Juliano, Fucito, & Harrell, 2011; Wesnes & Warburton, 1984).

In attention tasks, nicotine improves information processing by shortening times to detect stimuli. Wesnes and Warburton (1984) first demonstrated these effects, finding...
that nicotine improved the detection of targets during an 80-minute vigilance task consisting of identifying number of sequences from numbers scrolling across a display. David Warburton later reflected that this seminal study was first rejected from a journal because the editor refused to publish “anything good about nicotine” (Warburton, 2002).

Nicotine’s improvements in attention occur after chronic administration as well. For example, Perkins and colleagues (1994) used a Stroop test—a standard test of processing speed used for neuropsychological assessments that evaluates reaction times to mismatched stimulus presentations (Lansbergen & Kenemans, 2008)—to assess attention after nicotine administration in both nonsmokers and smokers. Nicotine improved reaction times in both test subjects, both nonsmokers and smokers.

Aside from information processing and attention, the effects of nicotine on memory are unclear. In the study by Perkins and colleagues (1994), nicotine also improved memory in a word list recall test, which required participants to remember words presented to them in a list. Nicotine’s memory improvements were greater in nonsmokers than in smokers, suggesting that smokers develop a tolerance to these effects. Yet many studies also fail to show improvements in memory after nicotine treatment, and some studies show that nicotine worsens memory in chronic smokers (Ernst et al., 2001; Myers, Taylor, Moolchan, & Heishman, 2007; Park, Knopick, McGurk, & Meltzer, 2000).

Many studies have evaluated nicotine for the treatment of Alzheimer’s disease. Biologically, nicotine reduces the destructive effects of amyloid β42 proteins in the hippocampus, an important characteristic of this disease. However, Deng and colleagues (2010) demonstrated that nicotine worsens the memory-inducing impairments caused
by amyloid β42 proteins in rats. Further, in a transgenic mouse model of Alzheimer’s disease, exposure to cigarette smoke caused greater production amyloid β42 proteins and other abnormalities in Alzheimer’s disease (Moreno-Gonzalez, Estrada, Sanchez-Mejas, & Soto, 2013). In humans, some studies report a decreased risk of Alzheimer’s disease in smokers, whereas other studies report an increased risk (Ulrich, Johannson-Locher, Seiler, & Stahelin, 1997; Ott et al., 1998). Heavy smoking, at least, is not beneficial for Alzheimer’s disease; in fact, Rusanen and colleagues (2011) found that heavy smoking increases the risk of Alzheimer’s disease by 157 percent.

**Nicotine’s Positive and Negative Subjective Effects**

Nicotine’s subjective effects vary greatly between acute and chronic administration. In non-tobacco users, nicotine can produce negative subjective effects, including nausea and disequilibrium. In addition, as described in the study by Perkins and colleagues (1994), nicotine produces feelings of jitteriness, tension, and confusion in nonsmokers. Yet acute tolerance to these negative subjective effects occurs after subsequent nicotine administrations. Further, many users instead feel relaxed after smoking for the first time. Researchers find a much greater risk of continued smoking for those feeling relaxed compared to those who experienced negative subjective effects (DiFranza et al., 2004).

A conditioned taste-aversion procedure can demonstrate nicotine’s aversive effects as well as acute tolerance to these aversive effects. The conditioned taste-aversion procedure is described in Box 7.1. Prus and colleagues (2007) used this procedure to link the timing of nicotine administration with the time course of nicotinic-receptor changes (Figure 7.15). For rats treated with nicotine 5 minutes before a pairing session with saccharin, less saccharin was consumed on the following day. This pairing session took place during the activated nicotinic-receptor state.

In this same study, another group of rats was treated with nicotine 90 minutes before the pairing session and given a second treatment of nicotine 5 minutes before the session. These rats drank more of the saccharin solution on the following day. For these rats, the second injection of nicotine occurred when the nicotinic receptors were desensitized, thus reducing aversive effects from occurring during or after the pairing session.

Long-term treatment with nicotine also causes tolerance to these negative subjective effects. Without negative subjective effects, chronic tobacco users experience only positive subjective effects from nicotine. In chronic smokers, nicotine administration produces feelings of vigor, arousal, and reduced fatigue (Perkins et al., 1994). Chronic smokers report that the effects of nicotine are pleasant and enjoyed and produce a positive mood (Myers et al., 2007). These smokers can detect a distinct rewarding effect with each puff of cigarette smoke.

The positive subjective effects of nicotine can be difficult to establish in animals. In a standard self-administration procedure (see Box 5.1), rats will not learn to self-administer nicotine because of the initial adverse effects experienced on first exposure to nicotine. In other words, if the effects are negative, an animal will avoid those effects rather than seek to achieve them. To observe the reinforcing effects of nicotine in this procedure, researchers use a variation on the standard self-administration design.

For example, Boules and colleagues (2011) used a common design variation to study nicotine self-administration in rats. First, these researchers trained rats to press a lever
for sucrose food pellets. Then the researchers changed the consequence for pressing a lever from the sucrose food pellet to an intravenous nicotine injection. Because the rats had learned to repeatedly press the lever for sucrose pellets in the past, they persisted in pressing the lever, resulting in further nicotine injections. Through this process, tolerance quickly developed to nicotine’s negative effects. After a tolerance developed to the negative effects, the reinforcing effects of nicotine administration were sufficient to maintain lever pressing.

Other components in tobacco may contribute to the reinforcing effects of nicotine. In particular, MAO inhibitors found in tobacco enhance nicotine-induced effects on nucleus accumbens dopamine levels. Self-administration of nicotine is enhanced by MAO inhibition (Guillem et al., 2005; Villégier, Lotfipour, McQuown, Belluzzi, & Leslie, 2007). For example, in a study by Villégier and colleagues (2007), the MAO inhibitor tranylcypromine facilitated self-administration for nicotine in rats. This facilitation avoided the need to have a prior training history, allowing the researchers to use a standard self-administration procedure. Rats that did not receive the MAO inhibitor were unable to self-administer nicotine without altering the standard procedure. These findings suggest that an addiction to tobacco may develop more rapidly than an addiction to only nicotine.

Adverse Effects of Tobacco Use

Many of the severely adverse effects associated with nicotine are the result of its vehicle: tobacco. Tobacco contains thousands of chemicals, including carcinogens such
Drugs and the Neuroscience of Behavior

A conditioned taste aversion is the result of a pairing process between a noxious stimulus and a novel-tasting substance. This procedure also is called the Garcia effect in recognition of a discovery by John Garcia in 1955 (Garcia, Kimeldorf, & Koellino, 1955). Garcia discovered that rats ingested less of a saccharin solution after an occasion in which prior consumption of the solution was followed by gastrointestinal pain. Conditioned taste aversion is a process resembling classical, or Pavlovian, conditioning procedures.

Many psychoactive drugs function as noxious stimuli, allowing them to be studied in a conditioned taste-aversion procedure. In a typical procedure, researchers give water-deprived rats access to two water bottles. One bottle contains the usual tap water, whereas the other bottle contains a novel, and often sweet-tasting, solution. After overcoming a neophobic reaction—that is, a rat’s natural fear response to ingesting novel substances—rats consume the novel solution.

After a session in which rats consume the novel-tasting substance, researchers conduct one or multiple pairing sessions with a drug or its placebo. The timing of a drug injection is set to produce noxious effects after a session when subjects consume the novel substance. We refer to this type of session as a pairing session. A conditioned taste aversion is demonstrated if significantly less solution is consumed during subsequent sessions.

For example, nicotine produces a robust conditioned taste aversion. In one of the earliest characterizations of nicotine in this procedure, Stöferman (1983) conducted repeated pairings over several sessions with nicotine and a flavored solution consisting of either saccharin or sodium chloride. Selected results from this study are shown in Figure 1. Over the course of several trials, the nicotine-paired solutions were consumed less, whereas saline-paired solutions were consumed at the normal level.

Although conditioned taste aversion appears to be only a measure of adverse effects, this

Nitrosamines
Chemicals shown to produce cancerous tumor growth

as nitrosamines. Nitrosamines are chemicals shown to produce cancerous tumor growth. The release and inhalation of tar from smoked tobacco provides direct contact of these carcinogens with tissue in the mouth, throat, esophagus, and lungs. E-liquids used for e-cigarettes tend to have low to no levels of nitrosamines (Pisinger & Døssing, 2014). Although safer in this regard, e-cigarette vapors include chemicals with potential to damage cells in the lungs, including aldehydes, which provide different flavorings for e-liquids, and formaldehyde (Pisinger & Døssing, 2014; Rowell & Tarran, 2015). The content of these and other chemicals varies considerably, however, across different e-liquid brands, as noted earlier.
Nicotine and Caffeine

Chapter 7

is not necessarily the case. For many recreational drugs, the doses used to achieve positive subjective effects are the same doses effective for producing conditioned taste aversions (Wise, Yokel, & Wit, 1976).

Smoked tobacco is a cause of pulmonary diseases such as emphysema, a type of chronic obstructive pulmonary disease (typically abbreviated as COPD) caused by irreversible lung damage (Figure 7.16). The symptoms of emphysema include shortness of breath, wheezing, chronic cough, and fatigue. Emphysema patients are treated with a bronchodilator inhaler such as albuterol to open lung passages.

Tobacco use also increases the risk of cardiovascular disease. Nicotine in tobacco causes arteries and blood vessels to narrow and constrict, increasing heart rate. Together, these effects increase the risk of heart attack, stroke, and diseases associated with impoverished blood to flow to other organs.

Copyright ©2018 by SAGE Publications, Inc.
This work may not be reproduced or distributed in any form or by any means without express written permission of the publisher.
During pregnancy, tobacco causes slower gestational development, preterm births, and low birth weight. Any number of chemicals in smoked tobacco can interfere with prenatal development, but reduced oxygen to the fetus is a significant contributor. Women who smoke also have an increased risk of breast cancer and may begin menopause at an earlier age than women who don’t smoke (Perkins, 2001).
Nicotine and Psychological Dependence

As noted at the beginning of this chapter, seven tobacco company CEOs famously testified that nicotine is non-addictive. This opinion, of course, lies in the best interest of tobacco companies, which seek to minimize tobacco regulation. Beyond this conflict of interest, the basis for their opinion depends on the different ways drug addiction has been defined.

As described in Chapter 5, traditional notions of drug addiction were largely based on opioids and alcohol. For drugs like these, addiction appears as intense motivation to seek and use a substance, often at the expense losing one’s career or jeopardizing relationships with friends or family. When considering addiction as only this, the CEOs likely felt comfortable asserting the non-addictive nature of nicotine.

The American Psychiatric Association’s *Diagnostic and Statistical Manual* (DSM-5), however, offers other features of *substance use disorders*; namely, that individuals express difficulty quitting or reducing use. When nicotine use discontinues, chronic users may experience a collection of psychological withdrawal symptoms called the *nicotine abstinence syndrome*, which is characterized by craving, irritability, anxiety, hostility, concentration difficulties, impatience, and insomnia. Avoidance of nicotine’s withdrawal effects is an important contributor to tobacco usage. Based on the dependence criteria described in the DSM, nicotine is an addictive substance. Further, as described previously in this chapter, nicotine exhibits a rapid tolerance to both

### STOP & CHECK

1. During sustained use, nicotine produces a(n) _______________ in locomotor activity.

2. Nicotine improves two particular aspects of attention: orientation to a stimulus and _______________.

3. On first using nicotine, the positive subjective effects are overshadowed by _______________ effects.

4. How might the reinforcing effects of tobacco differ in magnitude from the reinforcing effects of nicotine?

5. Many of the adverse effects associated with nicotine actually result from _______________, the nicotine vehicle.

6. Repeated nicotine use causes an upregulation of nicotinic receptors, which is the result of _______________ of nicotinic receptors.

---

**Nicotine abstinence syndrome** Nicotine withdrawal symptoms characterized by craving, irritability, anxiety, hostility, concentration difficulties, impatience, and insomnia.
physical and psychological effects during chronic use. Given our modern conceptions of substance dependence, few people would agree with a tobacco company’s claims that their products do not cause addiction.

**Environmental, Genetic, and Receptor Differences Between Light and Heavy Tobacco Users**

Humans vary in their susceptibility to nicotine addiction. People who are the most resistant to nicotine addiction are called **chippers**. These are light smokers who fail to develop an addiction to tobacco. **Chippers** are long-term smokers, but they typically smoke only a few cigarettes a day. They make up approximately one-third of all smokers (Shiffman, 1989). The term *chipper* can also be applied, as a slang term, to any occasional user of abused drugs.

Chippers smoke cigarettes the same way as normal smokers—that is, they fully inhale tobacco smoke, have the same puff duration, and have the same interval times between puffs (Brauer, Hatsuksami, Hanson, & Shiffman, 1996). Chippers and regular smokers have similar abilities to absorb and metabolize nicotine. However, chippers fail to show significant pharmacological effects from tobacco, and they fail to exhibit withdrawal symptoms when deprived of tobacco.

Exactly how chippers resist nicotine addiction is unknown. Two possible explanations concern environmental and genetic factors. For an environmental explanation, Shiffman (1989) found that chippers, more often than smokers, had greater coping skills, less stress, and better social support structures. These psychosocial factors may reduce an individual’s risk of developing a substance addiction.

Genetically, chippers and chronic smokers differ in gene expression for $\alpha_5$, $\alpha_3$, and $\beta_4$ receptor subunits, which are found on chromosome 15 (Saccone et al., 2007). Of these, the single nucleotide polymorphism Chrna4 for the $\alpha_5$ unit is particularly associated with greater risk of nicotine dependence. Although this subunit has not been directly implicated in the reinforcing effects of nicotine, this subunit alters state changes from active to desensitized in $\alpha_5$ subunit-containing nicotinic receptors (Ramirez-Latorre et al., 1996). As noted already in this chapter, $\alpha_4\beta_2$ receptors facilitate the reinforcing effects of nicotine.

These genetic variations suggest that differences in nicotinic receptors may facilitate the resistance of chippers for nicotine addiction. In particular, chippers may have weaker acute tolerance to the effects of nicotine because of diminished desensitization of nicotinic receptors. Reduced acute tolerance to nicotine would produce longer-lasting effects (Rosecrans, 1995).

To better understand nicotine tolerance in chippers, animal studies have assessed the association between nicotinic receptor desensitization and acute tolerance. For example, rats that differed in nicotinic receptor desensitization were studied in the conditioned taste-aversion procedure study by Prus and colleagues (2007) described previously. As in the earlier experiment, rats were injected with nicotine both 90 minutes and 5 minutes before a pairing session. The rats used for this experiment were either normal or had diminished nicotinic receptor desensitization. In the normal rats, saccharin consumption increased the following day because the injection of
nicotine 5 minutes before the pairing session occurred during the nicotine receptors’
desensitized state, preventing aversive effects. However, in the rats with diminished
nicotinic receptor desensitization, saccharin consumption decreased the following
day because the receptors were not desensitized and thus did not prevent aversive
effects (Figure 7.17).

These data suggest that differences in nicotinic receptor desensitization differ
between individuals and that these differences significantly alter acute tolerance to
nicotine.

**FIGURE 7.17** Nicotine administered during the desensitized nicotinic-
receptor state produces a conditioned taste aversion in rats
that exhibit reduced nicotinic-receptor desensitization. See
text for further details.

**STOP & CHECK**

1. Chippers smoke without developing a nicotine addiction, possibly because they
   exhibit weaker __________ tolerance to nicotine.

2. Which subunit of the nicotinic receptor appears most related to reduced sensi-
tization of nicotinic receptors?
Humans learn to use tobacco for many reasons. Many people begin smoking because their friends smoke. Smoking may also be common in an individual’s family or culture. Tobacco advertisers market cigarettes as fun, cool, sexy, and rebellious. Not too long ago, workers who smoked were allowed frequent short smoke breaks, whereas non-smokers had to continue working.

As smoking persists, an addiction to nicotine develops, serving as the primary reason for tobacco use. For frequent smokers, the effects of nicotine become associated with routine, everyday activities such as talking on a phone, watching TV, or working on a computer. Associative learning processes incentivize these conditioned responses, leading to the preoccupation and anticipation features of addiction as described in Chapter 5. Without having a cigarette, these stimuli lead to craving tobacco, which makes quitting difficult.

Many people succeed in quitting tobacco “cold turkey,” while others need to participate in a treatment plan. Many psychotherapeutic approaches address the behavioral cues that trigger a craving to smoke. Smokers learn to identify the causes of these cravings and make attempts to diminish the influence of these cravings. No matter the method, studies generally show that reaching 2 weeks of tobacco abstinence most strongly predicts long-term success.

Looking into the 2-week success correlation, Lussier and colleagues (2005) examined smokers using choice comparisons between desire to smoke versus earning small amounts of money among those who successfully or unsuccessfully abstained from smoking after 2 weeks. They found that far fewer of the abstinent smokers selected a desire to smoke over an option to earn money when given the choice. However, those still smoking after 2 weeks more often selected the desire to smoke option. Thus, the rewarding value of tobacco appears to weaken after reaching 2 weeks of tobacco abstinence. We also learn that 2 weeks of tobacco abstinence leads to less craving when exposed to stimuli associated with former tobacco use (Bradstreet et al., 2014).

Many treatment plans also employ pharmacological strategies in order to address the absence of nicotine in the body. As described previously, nicotinic receptors are upregulated during chronic nicotine administration, creating a need for nicotine to maintain this sensitized state. An abrupt drop in nicotine levels leaves these extra receptors inactivated, leading to withdrawal symptoms. Therefore, pharmacological treatments mostly fall into one of three categories: nicotine-replacement therapy, nicotinic-receptor agonism, and antidepressant drugs (Polosa & Benowitz, 2011).

**Nicotine replacement therapy** consists of using a non-tobacco nicotine product to minimize or prevent withdrawal symptoms. Nicotine replacement therapy products include nicotine skin patches, gum, nasal spray, and inhalers. To reduce their dependence on nicotine, users gradually reduce the dose of nicotine used until they reach a point where few withdrawal symptoms occur in the absence of nicotine. This approach may take weeks or prevent withdrawal months.

Yet even with regard to use of nicotine-replacement products, studies show that long-term smoking success relies on complete cessation of smoking. Kenford and colleagues...
(1994) evaluated smoking abstinence success among participants using a nicotine patch. In one of their experiments, they found that the 41 percent who were not smoking after 2 weeks from using the patch were still abstinent at a 6-month follow-up. These findings contrast dramatically with those using a patch but still smoking after 2 weeks using the patch: at a 6-month follow-up, 97 percent were still smoking. These and subsequent studies reveal that reaching 2 weeks of tobacco abstinence strongly predicts long-term success.

Nicotinic-receptor agonist medications also reduce withdrawal symptoms. The first drug approved from this class approved by the Food and Drug Administration is varenicline (Chantix), a partial agonist for nicotinic receptors (Coe et al., 2005). By acting as a partial agonist, less activation of nicotinic receptors occurs compared to a full agonist like nicotine. Varenicline also binds to the nicotine receptors that nicotine would normally bind to, preventing nicotine’s effects. This may reduce the amount of dopamine released compared to nicotine, but some dopamine release also serves to substitute for nicotine’s effects, which may help with nicotine withdrawal. When varenicline is taken, users report that smoking becomes less enjoyable and overall produces weaker effects (Gonzales et al., 2006; Polosa & Benowitz, 2011). However, these pharmacological actions tend to reduce smoking in fewer than half of all smokers (Gonzales et al., 2006).

**Drug Profile: varenicline**

| Trade name: | Chantix |
| Mechanism of action | Partial agonist for nicotinic receptors |
| Uses | Reduces withdrawal symptoms from nicotine dependence |

Antidepressant drugs reduce smoking by addressing nicotine’s effects on dopamine by acting as dopamine reuptake inhibitors. The most commonly prescribed antidepressant drug for nicotine cessation is bupropion (Zyban or Wellbutrin). By blocking reuptake of dopamine, bupropion elevates dopamine levels within synapses. Researchers hypothesize that when this occurs in the nucleus accumbens, the elevated dopamine levels compensate for dopamine elevations normally produced by nicotine. Although this drug produces pharmacological actions suggestive of reducing smoking, fewer than one-third of patients in clinical studies have successfully abstained from smoking when taking bupropion (Gonzales et al., 2006).

**Drug Profile: bupropion**

| Trade name: | Zyban or Wellbutrin |
| Mechanism of action | Blocks reuptake of dopamine |
| Uses | Reduces withdrawal symptoms from nicotine dependence by substituting for nicotine’s rewarding effects |
No matter the cessation treatment, rates of successful abstinence remain poor overall. There appear to be trends depending on gender, race, and socioeconomic status. In one study, Piper and colleagues (2010) evaluated 2,850 smokers enrolled in different types of cessation trials, including nicotine replacement therapies, bupropion, or a combination of bupropion and a nicotine replacement strategy. The smokers group consisted of men and women of either African or European American descent as well as different levels of socioeconomic status. After 6 months, the researchers found greater abstinence among men (vs. women), European Americans (vs. African Americans), and those with higher socioeconomic status (vs. low socioeconomic status). A combination of bupropion with a nicotine replacement product was most effective in men, whereas none of the therapies appeared ideal for African Americans. No matter the demographic characteristics or therapy used, none of the groups achieved greater than approximately 50 percent smoking abstinence at a 6-month follow-up.

In another examination of sex differences in smoking, Cosgrove and colleagues (2012) examined sex steroid hormone levels and used single-photon emission tomography (typically abbreviated as SPECT) to examine $\beta_2$-containing nicotinic receptor levels in smoking and nonsmoking men and women. They found that men who smoke express up-regulation of $\beta_2$ nicotinic receptors compared to men who do not smoke, while no upregulation was observed in women who smoke. Further, during the luteal phase when progesterone levels are high, women who smoked expressed greater cravings to smoke and more symptoms or nicotine withdrawal compared to the follicular phase when estradiol slowly rises from low levels during the phase and progesterone levels are low. These findings might suggest why nicotine replacement products appear less effective in women (i.e., no change in $\beta_2$ nicotinic receptor levels) and why women appear less susceptible to smoking relapse if therapy begins during the luteal phase of the menstrual cycle (Allen, Allen, Lunos, & Hatsukami, 2009). Overall, there remains much to learn about tobacco addiction and a great need for improved treatment approaches.

STOP & CHECK

1. Given that the first use of nicotine causes aversive effects, why does tobacco use continue?
2. Why are nicotine replacement therapies helpful for tobacco cessation programs?

Behavioral reasons account for the persistence of tobacco use at tolerance to adverse effects of nicotine withdrawal symptoms.

1. Behavioral reasons account for the persistence of tobacco use at tolerance to adverse effects of nicotine withdrawal symptoms.
2. Nicotine replacement therapy helps address these behavioral changes through the gradual reduction in physiological dependence. Genetic Nicotine Replacement System - nicotinic receptor - adenylyl cyclase system - produce a gradual reduction in physiological dependence.
Caffeine

Caffeine is a psychostimulant compound and a member of the xanthine chemical class. Other xanthines, including theobromine and theophylline, also exhibit psychostimulant effects. Caffeine is by far the most used. Approximately 90 percent of Americans consume caffeine on a regular basis and average about 227 milligrams (mg) of caffeine per person each day (Frary, Johnson, & Wang, 2005). Best estimates indicate that children consume about half the caffeine as adults, although data on young children are generally lacking (Temple, 2009). In one study, average caffeine intake consisted of 52 mg in 5–7 year olds and 109 mg in 8–12-year-olds (Warzak, Evans, Floress, Gross, & Stoolman, 2011).

Caffeine and Related Compounds in Plants

Caffeine, and to a lesser extent other xanthine compounds, exist in many plants grown naturally in the environment. Caffeine, theobromine, and theophylline are found in kola nuts and cocoa tree nuts, which we use for cola soft drinks and chocolate, respectively. Colas contain caffeine from kola nuts, and chocolate has caffeine from cocoa nuts. A large variety of tea leaves also contain caffeine, theobromine, and theophylline. Coffee beans, which are brewed for coffee drinks, are a significant source of caffeine. Because caffeine represents the most-used and strongest-acting compound among naturally occurring xanthines, this section of the chapter focuses on the use and properties of caffeine.

The caffeine content among products varies. A 10-ounce (oz.) cup of regular coffee contains approximately 200 mg of caffeine, and a 16-oz. coffee contains approximately 320 mg of caffeine. For coffee, the caffeine content varies, in part, with roasting time. Darker roast coffees, which are roasted longer, tend to have less caffeine content than lighter roast coffees. A 10-oz. cup of tea contains approximately 100 mg of caffeine, or half as much caffeine as coffee. A 1-oz. piece of chocolate contains approximately 25 mg of caffeine. Figure 7.18 lists the caffeine content of other popular substances.

Energy drinks are rapidly growing in popularity because of their invigorating properties. They contain a large amount of caffeine, often around 200 mg. Beyond describing energy-enhancing effects, advertisers also promote energy drinks for weight loss, physical stamina, and athletic performance. Individuals 25 years and younger, including a significant portion of children 12 and younger, consume nearly half of all energy drinks. College students report that between 39 percent and 57 percent had consumed energy drinks within the previous month (Malinauskas, Aeby, Overton, Carpenter-Aeby, & Barber-Heidal, 2007; Miller, 2008). Energy drinks are the fastest-growing beverage in the United States, accounting for $9 billion in sales in the United States in 2011 (Arria & O’Brien, 2011).

Energy drinks include not only caffeine as a direct ingredient but also may include caffeinated products such as kola nut, yerba maté, and cocoa. They often include other xanthines such as theobromine and theophylline. Many other chemicals in energy drinks, including sugar and a variety of herbs, amino acids, and plant extracts, promote energy-enhancing effects (Arria & O’Brien, 2011).
Alcoholic beverages have become a source of caffeine. These beverages, referred to as **caffeinated alcoholic beverages**, consist of mixing energy drinks such as Red Bull with alcohols such as vodka. Many concoctions are now sold this way, including Four Loko, a popular alcohol and energy drink beverage now banned in many states. The energy drink component of these beverages can temporarily counter alcohol’s intoxicating effects, thus facilitating excessive drinking and an increased risk of alcohol poisoning.

**Caffeine Has an Ancient History**

The plant products just listed were consumed long before the Europeans discovered them. Teas were used in China for thousands of years, and coffee beans were brewed in Arabia since at least A.D. 1000. In South and Central America, the Olmec, Maya, Toltec, and Aztec cultures consumed cocoa beans. European explorers subsequently brought cocoa seeds to Europe, and Europeans harvested the seeds and commonly prepared cocoa with sugars and milk to make chocolate drinks and candies.
The very first human discoveries of the invigorating properties of these plants are shrouded in stories passed through an oral history, as reviewed by Fredholm (2011). For example, scholars often report a story about an Ethiopian named Kaldi as the discoverer of coffee. Kaldi observed that his goats became excited after consuming berries from a coffee bush, which he confirmed on trying the berries himself.

Before A.D. 1000, people normally consumed coffee by eating coffee beans, but around A.D. 1000, brewed coffee became popular. Brewed coffee became a social drink in Arabia, and students and scholars consumed coffee in intellectual centers. In fact, a type of coffee bar consumed in intellectual centers in Turkey was given the name mekteb-i-irfan, meaning “the school of the wise.”

Coffee was not immediately accepted in Europe, and an attempt to persuade Pope Clement VIII (reign 1592 to 1605) to officially ban this “Muslim drink” led him to state, “This satanic drink is in truth so good that it would be a pity if only nonbelievers were allowed to drink it. We will fool Satan and baptize it so that it becomes a Christian drink, with no danger for the soul.” Thus, any social barriers to coffee consumption in Europe soon fell.

The first European cafés appeared in the early 1700s. These cafés were male-only establishments that not only served coffee but also sold newspapers and cultural reviews. The British, however, preferred tea, possibly because of the influence of the British East India Company, which facilitated a strong tea trade with India. Russia also preferred tea over coffee, possibly because of that nation’s ties with China.

Friedlieb Runge first extracted caffeine in 1819, and Emil Fischer identified caffeine’s chemical properties in 1881. Other xanthene discoveries came later. Theobromine was first extracted in 1841, and Fischer discovered its chemical structures in 1882. Soon after this, Fischer discovered theophylline, another xanthine.

STOP & CHECK

1. In addition to coffee, teas, and soda, energy drinks are a major source of ______________.
2. Coffee beans have been brewed since at least A.D. 1000 in ______________.

Caffeine Absorption, Duration, and Interaction With Other Psychoactive Drugs

Caffeine products are administered orally, in the form of beverages, food, or pills. Coffee contains a number of acids, called chlorogenic acids, that lower the pH of coffee to generally between from 5 to 6 with caffeine itself a weak base (Fujioka & Shibamoto, 2008). Once ingested, 100% percent of caffeine is absorbed through intestinal walls,
reaching peak blood levels after approximately 40 minutes (Blanchard & Sawers, 1983; Liguori, Hughes, & Grass, 1997). Caffeine penetrates both brain and placental blood barriers. The liver metabolizes caffeine primarily by the enzyme CYP-1A2 and, to a lesser extent, by the enzyme CYP-2E1. Most individuals metabolize approximately 90 percent of caffeine, although the amount of caffeine metabolized depends on the activity of these enzymes. For example, individuals with reduced CYP-1A2 enzymatic activity metabolize less caffeine, subsequently prolonging caffeine’s pharmacological effects.

Enzymatic involvement with other drugs also may alter the metabolism rate for caffeine. For example, many antidepressant drugs are CYP-1A2 enzyme inhibitors. Thus, individuals who take these antidepressant drugs metabolize less caffeine. Given that caffeine can produce anxiousness (see “Pharmacological Effects” later in chapter), this interaction effect may weaken an antidepressant drug’s effectiveness if caffeine intake is not monitored (Fredholm & Arnaud, 2011). At the same time, smoking enhances CYP-1A2 activity, resulting in increased metabolism of caffeine (Begas, Kouvaras, Tsakalof, Papakosta, & Asprodini, 2007; Joeres et al., 1988).

The metabolism of caffeine produces active metabolites that, like caffeine, belong to the xanthene class of drugs (Figure 7.19). In particular, these metabolites include theophylline, theobromine, and another xanthine compound with related psychoactive effects, paraxanthine. Unlike theophylline and theobromine—which, as stated earlier, occur naturally in plants—paraxanthine occurs only when metabolically converted from caffeine. The relative distribution of metabolites produced from caffeine consists of 70–80 percent paraxanthine, 7–8 percent theophylline, and 7–8 percent theobromine (Begas et al., 2007).

**FIGURE 7.19** The liver enzymes CYP-1A2 and CYP-2E1 convert caffeine into xanthine metabolites, including theophylline and theobromine. The dashed arrow indicates that less conversion occurs from CYP-1A2 to theophylline and theobromine.

![Diagram of caffeine metabolism](image)
The body primarily eliminates caffeine through the kidneys. The rate of elimination varies widely from approximately 3 to 10 hours (Blanchard & Sawers, 1983). The range in elimination rates may explain why some individuals have difficulty sleeping at night if they drink coffee in the afternoon, whereas other individuals have no difficulty sleeping at night after drinking coffee in the evening. Cigar or cigarette smoking doubles the rate of caffeine elimination because of the previously mentioned increased metabolic activity (Joeres et al., 1988). Because of this increased elimination rate, smokers may drink more coffee to maintain caffeine’s effects.

Caffeine: Antagonist for Adenosine Receptors

Caffeine’s primary mechanism of action is antagonism of adenosine A1 and A2 receptors. Adenosine is a neuromodulator that has inhibitory effects on neurons throughout the central and peripheral nervous system. In particular, adenosine has inhibitory effects on cholinergic neurons in the cerebral cortex and on dopamine neurons in the basal ganglia. Through these actions, we know adenosine as a chemical that contributes to sleepiness. By blocking adenosine receptors, caffeine prevents the inhibitory influence of adenosine within these parts of the brain, thus promoting alertness (Fisone, Borgkvist, & Usiello, 2004).

Caffeine: Mild Psychostimulant Effects

Caffeine exhibits many physiological, behavioral, and subjective effects, including increased heart rate, blood vessel constriction, breathing rate, reduced appetite, attention, alertness, and positive mood. Caffeinated products usually are consumed for their fatigue-fighting properties and are commonly consumed by people in the morning after waking up (Brecher, 1972) and when attempting to stay alert at work (Ker, Edwards, Felix, Blackhall, & Roberts, 2010).

Consuming high doses of caffeine leads to caffeineism, a condition characterized by agitation, anxiety, insomnia, and negative mood as well as rapid heart rate and high blood pressure. This condition can occur at doses of 500 to 1,000 mg of caffeine, although tolerance to caffeine may require higher doses before a person exhibits caffeineism.

STOP & CHECK

1. How can enzymatic activity in the liver influence caffeine’s effects?
2. Caffeine is an antagonist for ________ receptors.

Caffeinism Condition characterized by agitation, anxiety, insomnia, and negative mood as well as rapid heart rate and high blood pressure

Adenosine A neuromodulatory that has inhibitory effects on neurons throughout the central and peripheral nervous system

Caffeineism Condition characterized by agitation, anxiety, insomnia, and negative mood as well as rapid heart rate and high blood pressure

Copyright ©2018 by SAGE Publications, Inc. This work may not be reproduced or distributed in any form or by any means without express written permission of the publisher.
Based on the high caffeine content and the presence of other stimulant chemicals, the risk of adverse effects for energy drinks may be greater than for coffee, tea, and other traditional caffeinated products. In addition to caffeine’s adverse effects, energy drink ingredients can cause hypertension, abdominal pain, and seizures when administered at high enough quantities. Moreover, the chemical ingredients in energy drinks can interact with psychoactive medications. For example, two ingredients found in many energy drinks—5-hydroxytryptophan and yohimbine—can strengthen the adverse effects of antidepressant drugs (Arria & O’Brien, 2011).

**Tolerance and Dependence During Sustained Caffeine Use**

Tolerance occurs with many of caffeine’s acute subjective effects, including positive mood, improved alertness, and anxiousness, whereas tolerance may not occur with caffeine’s physiological effects, including changes in cardiovascular activity and blood vessel constriction (Hughes, Oliveto, Liguori, Carpenter, & Howard, 1998; Sigmon, Herning, Better, Cadet, & Griffiths, 2009). Daily consumption also leads to features of dependence, as demonstrated by the occurrence of withdrawal symptoms when first discontinuing use. In one survey, Juliano and colleagues (2012) recorded the prevalence of withdrawal symptoms among adult respondents who expressed interest in reducing or quitting caffeine use (Figure 7.20). These individuals reported an average of

![Figure 7.20](image.png)

**FIGURE 7.20** Many study respondents who reported a desire to reduce and quit caffeine reported withdrawal symptoms.

SOURCE: Data from Juliano et al., 2012.
548 mg of caffeine per day, approximately double the normal daily average intake for U.S. adults (Frary et al., 2005). Nearly 90 percent experienced headaches, and approximately 85 percent experienced cravings for caffeine. Other common withdrawal symptoms included difficulty in concentrating, fatigue, irritability, and anxious or depressed mood. The study authors also noted that more than 40 percent of participants felt functionally impaired without caffeine. These symptoms are also described for caffeine withdrawal in the DSM-5 (American Psychiatric Association, 2013).

STOP & CHECK

1. An increase in positive mood is one of the many ____________ effects of caffeine.
2. Excessive doses of caffeine can produce ____________, which is characterized by agitation, anxiety, insomnia, and other symptoms.
3. Other chemicals in energy drinks may interact with _________ drugs, causing an increase in adverse effects.
4. In the absence of caffeine, hostility, fatigue, and negative mood are indications of ________ on caffeine.

From Actions to Effects: Why People Consume Caffeinated Products

Improvements in mood and alertness are common reasons for seeking caffeinated products such as coffee, tea, and other caffeinated beverages. Moreover, these and other products, such as chocolate, taste good, which adds to their appeal. Yet during the course of repeated use, a dependence on caffeine, as indicated by withdrawal symptoms, may facilitate consumption of caffeinated products.

Given the prevalence of caffeine use, most readers of this text probably consume caffeinated products on a daily basis. In particular, you may use coffee, a soft drink, or an energy drink to help wake up in the morning. If this describes you, then consider this: Is the tiredness you feel in the morning natural—or is it caffeine withdrawal?

Assuming that you do not consume a caffeinated product within several hours before bedtime, sleeping 6–8 hours may provide for a total caffeine abstinence period of about 10–12 hours. This abstinence period exceeds caffeine’s elimination half-life, suggesting that your body’s caffeine levels will be low or absent by morning. Indeed, many studies describe morning as an early withdrawal state for chronic caffeine users (James & Rogers, 2005). Thus, for most people, caffeine’s ability to fight morning sleepiness may have a lot to do with removing caffeine’s withdrawal symptoms.

The DSM-5 considers caffeine intoxication, generally similar to caffeinism presented earlier, and caffeine withdrawal as two potential disruptive features of caffeine use.
Although the DSM-5 does not consider caffeine as generating a specific substance-use disorder, some clinical studies characterized problem caffeine use as meeting the general features of a disorder (Bernstein, Carroll, Thuras, Cosgrove, & Roth, 2002; Griffiths & Chausmer, 2000). In an assessment of caffeine dependence, Bernstein and colleagues (2002) evaluated caffeine use among a sample of U.S. teenagers. Among the 36 teenagers assessed, 22.2 percent exhibited a sufficient number of symptoms to meet the DSM diagnostic criteria for a substance use disorder. The most commonly observed symptoms included tolerance, withdrawal symptoms, desire to quit or unsuccessful efforts to control use, and continued use despite physical or psychological problems. The total group of teenagers studied reported 244 mg of caffeine per day, with values ranging from as little as 49 mg to as much as 767 mg of caffeine per day.

Although some researchers support applying substance use disorder criteria to caffeine use, others are unconvinced. In a review of scientific studies that assessed caffeine use, Satel (2006) concluded that caffeine does not meet substance dependence criteria. Key points in Satel’s study consist of weak or inconsistent reporting of withdrawal effects and a failure to demonstrate strong compulsions to use caffeine. Given that caffeine appears neither irresistible nor a cause of social disruption, Satel argues that caffeine fails a common-sense test as an addictive substance.

**Chapter Summary**

This chapter has covered two widely used psychostimulant drugs: nicotine and caffeine. Tobacco products are the key source of nicotine. Cigarette smoking is the most common form of nicotine administration, but other forms of tobacco such as smokeless tobacco and e-cigarettes are popular as well. Tobacco use has a long history, dating back to the ancient uses in the Americas and then reaching Europe after Columbus’s expedition to the New World.

Nicotine is delivered to the body from tobacco or e-liquids and is absorbed through tissues in the lungs, throat, mouth, and skin. Inhalation is the most efficient route for nicotine delivery. Nicotine is metabolized in the liver, producing cotinine, an active metabolite. Cotinine also is an agonist for these receptors, but it has a much weaker affinity than nicotine. Nicotine increases sympathetic nervous activity and increases locomotor activity during repeated administration. Nicotine also improves attention. Subjectively, nicotine produces adverse effects on first usage, but tolerance to the effects soon subsides to reveal positive subjective effects. Most of nicotine’s adverse effects are the result of tobacco, which contains many known cancer-causing agents. In addition to cancer, tobacco increases the risk of cardiovascular disease and lung disease. Because of desensitization at nicotinic receptors, upregulation of nicotinic receptors occurs during chronic use. Upregulation leads to a sensitized behavioral state.

Nicotine addiction accounts for chronic, habitual tobacco use. Quitting nicotine is difficult in part because of the association of tobacco use with everyday activities. Further, upregulation...
of nicotinic receptors facilitates a physiological dependent state, requiring sustained elevated nicotine levels for normal functioning.

Caffeine is a xanthine psychostimulant drug found naturally in kola nuts, cocoa tree nuts, and tea leaves. The most common caffeine sources include coffee, tea, and energy drinks. Caffeine-containing leaves and nuts were long used in China and Arabia, and teas and coffee were used throughout Europe beginning in the 1700s.

Caffeine is orally administered and is metabolized in the liver. Caffeine’s elimination rate varies, depending on liver enzymatic activity. Caffeine’s effects are derived through antagonism of adenosine receptors, not only producing an improvement in alertness, mood, and energy, but also a facilitation of dopamine’s effects on the sympathetic nervous system. Excessive caffeine intake produces caffeinism, which is characterized by agitation, anxiety, and negative mood. Tolerance soon develops to caffeine’s effects during chronic use, and continued caffeine use is mostly maintained by avoidance of caffeine-withdrawal symptoms.

Key Terms

Nicotine 204
Cigarette 204
Cigar 204
Hookah 205
Smokeless tobacco 206
E-cigarette 207
Vaping 208
Secondhand smoke 210
Thirdhand smoke 210
Flue curing 213
Tar 213
Cotinine 214
Functional antagonism 216
Upregulation 216
Acute tolerance 220
Nitrosamines 226
Emphysema 227
Nicotine abstinence syndrome 229
Chippers 230
Nicotine replacement therapy 232
Caffeine 235
Caffeinated alcoholic beverages 236
Caffeinism 239
Adenosine 239

Visit the Student Study Site at study.sagepub.com/prus2e to access additional study tools, including eFlashcards, web quizzes, video resources, web resources, SAGE journal articles, and more.