

# Tobacco Use and Dependence

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Long before Christopher Columbus traveled to the New World, tobacco use was widespread in the Americas—tobacco preparations were part of religious ceremonies for the Native Americans, and tobacco was also used medicinally. At that time, and for several subsequent centuries, little was known or suspected about the dangers of tobacco use. In retrospect, it is not surprising that these dangers were not recognized initially because the more pressing health issues at that time were related to life-threatening, acute diseases as opposed to chronic diseases such as those imposed by tobacco. However, it is now well established that tobacco is a detrimental substance, and its use dramatically increases a person's odds of dependence, disease, disability, and death.

Cigarettes are the only marketed consumable product that when used as intended will contribute to the death of half or more of its users.<sup>1</sup> Tobacco products are carefully engineered formulations that optimize the delivery of nicotine, a chemical that meets the criteria for an addictive substance: (a) nicotine induces psychoactive effects, (b) it is used in a highly controlled or compulsive manner, and (c) behavioral patterns of tobacco use are reinforced by the pharmacologic effects of nicotine.<sup>2</sup> As a major risk factor for a wide range of diseases, including cardiovascular conditions, cancers, and pulmonary disorders, tobacco is the primary known preventable cause of premature death in our society.<sup>3</sup> During the 20th century, 100 million deaths were caused by tobacco, and currently, an estimated

5.4 million deaths occur annually.<sup>3</sup> Unless tobacco control efforts are able to reverse this trend, the number of annual deaths is likely to exceed 8 million by the year 2030.<sup>4</sup> According to Dr. Margaret Chan, Director-General of the World Health Organization, “Reversing this entirely preventable epidemic must now rank as a top priority for public health and for political leaders in every country of the world.”<sup>4</sup>

In the United States, smoking is responsible for approximately 438,000 premature deaths each year.<sup>5</sup> In addition to the harm imposed on users of tobacco, exposure to secondhand smoke results in an estimated 50,000 deaths each year.<sup>6</sup> Furthermore, enormous economic burden accompanies tobacco use. Each pack of cigarettes smoked costs society \$7.18 for associated medical care (\$3.45) and productivity losses (\$3.73), for a total of \$157 billion in annual health-related economic losses.<sup>5</sup> Because of the health and societal burdens that it imposes, tobacco use and dependence should be addressed during each clinical encounter with all tobacco users.<sup>7</sup>

## EPIDEMIOLOGY OF TOBACCO USE AND DEPENDENCE

Nicotine addiction is a form of chronic brain disease resulting from alterations in brain chemistry.<sup>8</sup> Dr. Alan Leshner, former director of the National Institute on Drug Abuse, defines drug addiction as “compulsive use, without medical purpose, in the face of negative consequences.”<sup>8</sup> The addictive properties of nicotine are well documented.

In the United States, experimentation with cigarettes and the development of regular smoking typically occur during adolescence, with 88% to 89% of adult smokers having tried their first cigarette by 18 years of age<sup>9,10</sup> and 71% of adult daily smokers having become regular smokers by age 18.<sup>9</sup> Because most teens who smoke at least monthly continue to smoke in adulthood,<sup>9</sup> tobacco use trends among youth are a key indicator of the overall health trends for the nation.<sup>11</sup> According to the Centers for Disease Control and Prevention (CDC), the prevalence of current smoking (defined as having smoked at least one cigarette in the preceding 30 days) among high school students increased throughout the early and mid-1990s,<sup>12</sup> identifying an urgent need for tobacco prevention and cessation programs focused on younger age groups. These have led to subsequent decreases. In 2007, an estimated 21.6% of 12th graders (23.1% of males and 19.6% of females) had smoked one or more cigarettes in the past 30 days.<sup>13</sup>

Among adults, smoking prevalence varies by sociodemographic factors, including sex, race/ethnicity, education level, age, and poverty level. The CDC reported that in 2006, the percentage of current smokers (defined as having smoked 100 or more cigarettes during their lifetime and currently smoking every day or some days) was 20.8% (23.9% of men and 18.0% of women).<sup>14</sup> Table 85-1 summarizes the smoking prevalence estimates for various population subgroups, stratified by sex. In 2006, the highest median prevalence of current smoking was evident in Kentucky (28.6%), and the lowest prevalence was observed in Utah (9.8%).<sup>15</sup> An estimated 44.3% of cigarettes

**Table 85-1** Percentage of Current Smokers<sup>a</sup> Ages 18 Years and Older, by Sex and Selected Characteristics—National Health Interview Survey, United States, 2006

Characteristic	Category	Men (n = 10,715)	Women (n = 13,560)	Total (n = 24,275)
Race/ethnicity <sup>b</sup>	White, non-Hispanic	24.3	19.7	21.9
	Black, non-Hispanic	27.6	19.2	23.0
	Hispanic	20.1	10.1	15.2
	American Indian/Alaska Native, non-Hispanic	35.6	29.0	32.4
	Asian <sup>c</sup>	16.8	4.6	10.4
Education <sup>d</sup>	0–12 years (no diploma)	30.6	23.0	26.7
	GED <sup>e</sup> diploma	51.3	40.2	46.0
	High school diploma	27.6	20.4	23.8
	Associate degree	25.4	17.8	21.2
	Some college	26.1	20.0	22.7
	Undergraduate degree	10.8	8.4	9.6
	Graduate degree	7.3	5.8	6.6
Age group (years)	18–24	28.5	19.3	23.9
	25–44	26.0	21.0	23.5
	45–64	24.5	19.3	21.8
	65 and older	12.6	8.3	10.2
Poverty status <sup>f</sup>	At or above federal poverty level	22.9	17.8	20.4
	Below federal poverty level	34.0	28.0	30.6
	Unknown	23.3	14.2	18.3
<b>Total</b>		<b>23.9</b>	<b>18.0</b>	<b>20.8</b>

<sup>a</sup>Persons who reported having smoked  $\geq 100$  cigarettes during their lifetimes and who, at the time of interview, reported smoking every day or some days. Excludes 315 respondents whose smoking status was unknown.

<sup>b</sup>Excludes 266 respondents of unknown race or multiple races.

<sup>c</sup>Does not include Native Hawaiians and Other Pacific Islanders.

<sup>d</sup>Persons ages 25 years and older, excluding 305 persons whose educational level was unknown.

<sup>e</sup>GED, general educational development.

<sup>f</sup>Based on family income reported by respondents and 2005 poverty thresholds published by the U.S. Census Bureau. From reference 15.

smoked in the United States are among persons with mental illness.<sup>16</sup>

### Factors Contributing to Tobacco Use

Tobacco addiction is maintained by nicotine dependence.<sup>17</sup> Nicotine induces a variety of pharmacologic effects, described as follows, that lead to dependence.<sup>17,18</sup> However, tobacco dependence is not simply a matter of nicotine pharmacology—it is a result of the interplay of complex processes, including the desire for the direct pharmacologic actions of nicotine, the relief of withdrawal, learned associations, and environmental cues (e.g., advertising, the smell of a cigarette, or observing others who are smoking).<sup>17</sup> Physiological factors, such as pre-existing medical conditions (e.g., psychiatric comorbidities<sup>16</sup>) and one's genetic profile, also can predispose individuals to tobacco use. Notably, it has been estimated in twin studies that 40% to 60% of smoking is heritable.<sup>19–21</sup> The rapidity with which nicotine, the addictive component of tobacco, is absorbed and passes through the blood-brain barrier contributes to its addictive nature. After inhalation, nicotine reaches the brain within seconds.<sup>17</sup> As such, smokers experience nearly immediate onset of positive effects of nicotine, including pleasure, relief of anxiety, improved task performance, improved memory, mood modulation, and skeletal muscle relaxation.<sup>17</sup> These effects, mediated by alterations in neurotransmitter levels, reinforce continued use of nicotine-containing products.

### Nicotine Pharmacology

Nicotine (*Nicotiana tabacum*), which is composed of a pyridine ring and a pyrrolidine ring, is one of the few natural alkaloids that exist in the liquid state. Nicotine is a clear, weak base ( $pK_a = 8.0$ ) that turns brown and acquires the characteristic odor of tobacco after exposure to air.<sup>22,23</sup> In acidic media, nicotine is ionized and poorly absorbed; conversely, in alkaline media, nicotine is nonionized and well absorbed. Under physiological conditions ( $pH = 7.3–7.5$ ), approximately 31% of nicotine is nonionized and readily crosses cell membranes.<sup>22,24</sup> Given the relation between pH and absorption, the tobacco industry and pharmaceutical companies are able to titrate the pH of their tobacco products and nicotine replacement therapies (NRTs) to maximize the absorption potential of nicotine.<sup>17,25</sup>

Once absorbed, nicotine induces a variety of central nervous system, cardiovascular, and metabolic effects. Nicotine stimulates the release of several neurotransmitters, inducing a range of pharmacologic effects such as pleasure (dopamine), arousal (acetylcholine, norepinephrine), cognitive enhancement (acetylcholine), appetite suppression (dopamine, norepinephrine, serotonin), learning (glutamate), memory enhancement (glutamate), mood modulation (serotonin), and reduction of anxiety and tension ( $\beta$ -endorphin and GABA).<sup>18</sup> The dopamine reward pathway, a network of nervous tissue that elicits feelings of pleasure in response to certain stimuli, is central to drug-induced reward. Key structures of the reward pathway include the ventral tegmental area, nucleus accumbens, and prefrontal cortex (the area of the brain that is responsible for thinking and judgment). The neurons of the ventral tegmental area contain the neurotransmitter dopamine, which is released in the nucleus accumbens and in the prefrontal cortex. Immediately after inhalation, a bolus of nicotine enters

the brain, stimulating the release of dopamine, which induces nearly immediate feelings of pleasure, along with relief of the symptoms of nicotine withdrawal. This rapid dose response reinforces repeated administration of the drug and perpetuates the smoking behavior.<sup>18</sup>

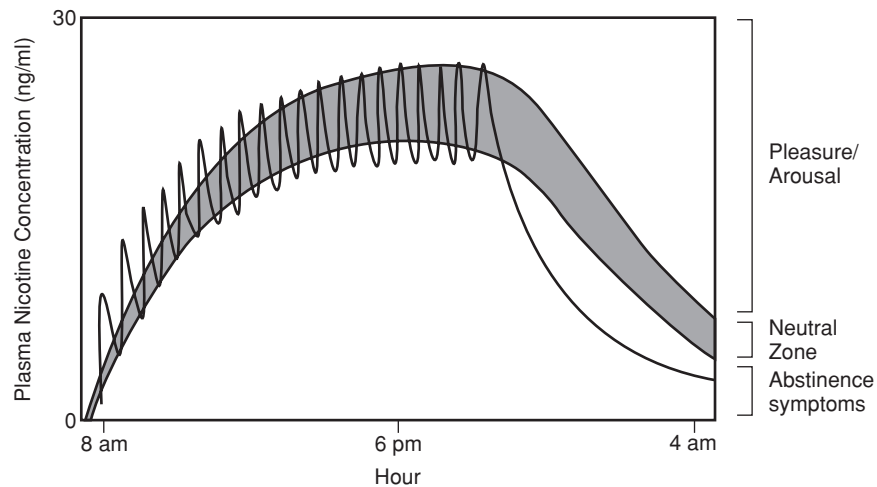
Chronic administration of nicotine has been shown to result in an increased number of nicotine receptors in specific regions of the brain,<sup>26</sup> which is believed to represent upregulation in response to nicotine-mediated desensitization of the receptors and may play a role in nicotine tolerance and dependence.<sup>18</sup> Chronic administration also leads to tolerance to the behavioral and cardiovascular effects of nicotine over the course of the day; however, tobacco users regain sensitivity to the effects of nicotine after overnight abstinence from nicotine, as shown in Figure 85-1.<sup>17,22</sup> Notably, after smoking the first cigarette of the day, the smoker experiences marked pharmacologic effects, particularly arousal. No other cigarette throughout the day produces the same degree of pleasure/arousal. For this reason, many smokers describe the first cigarette as the most important one of the day. Shortly after the initial cigarette, tolerance begins to develop. Accordingly, the threshold levels for both pleasure/arousal and abstinence rise progressively throughout the day as the smoker becomes tolerant to the effects of nicotine. With continued smoking, nicotine accumulates, leading to an even greater degree of tolerance. Late in the day, each individual cigarette produces only limited pleasure/arousal; instead, smoking primarily alleviates nicotine withdrawal symptoms. Lack of exposure to nicotine overnight results in resensitization of drug responses (i.e., loss of tolerance). Most dependent smokers tend to smoke a certain number of cigarettes per day and tend to consume sufficient nicotine per day to achieve the desired effects of cigarette smoking and minimize the symptoms of nicotine withdrawal.<sup>22</sup> Withdrawal symptoms include depression, insomnia, irritability, anxiety, difficulty concentrating, restlessness, and increased appetite.<sup>27–29</sup> Tobacco users become adept at titrating their nicotine levels throughout the day to avoid withdrawal symptoms, maintain pleasure and arousal, and modulate mood.

Nicotine is extensively metabolized in the liver and, to a lesser extent, in the kidney and lung. Approximately 70% to 80% of nicotine is metabolized to cotinine, an inactive metabolite.<sup>17,24</sup> The rapid metabolism of nicotine ( $t_{1/2} = 2$  hours) to inactive compounds underlies tobacco users' needs for frequent, repeated administration. The half-life of cotinine, however, is much longer ( $t_{1/2} = 18–20$  hours), and for this reason, cotinine is commonly used as marker of tobacco use as well as a marker for exposure to secondhand smoke.<sup>17</sup> Cotinine cannot, however, differentiate between the nicotine from tobacco products and the nicotine from NRT products.

Nicotine and other metabolites are excreted in the urine. Urinary excretion is pH dependent; the excretion rate is increased in acidic urine. Nicotine is excreted in breast milk and can be detected in the blood and urine of infants of nursing smokers.<sup>23,24</sup>

### Drug Interactions With Smoking

It is widely recognized that polycyclic aromatic hydrocarbons (PAHs), present in appreciably large quantities in tobacco smoke, are responsible for most drug interactions with smoking.<sup>30,31</sup> PAHs, which are the products of incomplete



**FIGURE 85-1 Nicotine addiction cycle throughout the day.**

- The sawtooth line represents venous plasma concentrations of nicotine as a cigarette is smoked every 40 minutes from 8 am to 9 pm.
- The upper solid line indicates the threshold concentration for nicotine to produce pleasure or arousal.
- The lower solid line indicates the concentrations at which symptoms of abstinence (i.e., withdrawal symptoms) from nicotine occur.
- The shaded area represents the zone of nicotine concentrations (neutral zone) in which the smoker is comfortable without experiencing either pleasure/arousal or abstinence symptoms.

Source: Reprinted from reference 22, with permission.

combustion of tobacco, are potent inducers of several hepatic cytochrome P450 microsomal enzymes (CYP1A1, CYP1A2, and possibly CYP2E1). Although other substances in tobacco smoke, including acetone, pyridines, benzene, nicotine, carbon monoxide, and heavy metals (e.g., cadmium), might also interact with hepatic enzymes, their effects appear to be less significant. Most drug interactions with tobacco smoke are pharmacokinetic, resulting from the induction of drug-metabolizing enzymes (especially CYP1A2) by compounds in tobacco smoke. Table 85-2 summarizes key interactions with smoking.<sup>30,32</sup> Patients who begin smoking, or quit smoking, might require dosage adjustments for some medications.

### Health Consequences of Tobacco Use

Smoking has a causal or contributory role in the development of a variety of medical conditions (Table 85-3).<sup>3</sup> In the United States, tobacco use accounts for nearly 1 in 5 deaths, and an estimated 8.6 million persons suffer from chronic conditions attributable to smoking.<sup>33</sup> Among current smokers, chronic bronchitis is the most common condition (49%), followed by emphysema (24%). Among former smokers, the most prevalent condition is chronic bronchitis (26%), followed by emphysema (24%) and previous heart attack (24%). Lung cancer, the leading cause of cancer-related mortality for both men and women in the United States and a disease for which the 5-year survival rate is approximately 15%,<sup>34</sup> accounts for an estimated 1% of all smoking-attributable morbidity (i.e., among those who are living) in current smokers and 2% in former smokers.<sup>33</sup>

### Secondhand Smoke Exposure

Exposure to secondhand smoke, which includes the smoke emanating from burning tobacco and that exhaled by the smoker, results in an estimated 50,000 deaths annually, in addition to contributing to numerous diseases among nonsmoking chil-

dren and adults.<sup>6</sup> Major conclusions of the 2006 Surgeon General's Health Effects of Involuntary Exposure to Tobacco Smoke<sup>6</sup> report include (a) Many millions of Americans, both children and adults, are still exposed to secondhand smoke in their homes and workplaces despite substantial progress in tobacco control; (b) Secondhand smoke exposure causes disease and premature death in children and adults who do not smoke; (c) Children exposed to secondhand smoke are at an increased risk for sudden infant death syndrome, acute respiratory infections, ear problems, and more severe asthma. Smoking by parents causes respiratory symptoms and slows lung growth in their children; (d) Exposure of adults to secondhand smoke has immediate adverse events on the cardiovascular system and causes coronary heart disease and lung cancer; (e) The scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke; and (f) Eliminating smoking in indoor spaces fully protects nonsmokers from exposure to secondhand smoke. Separating smokers from nonsmokers, cleaning the air, and ventilating buildings cannot eliminate exposures of nonsmokers to secondhand smoke. Supplementing evidence presented in the Surgeon General's report, in January 2006, the California Environmental Protection Agency designated secondhand smoke as a "toxic air contaminant" and, in addition to the list of diseases described in the Surgeon General's report, specified that exposure is associated with breast cancer in younger, primarily premenopausal women.<sup>35</sup>

### Benefits of Quitting

The 1990 Surgeon General's Report on the health benefits of smoking cessation describes numerous and substantial health benefits associated with quitting.<sup>36</sup> Benefits incurred soon after quitting (e.g., within 2 weeks to 3 months) include improvements in pulmonary function, circulation, and ambulation. Within 1 to 9 months of quitting, the ciliary function of

**Table 85-2 Drug Interactions<sup>a</sup> With Smoking**

<i>Drug/Class</i>	<i>Mechanism of Interaction and Effects</i>
<b>Pharmacokinetic Interactions</b>	
Alprazolam (Xanax)	● Conflicting data on significance of a PK interaction. Possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Bendamustine (Treanda)	● Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers due to likely ↓ bendamustine concentrations, with ↑ concentrations of its two active metabolites.
Caffeine	● ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%). ● Likely ↑ caffeine levels after cessation.
Chlorpromazine (Thorazine)	● ↓ Area under the curve (AUC) (36%) and serum concentrations (24%). ● ↓ Sedation and hypotension possible in smokers; smokers may need ↑ dosages.
Clozapine (Clozaril)	● ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%). ● ↑ Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.
Erlotinib (Tarceva)	● ↑ Clearance (24%); ↓ trough serum concentrations (2-fold).
Flecainide (Tambocor)	● ↑ Clearance (61%); ↓ trough serum concentrations (25%). ● Smokers may need ↑ dosages.
Fluvoxamine (Luvox)	● ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%) ↓ plasma concentrations (32%). ● Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Haloperidol (Haldol)	● ↑ Clearance (44%); ↓ serum concentrations (70%).
Heparin	● Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects. ● Smokers may need ↑ dosages due to PK and PD interactions.
Insulin, subcutaneous	● Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance. ● PK & PD interactions likely not clinically significant; smokers may need ↑ dosages.
Irinotecan (Camptosar)	● ↑ Clearance (18%); ↓ serum concentrations of active metabolite SN-38 (~40%; via induction of glucuronidation); ↓ systemic exposure resulting in lower hematologic toxicity and may reduce efficacy. ● Smokers may need ↑ dosages.
Mexiletine (Mexitol)	● ↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).
Olanzapine (Zyprexa)	● ↑ Metabolism (induction of CYP1A2): ↑ clearance (98%); ↓ serum concentrations (12%). ● Dosage modifications not routinely recommended but smokers may require ↑ dosages.
Propranolol (Inderal)	● ↑ Clearance (77%; via side-chain oxidation and glucuronidation)
Ropinirole (Requip)	● ↓ C <sub>max</sub> (38%) and AUC (30%) in study with patients with restless legs syndrome. ● Smokers may need ↑ dosages.
Tacrine (Cognex)	● ↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations three-fold lower. ● Smokers may need ↑ dosages.
Theophylline (Theo Dur, etc.)	● ↑ Metabolism (induction of CYP1A2); ↑ clearance (58–100%); ↓ half-life (63%). ● Levels should be monitored if smoking is initiated, discontinued, or changed. ● ↑ Clearance with second-hand smoke exposure. ● Maintenance doses are considerably higher in smokers.
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	● Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.
Tizanidine (Zanaflex)	● ↓ AUC (30–40%) and ↓ half-life (10%) observed in male smokers.
<b>Pharmacodynamic Interactions</b>	
Benzodiazepines (diazepam, chlordiazepoxide)	● ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.
Beta-blockers	● Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation. ● Smokers may need ↑ dosages.
Corticosteroids, inhaled	● Asthmatic smokers may have less of a response to inhaled corticosteroids.
Hormonal contraceptives	● ↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives. Ortho Evra patch users shown to have 2-fold ↑ risk of venous thromboembolism compared to oral contraceptive users, likely due to ↑ estrogen exposure (60% higher levels). ● ↑ Risk with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women age 35 and older.
Opioids (propoxyphene, pentazocine)	● ↓ Analgesic effect; smoking may ↑ the metabolism of propoxyphene (15–20%) and pentazocine (40%). Mechanism unknown. ● Smokers may need ↑ opioid dosages for pain relief.

<sup>a</sup>Shaded rows indicate the most clinically significant interactions.

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**Table 85-3 Health Consequences of Smoking<sup>3</sup>**

<b>Cancer</b>	Acute myeloid leukemia
	Bladder
	Cervical
	Esophageal
	Gastric
	Kidney
	Laryngeal
	Lung
	Oral cavity and pharyngeal
	Pancreatic
<b>Cardiovascular disease</b>	Abdominal aortic aneurysm
	Coronary heart disease (angina pectoris, ischemic heart disease, myocardial infarction)
	Cerebrovascular disease (transient ischemic attacks, stroke)
	Peripheral arterial disease
	Acute respiratory illnesses
<b>Pulmonary disease</b>	Upper respiratory tract (rhinitis, sinusitis, laryngitis, pharyngitis)
	Lower respiratory tract (bronchitis, pneumonia)
	Chronic respiratory illnesses
	Chronic obstructive pulmonary disease
	Respiratory symptoms
	Poor asthma control
	Reduced lung function
	Reduced fertility in women
<b>Reproductive effects</b>	Pregnancy and pregnancy outcomes
	Preterm, premature rupture of membranes
	Placenta previa
	Placental abruption
	Preterm delivery
	Low infant birth weight
	Infant mortality
Sudden infant death syndrome	
<b>Other effects</b>	Cataract
	Osteoporosis (reduced bone density in postmenopausal women, increased risk of hip fracture)
	Periodontitis
	Peptic ulcer disease (in patients who are infected with <i>Helicobacter pylori</i> )
	Surgical outcomes
	Poor wound healing
	Respiratory complications

the lung epithelial cells is restored; initially, this might result in increased coughing as the lungs clear excess mucus and tobacco smoke particulates. Smoking cessation results in measurable improvements in lung function<sup>37</sup> (see Chapter 23, Fig. 23-1). Over time, patients experience decreased coughing, sinus congestion, fatigue, shortness of breath, and risk of pulmonary infection. One year after cessation, the excess risk of coronary heart disease is reduced to half that of continuing smokers. After 5 to 15 years, the risk of stroke is reduced to a rate similar to that of people who are lifetime nonsmokers, and 10 years after quitting, the chance of dying of lung cancer is approximately half that of continuing smokers. In addition, the risk of developing mouth, throat, esophagus, bladder, kidney, or pancreatic cancer is decreased. Finally, 15 years after quitting, the risk of coronary heart disease is reduced to a rate that is similar to that of people who have never smoked.<sup>36</sup> Smoking cessation can also lead to a significant reduction in the cumulative risk of death from lung cancer, for both men and women.<sup>38</sup>

Quitting at ages 30, 40, 50, and 60 years is associated with 10, 9, 6, and 3 years of life gained, respectively. On average, cigarette smokers die approximately 10 years younger than do nonsmokers, and among those who continue smoking, at least half will die due to a tobacco-related disease. Persons who quit before age 35 add 10 years of life and have a life expectancy similar to those who have never smoked.<sup>1</sup> Reduction in smoking does not equate to a reduction in harm; even low levels of smoking (e.g., 1–4 cigarettes per day) have documented risks,<sup>39,40</sup> and therefore, a reduction in the number of cigarettes smoked per day should be viewed as a positive step toward quitting, but should not be recommended as a targeted end point. For any patient who uses tobacco, the target goal is complete, long-term abstinence from all nicotine-containing products. Thus, it is never too late to quit and to incur subsequent benefits of quitting. But quitting earlier is clearly advantageous.

### Tobacco Use and Dependence: Treatment Approaches

Most tobacco users attempt to quit without assistance, despite the fact that persons who receive assistance are more likely to be successful in quitting.<sup>7,41</sup> Given the complexity of the tobacco-dependence syndrome and the constellation of factors that contribute to tobacco use, treatment requires a multifaceted approach. To assist clinicians and other specialists in providing cessation treatment to patients who use tobacco, the U.S. Public Health Service published the Clinical Practice Guideline for Treating Tobacco Use and Dependence. This document, which represents a distillation of more than 8,700 published articles,<sup>7</sup> specifies that clinicians can have an important impact on their patients' ability to quit. A meta-analysis of 29 studies<sup>7</sup> determined that compared with patients who do not receive an intervention from a clinician, patients who receive a tobacco cessation intervention from a physician clinician or a non-physician clinician are 2.2 and 1.7 times, respectively, more likely to quit (at 5 or more months after cessation). Although even brief advice from a clinician has been shown to lead to increased odds of quitting,<sup>7</sup> more intensive counseling yields more dramatic increases in quit rates.<sup>7</sup>

Numerous effective medications are available for tobacco dependence, and clinicians should encourage their use by all patients attempting to quit smoking—except when medically contraindicated or with specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, adolescents).<sup>7</sup> Although both pharmacotherapy and behavioral counseling are effective independently, patients' odds of quitting are substantially increased when the two approaches are used simultaneously. The estimated efficacies of various treatment strategies are shown in Table 85-4. Clinicians can have a significant impact on a patient's likelihood of success by recommending pharmacotherapy agents and by supplementing medication use with behavioral counseling as described later in this chapter.

### Assisting Patients With Quitting

#### Behavioral Counseling Strategies

According to the Clinical Practice Guideline,<sup>7</sup> five key components comprise comprehensive counseling for tobacco cessation: (a) asking patients whether they use tobacco, (b) advising tobacco users to quit, (c) assessing patients' readiness to quit, (d) assisting patients with quitting, and (e) arranging

**Table 85-4 Efficacy of Treatment Methods for Tobacco Use and Dependence<sup>7</sup>**

Treatment Method	Estimated Odds Ratio <sup>a</sup> (95% CI)	Estimated Abstinence <sup>b</sup> Rate (95% CI)
<b>Behavioral interventions</b>		
<i>Advice to quit</i>		
No advice to quit	1.0	7.9
Physician advice to quit	1.3 (1.1–1.6)	10.2 (8.5–12.0)
<i>Clinician intervention</i>		
No counseling by a clinician	1.0	10.2
Counseling by a nonphysician clinician	1.7 (1.3–2.1)	15.8 (12.8–18.8)
Counseling by a physician	2.2 (1.5–3.2)	19.9 (13.7–26.2)
<i>Format of smoking cessation counseling</i>		
No format	1.0	10.8
Self-help	1.2 (1.0–1.3)	12.3 (10.9–13.6)
Proactive telephone counseling <sup>c</sup>	1.2 (1.1–1.4)	13.1 (11.4–14.8)
Group counseling	1.3 (1.1–1.6)	13.9 (11.6–16.1)
Individual counseling	1.7 (1.4–2.0)	16.8 (14.7–19.1)
<b>Pharmacotherapy interventions</b>		
Placebo	1.0	13.8
<i>First-line agents</i>		
Bupropion SR	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Nicotine gum (6–14 weeks)	1.5 (1.2–1.7)	19.0 (16.5–21.9)
Nicotine inhaler	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Nicotine lozenge (2 mg)	2.0 (1.4–2.8)	24.2 <sup>d</sup>
Nicotine patch (6–14 weeks)	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Nicotine nasal spray	2.3 (1.7–3.0)	26.7 (21.5–32.7)
Varenicline (2 mg/day)	3.1 (2.5–3.8)	33.2 (28.9–37.8)
<i>Second-line agents<sup>e</sup></i>		
Clonidine	2.1 (1.2–3.7)	25.0 (15.7–37.3)
Nortriptyline	1.8 (1.3–2.6)	22.5 (16.8–29.4)
<i>Combination therapy</i>		
Nicotine patch (> 14 weeks) + <i>ad lib</i> NRT (gum or nasal spray)	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Nicotine patch + bupropion SR	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Nicotine patch + nortriptyline	2.3 (1.3–4.2)	27.3 (17.2–40.4)
Nicotine patch + nicotine inhaler	2.2 (1.3–3.6)	25.8 (17.4–36.5)

<sup>a</sup>Estimated relative to referent group.

<sup>b</sup>Abstinence percentages for specified treatment method.

<sup>c</sup>A quitline that responds to incoming calls and makes outbound follow-up calls. Following an initial request by the smoker or via a fax-to-quit program, the clinician initiates telephone contact to counsel the patient.

<sup>d</sup>One qualifying randomized trial; 95% CI not reported in 2008 Clinical Practice Guideline.

<sup>e</sup>Not approved by the U.S. Food and Drug Administration as a smoking cessation aid; recommended by the USPHS Guideline as a second-line agent for treating tobacco use and dependence.

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follow-up care. These steps are referred to as the “5 A’s” and are described, in brief, as follows. Figure 85-2 can be used as a guide for structuring counseling interventions.

- **Ask:** Screening for tobacco use is essential and should be a routine component of clinical care. The following question can be used to identify tobacco users: “Do you ever smoke or use any type of tobacco?” At a minimum, tobacco use status (current, former, never user) and level of use (e.g., number of cigarettes smoked per day) should be assessed and documented in the medical record. Also, consider asking patients about exposure to secondhand smoke.
- **Advise:** All tobacco users should be advised to quit; the advice should be clear and compelling, yet delivered with sensitivity and a tone of voice that communicates concern and a willingness to assist with quitting. When possible, messages should be personalized by relating advice to factors such as a

patient’s health status, medication regimen, personal reasons for wanting to quit, or the impact of tobacco use on others. For example, “Ms. Crosby, I see that you now are on two different inhalers. It’s important that you know that quitting smoking is the single most important treatment for your emphysema. I strongly encourage you to quit, and I would like to help you.”

- **Assess:** Key to the provision of appropriate counseling interventions is the assessment of a patient’s readiness to quit. Patients should be categorized as being (a) not ready to quit in the next month; (b) ready to quit in the next month; (c) a recent quitter, having quit in the past 6 months; or (d) a former user, having quit more than 6 months ago.<sup>7,42</sup> This classification defines the clinician’s next step, which is to provide counseling that is tailored to the patient’s level of readiness to quit. As an example for a current smoker: “Mr. Malkin, are you considering quitting, maybe sometime in the next

<p><b>STEP One: ASK</b> about Tobacco Use</p> <p>➔ Suggested Dialogue</p> <ul style="list-style-type: none"> <li>– “Do you ever smoke or use any type of tobacco?”</li> <li>– “I take time to talk with all of my patients about tobacco use—because it’s important.”</li> <li>– “Medication X often is used for conditions linked with or caused by smoking. Do you, or does someone in your household smoke?”</li> <li>– “Condition X often is caused or worsened by exposure to tobacco smoke. Do you, or does someone in your household smoke?”</li> </ul>	<p><b>STEP Four: ASSIST</b> with Quitting</p> <ul style="list-style-type: none"> <li>✓ <b>Assess Tobacco Use History</b> <ul style="list-style-type: none"> <li>• Current use: type(s) of tobacco used, brand, amount</li> <li>• Past use:                             <ul style="list-style-type: none"> <li>– Duration of tobacco use</li> <li>– Changes in levels of use recently</li> </ul> </li> <li>• Past quit attempts:                             <ul style="list-style-type: none"> <li>– Number of attempts, date of most recent attempt, duration</li> <li>– Methods used previously—What did or didn’t work? Why or why not?</li> <li>– Prior medication administration, dose, compliance, duration of treatment</li> <li>– Reasons for relapse</li> </ul> </li> </ul> </li> <li>✓ <b>Discuss Key Issues</b> (for the upcoming or current quit attempt)                     <ul style="list-style-type: none"> <li>• Reasons/motivation for wanting to quit (or avoid relapse)</li> <li>• Confidence in ability to quit (or avoid relapse)</li> <li>• Triggers for tobacco use</li> <li>• Routines and situations associated with tobacco use</li> <li>• Stress-related tobacco use</li> <li>• Social support for quitting</li> <li>• Concerns about weight gain</li> <li>• Concerns about withdrawal symptoms</li> </ul> </li> <li>✓ <b>Facilitate Quitting Process</b> <ul style="list-style-type: none"> <li>• Discuss methods for quitting: pros and cons of the different methods</li> <li>• Set a quit date: more than 2–3 days away but less than 2 weeks away</li> <li>• Recommend completion of a Tobacco Use Log</li> <li>• Discuss coping strategies (cognitive, behavioral) for key issues</li> <li>• Discuss withdrawal symptoms</li> <li>• Discuss concept of “slip” versus relapse</li> <li>• Provide medication counseling: compliance, proper use, with demonstration</li> <li>• Offer to assist throughout the quit attempt</li> </ul> </li> <li>✓ <b>Evaluate the Quit Attempt</b> (at follow-up)                     <ul style="list-style-type: none"> <li>• Status of attempt</li> <li>• Inquire about “slips” and relapse</li> <li>• Medication compliance and plans for discontinuation</li> </ul> </li> </ul>
<p><b>STEP Two: Strongly ADVISE</b> to Quit</p> <p>Advice should be clear, strong, and personalized yet delivered sensitively, with a tone conveying concern for the patient’s health and a sincere commitment to help with quitting.</p> <p>➔ Suggested Dialogue</p> <ul style="list-style-type: none"> <li>– “It’s important that you quit as soon as possible, and I can help you.”</li> <li>– “I realize that quitting is difficult. It is the most important thing you can do to protect your health now and in the future. I have training to help my patients quit, and when you are ready I will work with you to design a specialized treatment plan.”</li> </ul>	
<p><b>STEP Three: ASSESS</b> Readiness to Quit</p> <div style="text-align: center;"> <p>Does the patient now use tobacco?</p> <p>YES → Is the patient now willing to quit?</p> <p>NO → Did the patient use tobacco previously?</p> </div> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Is the patient now willing to quit?</p> <p>YES → Provide appropriate tobacco dependence treatment</p> <p>NO → Promote motivation to quit</p> </div> <div style="text-align: center;"> <p>Did the patient use tobacco previously?</p> <p>YES → Prevent relapse*</p> <p>NO → Encourage continued abstinence</p> </div> </div> <p><small>* Relapse prevention interventions not necessary in the case of the adult who has not used tobacco for many years.</small></p> <p><small>Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service. May 2008.</small></p>	
	<p><b>STEP Five: ARRANGE</b> Follow-up Counseling</p> <ul style="list-style-type: none"> <li>✓ Monitor patients’ progress throughout the quit attempt. Follow-up contact should occur during the first week after quitting. A second follow-up contact is recommended in the first month. Additional contacts should be scheduled as needed. Counseling contacts can occur face-to-face, by telephone, or by e-mail. Keep patient progress notes.</li> <li>✓ Address temptations and triggers; discuss relapse prevention strategies.</li> <li>✓ Congratulate patients for continued success.</li> </ul>

**FIGURE 85-2 Tobacco Cessation Counseling Guide Sheet.** Source: Reprinted from reference 32, with permission. Copyright © 1999–2008 The Regents of the University of California, University of Southern California, and Western University of Health Sciences. All rights reserved.

month?” The counseling interventions for patients who are ready to quit will be different from those for patients who are not considering quitting.

- **Assist:** When counseling tobacco users, it is important that clinicians view quitting as a process that might take months or even years to achieve, rather than a “now or never” event. The goal is to promote “forward progress” in the process of change, with the target end point being sustained abstinence.

When counseling patients who are not ready to quit, an important first step is to promote motivation. Some patients who are not ready to quit truly might not believe that they need to quit; however, most will recognize the need to quit but are simply not ready to make the commitment to do so. Often, patients have tried to quit multiple times, and failed, and thus are too discouraged to try again. Strategies for working with patients who are not ready to quit involves promoting motivation to quit, and this can be accomplished by applying the “5 R’s”<sup>7</sup> (Table 85-5) and by offering to work closely with the patient in designing a treatment plan. Although it might be useful to educate patients about the pharmacotherapy options, it is inappropriate to prescribe a treatment regimen for patients who are not ready to quit. For patients who are not ready to quit, encourage them to seriously consider quitting by asking the following series of three questions:

1. *Do you ever plan to quit?*  
Most patients will respond “yes,” in which case the clinician should continue with question 2. If they respond “no,” the clinician should strongly advise the patient to quit and offer to assist, if the patient changes his or her mind.
2. *How would it benefit you to quit later, as opposed to now?*  
Most patients will agree that there is never an ideal time to quit, and procrastinating a quit date has more negative effects than positive.
3. *What is the worst thing that would happen if you were to quit now?*  
This question probes patients’ perceptions of quitting, which reveals some of the barriers to quitting that can then be addressed by the clinician.

For patients who are ready to quit (i.e., in the next month), the goal is to work with the patient in designing an individualized treatment plan, addressing the key issues listed under the “Assist” component of Figure 85-2.<sup>32</sup> Except when medically contraindicated or with specific populations for which there is insufficient evidence of effectiveness, patients should be encouraged to use pharmacotherapy (described later in this chapter) in combination with a behavioral intervention.<sup>7</sup> The first steps are to discuss the patient’s tobacco use history, inquiring about levels of smoking, number of years smoked, methods

**Table 85-5 Enhancing Motivation to Quit: The “5 R’s” for Tobacco Cessation Counseling<sup>7</sup>**

- **Relevance**—Encourage patients to think about the reasons why quitting is important. Counseling should be framed such that it relates to the patient’s risk for disease or exacerbation of disease, family or social situations (e.g., having children with asthma), health concerns, age, or other patient factors, such as prior experience with quitting.
- **Risks**—Ask patients to identify potential negative health consequences of smoking, such as acute risks (shortness of breath, asthma exacerbations, harm to pregnancy, infertility), long-term risks (cancer, cardiac, and pulmonary disease), and environmental risks (promoting smoking among children by being a negative role model; effects of second-hand smoke on others, including children and pets).
- **Rewards**—Ask patients to identify potential benefits that they anticipate from quitting, such as improved health, enhanced physical performance, enhanced taste and smell, reduced expenditures for tobacco, less time wasted or work missed, reduced health risks to others (fetus, children, housemates), and reduced aging of the skin.
- **Roadblocks**—Help patients identify barriers to quitting and assist in developing coping strategies (Table 85-6) for addressing each barrier. Common barriers include nicotine withdrawal symptoms (Table 85-7), fear of failure, a need for social support while quitting, depression, weight gain, and a sense of deprivation or loss.
- **Repetition**—Continue to work with patients who are successful in their quit attempt. Discuss circumstances in which smoking occurred to identify the trigger(s) for relapse; this is part of the learning process and will be useful information for the next quit attempt. Repeat interventions when possible.

used previously for quitting (what worked, what did not work and why), and reasons for previous failed quit attempts. Clinicians should elicit patients’ opinions about the different pharmacotherapies for quitting and should work with patients in selecting the quitting methods (e.g., medications, behavioral counseling programs). Although it is important to recognize that pharmaceutical agents might not be appropriate, desirable, or affordable for all patients, clinicians should educate patients that medications, when taken correctly, can substantially increase the likelihood of success by making them more comfortable while quitting.

Patients should be advised to select a quit date that is more than 3 days but less than 2 weeks away. This time frame provides patients with sufficient time to prepare for the quit attempt, including mental preparation, as well as preparation of the environment, such as by removing all tobacco products and ashtrays from the home, car, and workspace and informing their family, friends, and coworkers about their upcoming quit attempt and requesting their support. Additional strategies for coping with quitting are shown in Table 85-6.<sup>32</sup> Patients should be counseled about coping with withdrawal symptoms (Table 85-7)<sup>32</sup> and medication use and compliance, and it is crucial to emphasize the importance of receiving behavioral counseling throughout the quit attempt. Finally, patients should be commended for taking important steps toward improving their health.

- **Arrange:** Because patients’ ability to quit increases when multiple counseling interactions are provided, arranging follow-up counseling is an important, yet typically neglected, element of treatment for tobacco dependence. Follow-up contact should occur soon after the quit date, preferably during the first week. A second follow-up contact is recommended within the first month after quitting.<sup>7</sup> Periodically, additional follow-up contacts should occur to monitor patient progress, assess compliance with pharmacotherapy regimens, and provide additional support.

Relapse prevention counseling should be part of every follow-up contact with patients who have recently quit smoking. When counseling recent quitters, it is important to address challenges in countering withdrawal symptoms (Table 85-7)<sup>32</sup> and cravings or temptations to use tobacco. A list of strategies for key triggers or temptations for tobacco use is provided in Table 85-6.<sup>32</sup> Importantly, because tobacco use is a habitual

behavior, patients should be advised to alter their daily routines; this helps disassociate specific behaviors from the use of tobacco. Patients who slip and smoke a cigarette (or use any form of tobacco) or experience a full relapse back to habitual tobacco use should be encouraged to think through the scenario in which tobacco use first occurred and identify the trigger(s) for relapse. This process provides valuable information for future quit attempts.

#### TELEPHONE QUITLINES

Clinicians should become aware of local, community-based resources for tobacco cessation, including telephone quitlines. When time or expertise do not afford provision of comprehensive tobacco cessation counseling during a patient visit, clinicians are encouraged to apply a truncated 5 A’s model, whereby they *Ask* about tobacco use, *Advise* tobacco users to quit, and *Refer* patients to quit to a telephone quitline. This generally can be accomplished in less than one minute. Telephone services that provide tobacco cessation counseling have proliferated since the late 1990s; these services provide low-cost interventions that can reach patients who might otherwise have limited access to medical treatment because of geographic location or lack of insurance or financial resources. In clinical trials, telephone counseling services for which at least some of the contacts are initiated by the quit line counselor have been shown to be effective in promoting abstinence,<sup>7</sup> and these positive results have been shown to translate into real world effectiveness.<sup>41</sup> The addition of medication to quitline counseling significantly improves abstinence rates compared to medication alone.<sup>7</sup> In addition, preliminary evidence suggests that quitlines are also effective for smokeless tobacco cessation.<sup>43</sup> The telephone number for the tollfree tobacco quitline is 1-800-QUIT NOW. In some states, clinicians can submit a fax referral form, on behalf of a patient, to the quitline. This form initiates a process whereby a quitline counselor then contacts the patient directly.

#### Pharmacotherapy Options

All smokers who are trying to quit should be encouraged to use one or more U.S. Food and Drug Administration (FDA)-approved pharmacologic aids for cessation; potential exceptions that require special consideration include medical contraindications or use in specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, adolescents).<sup>7</sup>

**Table 85-6 Cognitive and Behavioral Strategies for Tobacco Cessation****Cognitive strategies**

Focus on *retraining the way a patient thinks*. Often, patients mentally deliberate on the fact that they are thinking about a cigarette, and this leads to relapse. Patients must recognize that thinking about a cigarette does not mean they need to have one.

Review commitment to quit, focus on downside of tobacco	Reminding oneself that cravings and temptations are temporary and will pass. Have patient announce, either silently or aloud, “I want to be a nonsmoker, and the temptation will pass.”
Distractive thinking	Deliberate, immediate refocusing of thinking when cued by thoughts about tobacco use.
Positive self-talks, “pep talks”	Saying “I can do this” and reminding oneself of previous difficult situations in which tobacco use was avoided with success.
Relaxation through imagery	Centering of mind toward positive, relaxing thoughts.
Mental rehearsal, visualization	Preparing for situations that might arise by envisioning how best to handle them. For example, a patient might envision what would happen if he or she were offered a cigarette by a friend—the patient would mentally craft and rehearse a response, and perhaps even practice it by saying it aloud.

**Behavioral strategies**

Involve *specific actions to reduce risk for relapse*. For maximal effectiveness, these should be considered prior to quitting, after determining patient-specific triggers for tobacco use. Here, we list some behavioral strategies for several common cues or triggers for relapse.

Stress	Anticipate upcoming challenges at work, at school, or in personal life. Develop a substitute plan for tobacco use during times of stress (e.g., deep breathing, take a break/leave the situation, call supportive friend or family member, self-massage, use nicotine replacement therapy).
Alcohol	Drinking alcohol can lead to relapse. Patient should consider limiting/abstaining from alcohol during the early stages of quitting.
Other tobacco users	Quitting is more difficult if the patient is around other tobacco users. This is especially difficult if there is another tobacco user in the household. Patients should limit prolonged contact with individuals who are using tobacco during the early stages of quitting. Ask coworkers, friends, and housemates not to smoke or use tobacco in their presence.
Oral gratification needs	Have nontobacco oral substitutes (e.g., gum, sugarless candy, straws, toothpicks, lip balm, toothbrush, nicotine replacement therapy, bottled water) readily available.
Automatic smoking routines	Anticipate routines that are associated with tobacco use and develop an alternative plan. Examples: <i>Morning coffee with cigarettes:</i> change morning routine, drink tea instead of coffee, take shower before drinking coffee, take a brisk walk shortly after awakening. <i>Smoking while driving:</i> remove all tobacco from car, have car interior detailed, listen to a book on tape or talk radio, use oral substitute. <i>Smoking while on the phone:</i> stand while talking, limit call duration, change phone location, keep hands occupied by doodling or sketching. <i>Smoking after meals:</i> get up and immediately do dishes or take a brisk walk after eating, call supportive friend.
Postcessation weight gain	The majority of tobacco users gain weight after quitting. Most quitters will gain <10 lb, but there is a broad range of weight gain reported, with up to 10% of quitters gaining as much as 30 lb. Advise patient not to attempt to modify multiple behaviors at one time. If weight gain is a barrier to quitting, advise patient to engage in regular physical activity and adhere to a healthful diet (as opposed to strict dieting). Carefully plan and prepare meals, increase fruit and water intake to create a feeling of fullness, and chew sugarless gum or eat sugarless candies. Consider use of pharmacotherapy shown to delay weight gain (e.g., the 4-mg nicotine gum or lozenge or bupropion SR).
Cravings for tobacco	Cravings for tobacco are temporary and usually pass within 5–10 minutes. Handle cravings through distractive thinking, take a break, change activities/tasks, take deep breaths, or perform self-massage.

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**Table 85-7 Postcessation Withdrawal Symptoms**

<b>Symptoms</b>	<b>Duration</b>
Chest tightness	A few days
Constipation, stomach pain, gas	1–2 weeks
Cough, dry throat, nasal drip	A few days
Craving for a cigarette	Frequent for 2–3 days; can persist for months or years
Difficulty concentrating	2–4 weeks
Dizziness	1–2 days
Fatigue	2–4 weeks
Hunger	Up to several weeks
Insomnia	1 week
Irritability	2–4 weeks

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Currently, the FDA-approved first-line agents<sup>7</sup> include five NRT dosage forms, sustained-release bupropion (bupropion SR), and varenicline. Pharmacologic agents that have not received FDA approval for smoking cessation but are recommended as second-line agents<sup>7</sup> include clonidine and nortriptyline.

The first approved medication for smoking cessation was the nicotine gum, which was marketed in 1984. This was later followed by the nicotine transdermal patch (prescription-only formulation in 1991 and nonprescription formulations in 1996), bupropion SR and nicotine nasal spray in 1996, the nicotine oral inhaler in 1997, the nicotine lozenge in 2002, and varenicline in 2006. Each product has been shown to be effective in promoting smoking cessation. Dosing information, precautions, and adverse effects for the first-line agents are shown in Table 85-8.

**Table 85-8 Pharmacotherapy Options: Products, Warnings/Contraindications and Adverse Effects**

Gum	NRT Formulations					Varenicline
	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler	Bupropion SR	
<b>Product</b>						
<b>Nicorette,<sup>a</sup> Generic</b>	<b>Commit,<sup>a</sup> Generic</b>	<b>Nicoderm CQ,<sup>a</sup> Generic<sup>b</sup></b>	<b>Nicotrol NS<sup>c</sup></b>	<b>Nicotrol Inhaler<sup>c</sup></b>	<b>Zyban,<sup>a</sup> Generic</b>	<b>Chantix<sup>c</sup></b>
OTC	OTC	OTC (NicoDerm CQ, generic)	Rx	Rx	Rx	Rx
2 mg, 4 mg	2 mg, 4 mg	Rx (generic)	Metered spray	10 mg cartridge	150 mg sustained-release tablet	0.5 mg, 1 mg tablet
Original, cinnamon, fruit, mint (various), orange	Cherry, mint	7 mg, 14 mg, 21 mg (24-hour release)	0.5 mg nicotine in 50 $\mu$ L aqueous nicotine solution	Delivers 4 mg inhaled nicotine vapor		
<b>Precautions/Warnings and Contraindications</b>						
<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Temporomandibular joint disease</li> <li>Pregnancy category: not applicable for OTC formulations</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Pregnancy category: not applicable for OTC formulations</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Pregnancy category: D for prescription patch, not applicable for OTC formulations</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis)</li> <li>Severe reactive airway disease</li> <li>Pregnancy category: D</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Bronchospastic disease</li> <li>Pregnancy category: D</li> </ul>	<ul style="list-style-type: none"> <li>Concomitant therapy with medications or medical conditions known to lower seizure threshold</li> <li>Severe hepatic cirrhosis</li> <li>Pregnancy category: C</li> </ul> <p><b>Contraindications:</b></p> <ul style="list-style-type: none"> <li>Seizure disorder</li> <li>Concomitant bupropion (e.g., Wellbutrin) therapy</li> <li>Current or prior diagnosis of bulimia or anorexia nervosa</li> <li>Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)</li> <li>Monoamine oxidase inhibitor therapy in previous 14 days</li> </ul>	<ul style="list-style-type: none"> <li>Severe renal impairment (dosage adjustment is necessary)</li> <li>Neuropsychiatric symptoms (behavior changes, suicidal ideation or behavior)</li> <li>Safety and efficacy have not been established in patients with serious psychiatric illness</li> <li>Pregnancy category: C</li> </ul>

(continued)

**Table 85-8 Pharmacotherapy Options: Products, Dosing, and Adverse Effects (Continued)**

NRT Formulations						
Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler	Bupropion SR	Varenicline
<b>Dosing</b>						
<ul style="list-style-type: none"> <li>• ≥25 cigarettes/day: 4 mg</li> <li>• &lt;25 cigarettes/day: 2 mg</li> </ul>	<ul style="list-style-type: none"> <li>• First cigarette ≤30 minutes after waking: 4 mg</li> <li>• First cigarette &gt;30 minutes after waking: 2 mg</li> </ul>	<ul style="list-style-type: none"> <li>• &gt;10 cigarettes/day: 21 mg/day</li> <li>• × 4 weeks (generic)</li> <li>• × 6 weeks (Nicoderm CO)</li> </ul>	<ul style="list-style-type: none"> <li>• 1–2 doses/hr (8–40 doses/day)</li> <li>• One dose = 2 sprays (one in each nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa</li> </ul>	<ul style="list-style-type: none"> <li>• 6–16 cartridges/day</li> <li>• Individualize dosing: initially use 1 cartridge Q 1–2 hr</li> </ul>	<ul style="list-style-type: none"> <li>• 150 mg PO Q am × 3 days, then increase to 150 mg PO BID</li> </ul>	<ul style="list-style-type: none"> <li>• Days 1–3: 0.5 mg PO Q am</li> <li>• Days 4–7: 0.5 mg PO BID</li> <li>• Weeks 2–12: 1 mg PO BID</li> </ul>
<ul style="list-style-type: none"> <li>• Weeks 1–6: 1 piece Q 1–2 hr</li> <li>• Weeks 7–9: 1 piece Q 2–4 hr</li> <li>• Weeks 10–12: 1 piece Q 4–8 hr</li> </ul>	<ul style="list-style-type: none"> <li>• Weeks 1–6: 1 lozenge Q 1–2 hr</li> <li>• Weeks 7–9: 1 lozenge Q 2–4 hr</li> <li>• Weeks 10–12: 1 lozenge Q 4–8 hr</li> </ul>	<ul style="list-style-type: none"> <li>• ≤10 cigarettes/day: 14 mg/day × 2 weeks</li> <li>• 7 mg/day × 2 weeks</li> <li>• ≤10 cigarettes/day: 14 mg/day × 6 weeks</li> <li>• 7 mg/day × 2 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Maximum – 5 doses/hr</li> <li>• – 40 doses/day</li> <li>• For best results, initially use at least 8 doses/day</li> <li>• Patients should not sniff, swallow, or inhale through the nose as the spray is being administered</li> </ul>	<ul style="list-style-type: none"> <li>• Best effects with continuous puffing for 20 minutes</li> <li>• Nicotine in cartridge is depleted after 20 minutes of active puffing</li> <li>• Patient should inhale into back of throat or puff in short breaths</li> <li>• Do NOT inhale into the lungs (like a cigarette) but “puff” as if lighting a pipe</li> <li>• Open cartridge retains potency for 24 hours</li> <li>• Duration: up to 6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Do not exceed 300 mg/day</li> <li>• Treatment should be initiated while patient is still smoking</li> <li>• Set quit date 1–2 weeks after initiation of therapy</li> <li>• Allow at least 8 hours between doses</li> <li>• Avoid bedtime dosing to minimize insomnia</li> <li>• Dose tapering is not necessary</li> <li>• Nausea and insomnia are usually temporary side effects</li> <li>• Duration: 12 weeks; an additional 12-week course may be used in selected patients</li> </ul>	<ul style="list-style-type: none"> <li>• Patients should begin therapy 1 week prior to quit date</li> <li>• Take dose after eating with a full glass of water</li> <li>• Dose tapering is not necessary</li> <li>• Nausea and insomnia are usually temporary side effects</li> <li>• Duration: 12 weeks; an additional 12-week course may be used in selected patients</li> </ul>
<ul style="list-style-type: none"> <li>• Maximum, 24 pieces/day</li> <li>• Chew each piece slowly</li> <li>• Park between cheek and gum when peppery or tingling sensation appears (~15–30 chew)</li> <li>• Resume chewing when taste or tingle fades</li> <li>• Repeat chew/park steps until most of nicotine is gone (taste or tingle does not return; generally 30 minutes)</li> <li>• Park in different areas of mouth</li> <li>• No food or beverages 15 minutes before or during use</li> <li>• Duration: up to 12 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• First cigarette ≤30 minutes after waking: 2 mg</li> <li>• First cigarette &gt;30 minutes after waking: 1 mg</li> <li>• Weeks 1–6: 1 lozenge Q 1–2 hr</li> <li>• Weeks 7–9: 1 lozenge Q 2–4 hr</li> <li>• Weeks 10–12: 1 lozenge Q 4–8 hr</li> <li>• Maximum, 20 lozenges/day</li> <li>• Allow to dissolve slowly (20–30 minutes)</li> <li>• Nicotine release may cause a warm, tingling sensation or tingle fades</li> <li>• Occasionally rotate to different areas of the mouth</li> <li>• No food or beverages 15 minutes before or during use</li> <li>• Duration: up to 12 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime)</li> <li>• Duration: 8–10 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Nasal and/or throat irritation (hot, peppery, or burning sensation)</li> <li>• Rhinitis</li> <li>• Tearing</li> <li>• Sneezing</li> <li>• Cough</li> <li>• Headache</li> </ul>	<ul style="list-style-type: none"> <li>• Mouth and/or throat irritation</li> <li>• Cough</li> <li>• Rhinitis</li> <li>• Dyspepsia</li> <li>• Hiccups</li> <li>• Headache</li> </ul>	<ul style="list-style-type: none"> <li>• Insomnia</li> <li>• Dry mouth</li> <li>• Nervousness/difficulty concentrating</li> <li>• Rash</li> <li>• Constipation</li> <li>• Seizures (risk is 1/1,000 [0.1%])</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Sleep disturbances (insomnia, abnormal/vivid dreams)</li> <li>• Constipation</li> <li>• Flatulence</li> <li>• Vomiting</li> <li>• Neuropsychiatric symptoms (rare; see PRECAUTIONS)</li> </ul>
<b>Adverse Effects</b>						
<ul style="list-style-type: none"> <li>• Mouth/jaw soreness</li> <li>• Hiccups</li> <li>• Cough</li> <li>• Dyspepsia</li> <li>• Hypersalivation</li> <li>• Effects associated with incorrect chewing technique: <ul style="list-style-type: none"> <li>– Lightheadedness</li> <li>– Nausea/vomiting</li> <li>– Throat and mouth irritation</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Local skin reactions (erythema, pruritus, burning)</li> <li>• Headache</li> <li>• Sleep disturbances (insomnia, abnormal/vivid dreams); associated with nocturnal nicotine absorption</li> </ul>	<ul style="list-style-type: none"> <li>• Local skin reactions (erythema, pruritus, burning)</li> <li>• Headache</li> <li>• Sleep disturbances (insomnia, abnormal/vivid dreams); associated with nocturnal nicotine absorption</li> </ul>	<ul style="list-style-type: none"> <li>• Nasal and/or throat irritation (hot, peppery, or burning sensation)</li> <li>• Rhinitis</li> <li>• Tearing</li> <li>• Sneezing</li> <li>• Cough</li> <li>• Headache</li> </ul>	<ul style="list-style-type: none"> <li>• Mouth and/or throat irritation</li> <li>• Cough</li> <li>• Rhinitis</li> <li>• Dyspepsia</li> <li>• Hiccups</li> <li>• Headache</li> </ul>	<ul style="list-style-type: none"> <li>• Insomnia</li> <li>• Dry mouth</li> <li>• Nervousness/difficulty concentrating</li> <li>• Rash</li> <li>• Constipation</li> <li>• Seizures (risk is 1/1,000 [0.1%])</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Sleep disturbances (insomnia, abnormal/vivid dreams)</li> <li>• Constipation</li> <li>• Flatulence</li> <li>• Vomiting</li> <li>• Neuropsychiatric symptoms (rare; see PRECAUTIONS)</li> </ul>

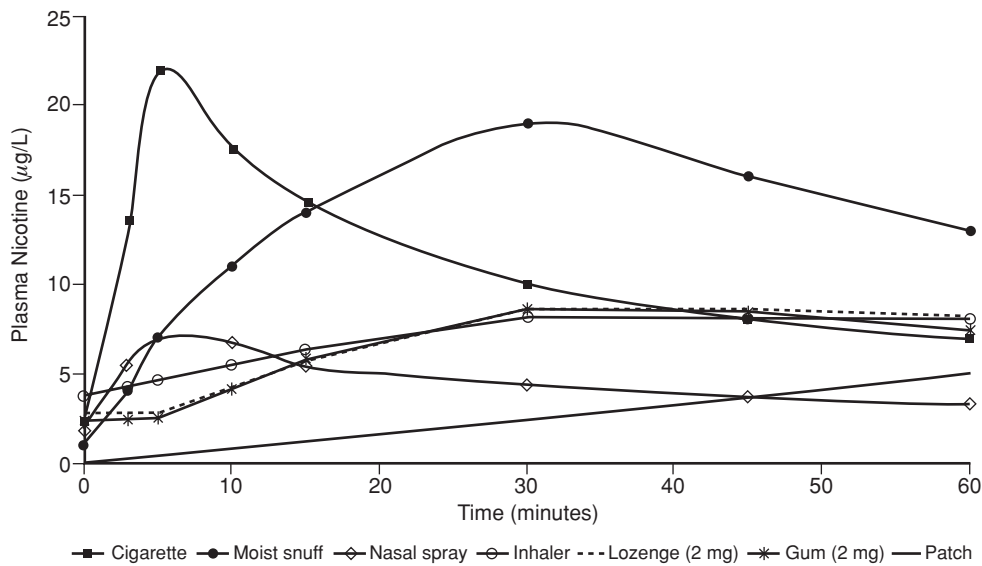
<sup>a</sup>Marketed by GlaxoSmithKline.

<sup>b</sup>Transdermal patch formulation previously marketed as Habitrol.

<sup>c</sup>Marketed by Pfizer.

NRT, nicotine replacement therapy; OTC, over the counter (nonprescription); Rx, prescription. For complete prescribing information, refer to the manufacturers' package inserts.

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**FIGURE 85-3 Plasma nicotine concentrations for various nicotine-containing products.** Source: Reprinted from reference 32, with permission. Copyright © 1999–2008 The Regents of the University of California, University of Southern California, and Western University of Health Sciences. All rights reserved. Plasma nicotine concentration curves derived from references 52, 66, and 127.

### First-Line Agents

#### NICOTINE REPLACEMENT THERAPY

NRT increases success for quitting by reducing the physical withdrawal symptoms associated with tobacco cessation while the patient focuses on modifying his or her behavior and coping with the psychological aspects of quitting. In addition, because the onset of action for NRT is not as rapid as that of nicotine obtained through smoking, patients become less accustomed to the nearly immediate, reinforcing effects of inhaled tobacco. A meta-analysis of 111 controlled trials, enrolling more than 43,000 participants, found that all NRT formulations (gum, inhaler, lozenge, patch, and nasal spray) result in statistically significant improvements in abstinence rates when compared with placebo. Patients using NRT are 1.6 times as likely to quit smoking than are those receiving placebo.<sup>44</sup> Figure 85-3 depicts the concentration time curves for the various NRT formulations, compared with a cigarette and moist snuff (a form of smokeless tobacco). It can be seen that of the five NRT dosage forms, the nicotine nasal spray reaches its peak concentration most rapidly. The nicotine gum, lozenge, and oral inhaler have similar concentration curves, and the nicotine transdermal patch has the slowest onset, but offers more consistent blood levels of nicotine over a sustained period of time.

#### BUPROPION SR

Bupropion SR is an atypical antidepressant medication hypothesized to promote smoking cessation by blocking the reuptake of dopamine and norepinephrine in the central nervous system and possibly by acting as a nicotine receptor antagonist. These neurochemical effects are believed to modulate the dopamine reward pathway and reduce cravings for nicotine and symptoms of withdrawal.<sup>7</sup> Use of bupropion SR approximately doubles the long-term abstinence rate when compared with placebo.<sup>7,45</sup>

#### VARENICLINE

Varenicline is a partial agonist, highly selective for the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor.<sup>46</sup> The efficacy of varenicline in smoking cessation is believed to be the result of sustained, low-level agonist activity at the receptor site combined with competitive inhibition of nicotine binding. The partial agonist activity induces modest receptor stimulation leading to increased dopamine levels that attenuate the symptoms of nicotine withdrawal. In addition, by competitively blocking the binding of nicotine to nicotinic acetylcholine receptors in the central nervous system, varenicline inhibits the surges of dopamine release that occur immediately following inhalation of tobacco smoke. The latter mechanism may be effective in preventing relapse by reducing the pleasure associated with smoking.<sup>47</sup> A recent meta-analysis has found that varenicline (2 mg/day) more than triples the likelihood of long-term abstinence from smoking relative to placebo.<sup>7</sup>

#### Second-Line Agents

Although not FDA-approved specifically for smoking cessation, the prescription medications clonidine and nortriptyline are recommended as second-line agents.<sup>7</sup> Lack of an FDA-approved indication for smoking cessation and side effect profiles currently prohibit these agents from achieving first-line classification.<sup>7</sup>

## PHARMACOTHERAPY FOR TREATING TOBACCO USE AND DEPENDENCE

### Transdermal Nicotine Patch

**1.** T.B. is a 32-year-old woman who is enrolled in a work-site smoking cessation program. During the previous group session, the cessation counselor discussed the various medications for

cessation. T.B. has set her quit date for 1 week from today, and she is interested in starting the nicotine transdermal patch. She is currently smoking 1 pack per day (PPD), which is a reduction from the 1.5 PPD she had been smoking for the past 10 years. T.B. reports she smokes several cigarettes in succession immediately after waking in the morning. She takes no medications and has no medical problems. Which nicotine transdermal product should T.B. select, and how should it be used?

Two different transdermal nicotine patch systems are currently marketed. Transdermal nicotine delivery systems consist of an impermeable surface layer, a nicotine reservoir, an adhesive layer, and a removable protective liner. The technology for delivery of nicotine across the skin varies by manufacturer. NicoDerm CQ uses a rate-controlling membrane. The generic patches (previously marketed as Habitrol) use drug-dispersion-type systems whereby release of nicotine is controlled by diffusion of the drug across an adhesive layer.<sup>48</sup> The currently marketed formulations (which continuously release nicotine over 24 hours) deliver nicotine more slowly than the gum, lozenge, nasal spray, and inhaler (Fig. 85-3). Plasma nicotine levels obtained via transdermal delivery are approximately 50% lower than those achieved with cigarette smoking but still alleviate the symptoms of withdrawal.<sup>49</sup>

The efficacy of the transdermal nicotine patch is well documented with significantly improved abstinence rates relative to placebo (Table 85-4).<sup>7,44</sup> A meta-analysis of 25 randomized, controlled trials found treatment with the nicotine patch (6–14 weeks) approximately doubled the likelihood of long-term abstinence compared to placebo.<sup>7</sup>

### Dosing

The manufacturers' recommended dosages are listed in Table 85-8. In general, higher levels of smoking necessitate the use of higher-strength formulations and a longer duration of therapy. Ultimately, the starting dose, rate of tapering, and total duration of therapy must be individualized to the patient's baseline smoking levels, development of side effects (e.g., nausea, dyspepsia, nervousness, dizziness, sweating), and the presence or absence of withdrawal symptoms (Table 85-7). T.B. currently smokes 20 cigarettes per day, and thus she should initiate the regimen using the 21-mg/day patch.

### Patient Education

Regardless of the product selected, T.B. should be instructed to apply the patch to a clean, dry, hairless area of skin on the upper body or the upper outer part of her arm at approximately the same time each day. To minimize the potential for local skin reactions, the patch application site should be rotated daily, and the same area should not be used again for at least 1 week. After patch application, T.B. should ensure that the patch adheres well to the skin, especially around the edges. The clinician should reassure T.B. that water will not reduce the effectiveness of the nicotine patch if it is applied correctly, and she may bathe, shower, swim, or exercise while wearing the patch. Finally, T.B. should be advised to discontinue use of the nicotine patch and contact a health care provider if skin redness caused by the patch does not resolve after 4 days, if the skin swells or a rash develops; if irregular heartbeat or palpitations occur; or if she experiences symptoms of nicotine overdose such as

nausea, vomiting, dizziness, diarrhea, sweating, weakness, or rapid heartbeat.

### Adverse Reactions

**2.** Ten days later, T.B. calls to complain of an itchy rash that she believes is caused by the nicotine patch. She noticed the rash yesterday when she removed the first patch from her left upper arm. This morning, after removing the second patch from her right upper arm, she noticed a similar rash. T.B. describes the skin on her right arm as slightly red but not swollen; the rash on her left arm has only a faint trace of pink discoloration. Her last cigarette was 2 days ago. How should T.B. be managed at this time?

The most common side effects associated with the nicotine patch are local reactions (erythema, burning, and pruritus) at the skin application site. These reactions are generally caused by skin occlusion or sensitivity to the patch adhesives. Rotating the patch application sites on a daily basis minimizes skin irritation; nonetheless, skin reactions to the patch adhesives occur in up to 50% of patch users. Less than 5% of patients discontinue therapy because of a skin reaction.<sup>7</sup> T.B. appears to be experiencing a mild skin reaction and should be reassured that it is normal for the skin to appear erythematous for up to 24 to 48 hours after the patch is removed. T.B. can apply topical hydrocortisone cream (0.5% or 1%) or triamcinolone cream (0.5%), or can take an oral antihistamine for symptomatic treatment.<sup>7</sup> Because the rash on her left arm has nearly resolved, it is reasonable for T.B. to continue using the nicotine transdermal patch provided that the erythema is not too bothersome.

Other less common side effects associated with the transdermal nicotine patch include vivid or abnormal dreams, insomnia, and headache. Sleep disturbances likely result from nocturnal nicotine absorption. Patients experiencing troublesome sleep disturbances should be instructed to remove the patch prior to bedtime and apply a new patch as soon as possible after waking the following morning.<sup>7</sup>

The clinician should also provide behavioral counseling support by asking T.B. about the current quit attempt. Appropriate issues to address include her confidence in remaining tobacco free, situations in which she has been tempted to smoke and potential triggers for relapse, nicotine withdrawal symptoms, her social support system for quitting, and any other questions or concerns she might have. It is reasonable to review potential coping strategies (behavioral and cognitive; Table 85-6) and schedule a future follow-up call. The clinician should commend T.B. for her decision to quit, congratulate her for remaining tobacco free for 48 hours, and reassure her that skin irritation is a common, yet generally manageable, complication with the nicotine patch.

### Product Selection Considerations

The primary advantage of the transdermal nicotine patch compared with other NRT formulations is that the patch is easy to use and conceal, releases a continuous dose of nicotine throughout the day, and requires administration only once daily. As a result, patients who have difficulty adhering to regimens that require taking multiple doses of medications throughout the day or those who want a simplified regimen are likely to

be more successful with the nicotine patch. Disadvantages of the patch include a high incidence of skin irritation associated with the patch adhesives and the inability to acutely adjust the dose of nicotine to alleviate symptoms of withdrawal. Finally, patients with underlying dermatologic conditions (e.g., psoriasis, eczema, atopic dermatitis) should not use the patch because they are more likely to experience skin irritation.<sup>7</sup>

## Nicotine Gum

### 3. T.B. would like to discontinue the nicotine transdermal patch. She wants to know if the gum is an effective alternative.

Nicotine polacrilex gum is a resin complex of nicotine and polacrillin in a chewing gum base that allows for slow release and absorption of nicotine across the oral mucosa. The product is available as 2- and 4-mg strengths, in multiple flavors (regular, cinnamon, fruit, mint, and orange). The gum has a distinct, tobacco-like, slightly peppery, minty, or fruity taste and contains buffering agents (sodium carbonate and sodium bicarbonate) to increase the salivary pH, which enhances the buccal absorption of nicotine. The amount of nicotine absorbed from each piece is variable, but approximately 1.1 and 2.9 mg of nicotine are extracted from the 2- and 4-mg gum formulations, respectively.<sup>50</sup> Peak plasma concentrations of nicotine are achieved approximately 30 minutes after chewing a single piece of gum and then slowly decline thereafter (Fig. 85-3). Patients using short-term (6–14 weeks) or long-term (>14 weeks) treatment with nicotine gum are significantly more likely to remain abstinent compared to those receiving placebo (Table 85-4).<sup>7</sup>

### Dosing

Table 85-8 outlines the manufacturer's recommended dosing schedule for the nicotine gum. Individuals who smoke <25 cigarettes per day should use the 2-mg strength, and those smoking more should use the 4-mg strength. During the initial 6 weeks of therapy, patients should use 1 piece of gum every 1 to 2 hours while awake. In general, this amounts to at least 9 pieces of gum daily. The "chew and park" method described here allows for the slow, consistent release of nicotine from the polacrillin resin. Patients can use additional pieces of gum (to the daily maximum of 24 pieces per day) if cravings occur between scheduled doses. In general, patients who smoke a greater number of cigarettes per day will require more nicotine gum to alleviate their cravings than will patients who smoke fewer cigarettes per day. It is preferable to use the gum on a fixed schedule of administration, tapering over 1 to 3 months rather than using it "as needed" to control cravings.<sup>7</sup>

### Patient Education

Proper chewing technique is crucial when using the nicotine gum. Patients should be instructed to chew the gum slowly until a peppery, minty, or fruity taste, or a slight tingling sensation in the mouth is detected; this varies but generally occurs after about 15 chews. When the taste or tingling sensation is noted, the patient should "park" the gum between the cheek and gum to allow absorption of nicotine across the buccal mucosa. When the taste or tingling dissipates (generally after 1–2

minutes), the patient should resume chewing slowly. When the taste or tingle returns, the patient should stop chewing and park the gum in a different area in the mouth. Rotating the gum placement site within the mouth helps decrease the incidence of oral irritation. The chew/park steps should be repeated until most of the nicotine is extracted; this generally occurs after 30 minutes and becomes obvious when chewing no longer elicits the characteristic taste or tingling sensation.

Patients should be warned that the absorption and therefore effectiveness of nicotine gum might be reduced by acidic beverages (e.g., coffee, juices, wine, soft drinks),<sup>51</sup> which transiently reduce the salivary pH. To prevent this interaction, patients should be advised not to eat or drink (except water) for 15 minutes before or while using the nicotine gum.

### Product Selection Considerations

Advantages of nicotine gum include the fact that this formulation may be used to satisfy oral cravings and the 4-mg strength might delay weight gain.<sup>7</sup> For these reasons, the gum may be particularly beneficial for patients who have weight gain concerns or for patients who report boredom as a trigger for smoking. The gum might also be advantageous for patients who desire flexibility in dosing and prefer the ability to self-regulate nicotine levels to manage withdrawal symptoms. Some patients may find that the viscous consistency of the gum makes it difficult to use because it sticks to dental work. Others may find it difficult or socially unacceptable to chew the gum so frequently. Nicotine gum should not be used by patients with temporomandibular joint (TMJ) conditions. Finally, to minimize adverse effects and derive maximal therapeutic benefit, it is imperative that patients use enough gum each day and use the correct chewing technique.

## Nicotine Lozenge

### 4. How does the nicotine lozenge differ from the nicotine gum?

The nicotine polacrilex lozenge is a resin complex of nicotine and polacrillin in a sugarfree, light mint, or cherry-flavored lozenge. The product is available in 2- and 4-mg strengths, which are meant to be consumed like hard candy or other medicinal lozenges (e.g., sucked and moved from side to side in the mouth until fully dissolved). Because the nicotine lozenge dissolves completely, it delivers approximately 25% more nicotine than does an equivalent dose of nicotine gum.<sup>52</sup> Like the nicotine gum, the lozenge also contains buffering agents (sodium carbonate and potassium bicarbonate) to increase salivary pH, thereby enhancing buccal absorption of the nicotine. Peak nicotine concentrations of nicotine with the lozenge are achieved after 30 to 60 minutes of use and then slowly decline thereafter (Fig. 85-3). In a trial evaluating the formulation currently available in the United States, the nicotine lozenge approximately doubled the 6-month abstinence rates compared with placebo (23.9% vs. 12.3%).<sup>53</sup> A recent meta-analysis of five studies using either the nicotine lozenge (nicotine polacrillin) or sublingual tablet (not available in the United States) concluded that the odds of abstinence at 6 or more months was 2.0 with the tablet/lozenge relative to placebo (95% CI, 1.6–2.5).<sup>44</sup>

**Dosing**

Unlike other NRT formulations, which use the number of cigarettes smoked per day as the basis for dosing, the recommended dosage of the nicotine lozenge is based on the time to first cigarette (TTFC). Some experts believe that the best indicator of nicotine dependence is the need to smoke soon after waking.<sup>54</sup> Based on this method, people who smoke their first cigarette of the day within 30 minutes of waking are considered more highly dependent on nicotine than those who smoke their first cigarette more than 30 minutes after waking. Because the nicotine polacrillin lozenge has been studied using the TTFC as a dosage selector, the product is licensed for use in the following manner: Patients who smoke their first cigarette of the day within 30 minutes of waking should use the 4-mg strength lozenge, and patients who smoke their first cigarette of the day more than 30 minutes after waking should use the 2-mg strength lozenge. Patients are more likely to succeed if they use the lozenge on a fixed schedule rather than as needed. During the initial 6 weeks of therapy, patients should use 1 lozenge every 1 to 2 hours while awake. In general, this amounts to at least 9 lozenges daily. Patients can use additional lozenges (up to 5 lozenges in 6 hours or a maximum of 20 lozenges per day) if cravings occur between scheduled doses.

**Patient Education**

Similar to the gum, the nicotine lozenge is a specially formulated nicotine delivery system that must be used properly for optimal results. The lozenge should be allowed to dissolve slowly in the mouth; when nicotine is released from the polacrillin resin, a warm, tingling sensation may be experienced. The patient should occasionally rotate the lozenge to different areas of the mouth to reduce the potential for mucosal irritation. When used correctly, the lozenge should completely dissolve within 30 minutes. Patients should be counseled not to chew or swallow the lozenge because this increases the incidence of gastrointestinal-related side effects.

Because the nicotine in the lozenge is dissolved in saliva and absorbed through the buccal mucosa, patients should be cautioned that the effectiveness of the nicotine lozenge may be reduced by acidic beverages such as coffee, juices, wine, or soft drinks. As recommended for the nicotine gum, patients should be advised not to eat or drink (except water) for 15 minutes before or while using the nicotine lozenge.

**Adverse Reactions**

In general, the nicotine lozenge is well tolerated. The most common side effects include nausea, hiccups, cough, dyspepsia, headache, and flatulence. Patients who use more than one lozenge at a time, continuously use one lozenge after another, or chew or swallow the lozenge are more likely to experience dyspepsia or hiccups.

**Product Selection Considerations**

The nicotine lozenge is similar to the nicotine gum formulation in that it may be used to satisfy oral cravings, the 4-mg strength might delay weight gain,<sup>7,53</sup> and patients can self-titrate therapy to acutely manage withdrawal symptoms. Because the lozenge does not require chewing, many patients find this to be a more discrete nicotine delivery system. The disadvantages of the lozenge are the fact that it requires frequent dosing, and the

gastrointestinal side effects (nausea, hiccups, and heartburn) may be bothersome.

**Postcessation Weight Gain**

**5. T.B. is worried about gaining weight after she quits smoking. Is weight gain common after quitting, and if so, how can this be prevented?**

Most tobacco users gain weight after quitting, and clinicians should neither deny the likelihood of weight gain nor minimize its significance.<sup>7</sup> For nearly all patients, the health risks associated with postcessation weight gain are negligible compared to the risks of continued smoking.

Studies suggest that most quitters gain less than 10 lb, but there is a broad range of weight gain reported, with up to 10% of quitters gaining as much as 30 lb.<sup>7</sup> In general, women tend to gain more weight than men. In a study of nearly 6,000 smokers who were followed up for 5 years after quitting, the average weight gain during the follow-up period was 19.2 and 16.7 lb among women and men, respectively.<sup>55</sup> For men and women, subgroups that are more likely to gain weight after quitting are African Americans, younger tobacco users (younger than 55 years), and heavier tobacco users (those smoking more than 25 cigarettes per day).

The weight-suppressing effects of tobacco are well known. However, the mechanisms to explain why most successful quitters gain weight are not completely understood. Smokers have been found to have an approximately 10% higher metabolic rate compared with nonsmokers.<sup>56</sup> In some studies, higher caloric intakes were documented after cessation.<sup>57,58</sup> The increased caloric intake may result from an increase in appetite, improved sense of taste, or a change in the hand-to-mouth ritual through the substitution of tobacco with food.

In general, a patient is less likely to be successful if he or she attempts to change multiple behaviors at once. For this reason, strict dieting to prevent weight gain, especially during the early stages of quitting, is generally not recommended.<sup>7</sup> T.B. should be counseled that the average weight gain of less than 10 lb is less detrimental to her overall health than is continued smoking. Because she is concerned about weight gain, it is reasonable for the clinician to recommend that T.B. engage in some form of regular physical activity. Even modest physical activity (e.g., walking 30 minutes daily) has been found to attenuate the weight gain associated with smoking cessation.<sup>58</sup> Although strict dieting is not recommended, T.B. should carefully plan and prepare meals to avoid binge eating, increase her water intake to create a feeling of fullness, chew sugarless gum, and limit alcohol consumption. Furthermore, T.B. may consider pharmacotherapy options that have been shown to delay weight gain—this would include the 4-mg nicotine gum or lozenge or bupropion SR.<sup>7</sup> It is important to note, however, that once the medication is terminated, the quitter gains, on average, an amount of weight that is comparable to that which would have been gained in the absence of medication.<sup>7</sup>

**Relapse Back to Smoking**

**6. During a follow-up contact, the clinician learns that T.B. smoked half a pack of cigarettes at a party over the weekend**

**and has relapsed to her previous smoking levels after not having smoked for just over a month. How should the clinician respond?**

The clinician should thank T.B. for being honest about her smoking and ask her to discuss the circumstances during which the smoking occurred. At the time of her smoking, where was she, who was she with, how did she get access to cigarettes, and how was she feeling at the time? What, specifically, were the triggers for her relapse (e.g., alcohol, depression, friends who were smoking around her)? It is important that the clinician help the patient to use this information as part of the learning process, but it also is important to focus on the “positive,” such as T.B.’s ability to have remained tobacco free for more than 1 month. After being smoke free for more than 4 weeks, most physical effects of nicotine withdrawal have completely resolved, and thus, the relapse trigger for T.B. likely was psychological or situational and could be abated through application of effective coping techniques. After an informal discussion about the situation in which the smoking occurred, it is important that the clinician work with the patient in identifying strategies for avoiding relapse in the future (Table 85-6).

## Smoking and Cardiovascular Disease

**7.** P.J. is a 62-year-old man admitted for an elective coronary artery bypass graft (CABG) procedure. His medical history is significant for angina, hypertension, dyslipidemia, peripheral vascular disease (PVD), and allergic rhinitis. He underwent a bilateral carotid endarterectomy procedure 2 years ago and had iliac artery angioplasty with stent placement 5 years ago for PVD. P.J.’s social history is significant for tobacco use (1.5–2 PPD) and alcohol (3–4 drinks/day). He is approximately 10 lb overweight. His preoperative laboratory results are significant for a total cholesterol of 270 mg/dL (desirable, <200), low-density lipoprotein cholesterol count (LDL-C) of 163 mg/dL (optimal, <70), high-density lipoprotein cholesterol count (HDL-C) of 35 mg/dL (low, <40), and triglycerides of 350 mg/dL (normal, <150). His medications before admission include atenolol 50 mg QD, aspirin 81 mg QD, isosorbide dinitrate 20 mg TID, atorvastatin 20 mg QD, fluticasone nasal spray (50 mcg/spray) 1 spray/nosril QD, and nitroglycerin 0.4 mg SL as needed. Which of P.J.’s chronic medical conditions may be caused or exacerbated by his tobacco use?

A wealth of evidence suggests that cigarette smoking is a major cause of cardiovascular disease and is responsible for approximately 138,000 premature cardiovascular-related deaths each year.<sup>5</sup> Smoking is known to accelerate the process of atherosclerosis, leading to chronic cardiovascular disorders, including coronary heart disease, cerebrovascular disease, PVD, aortic aneurysm, and congestive heart failure.<sup>3</sup> In addition, smoking greatly elevates the risk for acute cardiovascular events, including sudden death, myocardial infarction (MI), stroke, and reocclusion of coronary or peripheral vessels after graft surgery or angioplasty.<sup>3,59</sup>

There are numerous plausible pathophysiological mechanisms whereby tobacco smoking contributes to the development of cardiovascular disease. Oxidant gases and other compounds in tobacco smoke are believed to induce a hypercoagulable state characterized by increased platelet aggregation and thrombosis, which greatly increases the risk of MI and

sudden death.<sup>59,60</sup> The carbon monoxide in smoke reduces the amount of oxygen available to tissues and organs, including myocardial tissue, and may reduce the ventricular fibrillation threshold.<sup>59</sup> Smoking may accelerate atherosclerosis through effects on serum lipids; smokers tend to have higher levels of total cholesterol, LDL-C, and triglycerides and lower HDL-C than nonsmokers.<sup>3</sup> Smoking increases the levels of inflammatory mediators (C-reactive protein, leukocytes, and fibrinogen), which may contribute to the development and progression of atherosclerosis.<sup>61</sup> Finally, smoking stimulates the release of neurotransmitters (e.g., epinephrine, norepinephrine) that increase myocardial workload and induce coronary vasoconstriction leading to ischemia, arrhythmias, and sudden death.<sup>3,59</sup>

P.J.’s hospital admission for a CABG procedure for coronary heart disease and angina, as well as previous procedures for peripheral vascular disease (angioplasty with stent placement) and cerebrovascular disease (bilateral carotid endarterectomy), are all conditions associated with chronic tobacco use. His elevated total cholesterol, LDL-C, and triglycerides and reduced HDL-C levels are consistent with smoking-induced dyslipidemia. Cigarette smoking in combination with P.J.’s other established cardiovascular risk factors (hypertension, dyslipidemia) have synergistically increased his risk for serious cardiovascular disease.<sup>3,59</sup> Fortunately, the effects of smoking on lipids, coagulation, myocardial workload, and coronary blood flow appear to be reversible, and P.J.’s risk of developing further cardiovascular-related complications will markedly decrease if he is able to quit smoking.<sup>36,62</sup> The clinician should approach this hospitalization as an opportunity to motivate and assist P.J. with quitting smoking.<sup>7</sup> Furthermore, data suggest the initiation of intensive cessation counseling interventions in hospitalized patients is effective in achieving long-term abstinence.<sup>63</sup>

**8.** The cardiothoracic surgeon has strongly advised P.J. to quit smoking. P.J. is willing to quit completely, but he is worried because he has tried to quit smoking “hundreds of times” and has never been able to quit for longer than 1 week. He expresses a desire for a medication to assist him during this quit attempt. He has tried the nicotine gum and transdermal patch during three previous quit attempts. He did not like the gum because it made his jaw sore. He had temporary success with the nicotine patch but found it to be less flexible than the gum. For example, when he needed extra nicotine during stressful situations, he could not apply a second patch. What treatment alternatives are reasonable for P.J.?

P.J. has failed treatment with the nicotine gum and transdermal patch. First-line treatment options that he has not tried include the nicotine lozenge (see question 4), nicotine nasal spray, nicotine inhaler, bupropion SR, and varenicline. P.J. might also be a candidate for combination therapy (see question 10).

## Nicotine Nasal Spray

The nicotine nasal spray is an aqueous solution of nicotine available in a metered-spray pump for administration to the nasal mucosa. Each actuation delivers a metered 50-mcL spray containing 0.5 mg of nicotine. Nicotine in the nasal spray is more rapidly absorbed than other NRT formulations (Fig. 85-3), with peak venous nicotine concentrations achieved within

11 to 18 minutes after administration.<sup>24</sup> Use of the nicotine nasal spray more than doubles long-term (>6 months) abstinence rates when compared to placebo (Table 85-4).<sup>7,44</sup>

### Dosing

A dose of nicotine (1 mg) is administered as two sprays, one (0.5-mg spray) in *each* nostril. The recommended initial regimen is one to two doses every hour while awake for 6 to 8 weeks. This may be increased, as needed, to a maximum recommended dosage of five doses per hour or 40 mg/day. For best results, patients should be encouraged to use at least eight doses per day during the initial 6 to 8 weeks of therapy because less frequent administration may be less effective. After 6 to 8 weeks, the dose should be gradually decreased over an additional 4 to 6 weeks.

### Patient Education

Before using the nasal spray for the first time, the nicotine nasal spray pump must be primed. This is done by actuating the device into a tissue until a fine spray is visible (about six to eight times). When administering a dose, the patient should tilt the head back slightly and insert the tip of the bottle into the nostril as far as is comfortable. After actuation of the pump, the patient should not sniff, swallow, or inhale through the nose because this increases the irritant effects of the spray. Patients should wait 5 minutes before driving or operating heavy machinery (because of the increased likelihood of tearing, coughing, and sneezing).

### Adverse Reactions

Side effects commonly reported with the nicotine nasal spray include nasal and throat irritation (hot peppery sensation), sneezing, coughing, watery eyes, and rhinorrhea. In clinical trials, 94% of patients report moderate-severe nasal irritation during the first 2 days of therapy; 81% of patients still reported mild-moderate nasal irritation after 3 weeks of therapy.<sup>7</sup> Nasal congestion and transient changes in taste and smell have also been reported.<sup>7</sup> Despite the high incidence of local adverse effects, with regular use during the first week, most patients become tolerant to the irritant effects of the spray.<sup>64</sup>

### Product Selection Considerations

The primary advantage in using the nicotine nasal spray is the ability to rapidly titrate therapy to manage withdrawal symptoms. However, because nicotine from the spray more rapidly penetrates the central nervous system, there may be higher likelihood of developing dependence during treatment. The nicotine nasal spray has a dependence potential intermediate between tobacco products and other NRT products. About 15% to 20% of patients continue to use the nicotine nasal spray for longer periods than recommended (6–12 months), and 5% use the spray at higher doses than recommended.<sup>7</sup> Individuals with chronic nasal disorders (e.g., rhinitis, polyps, sinusitis) or severe reactive airway disease should not use the nicotine nasal spray because of its irritant effects. Exacerbation of asthma has been reported after use of the nicotine nasal spray.<sup>65</sup>

### Nicotine Inhaler

The nicotine inhaler consists of a two-piece plastic device designed to deliver nicotine contained in individual cartridges. Each foil-sealed cartridge contains a porous plug with 10 mg

of nicotine and 1 mg of menthol. Menthol is added to reduce the irritant effect of nicotine. Plastic spikes located on the interior of both mouthpiece components pierce the protective foil covering on the cartridge, allowing the release of 4 mg of nicotine vapor following inhalation.

Given that the usual pack-a-day smoker repeats the hand-to-mouth motion up to 200 times per day or 73,000 times each year, it is not surprising that many smokers find they miss the physical manipulation of the cigarette and associated behaviors that accompany smoking. The nicotine inhaler was designed to provide nicotine replacement in a manner similar to smoking while addressing the sensory and ritualistic factors that are important to many patients who smoke.<sup>66</sup>

As a patient puffs on the inhaler, the nicotine vapor is delivered to the mouth and throat, where it is absorbed through the mucosa. Only a small amount (<5% of a dose) of nicotine reaches the lower respiratory tract.<sup>67</sup> With an intensive inhalation regimen (80 puffs over 20 minutes), about 4 mg of nicotine is delivered, and of that, 2 mg is absorbed.<sup>68</sup> Peak plasma nicotine concentrations with the inhaler are achieved after approximately 30 minutes of use<sup>24</sup> and then slowly decline thereafter (Fig. 85-3). Use of the nicotine inhaler approximately doubles long-term (>6 months) abstinence rates when compared to placebo (Table 85-4).<sup>7,44</sup>

### Dosing

During the initial 3 to 6 weeks of treatment, the patient should use one cartridge every 1 to 2 hours while awake. This should be increased, as needed, to a maximum of 16 cartridges per day. In clinical trials, most successful quitters used an average of 6 to 16 cartridges per day. The manufacturer recommends that each cartridge be depleted of nicotine by frequent continuous puffing over 20 minutes. The recommended duration of treatment is 3 months, after which patients may be weaned from the inhaler by gradual reduction of the daily dose over the following 6 to 12 weeks.

### Patient Education

Patients should be instructed to inhale shallowly (as if puffing a pipe) to minimize the likelihood of throat irritation. When used correctly, 100 shallow puffs from the inhaler mouthpiece over 20 minutes approximates 10 puffs from one cigarette over 5 minutes.<sup>66</sup> The release of delivery of nicotine from the inhaler is temperature dependent and significantly reduced at temperatures below 40°F.<sup>7,66</sup> In cold conditions, patients should store the inhaler and cartridges in a warm place (e.g., inside pocket).<sup>7</sup> Conversely, under warmer conditions, more nicotine is released per puff. However, nicotine plasma concentrations achieved using the inhaler in hot climates at maximal doses will not exceed levels normally achieved with smoking.<sup>66</sup>

As with other forms of NRT that are absorbed across the buccal mucosa, the effectiveness of the nicotine inhaler may be reduced by acidic foods and beverages, such as coffee, juices, wine, or soft drinks. Therefore, patients should be instructed not to eat or drink anything (except water) for 15 minutes before or while using the inhaler.

### Adverse Reactions

The most common side effects associated with the nicotine inhaler include mouth/throat irritation (40%) and cough (32%).<sup>7</sup> Most patients rated cough and mouth and throat irritation symptoms as mild, decreasing with continued use. Other

less common side effects are rhinitis, dyspepsia, hiccups, and headache. Adverse reactions necessitating discontinuation of treatment occurred in less than 5% of patients using the inhaler.

### **Product Selection Considerations**

Patients who express a preference for therapy that can be easily titrated to manage withdrawal symptoms or one that mimics the hand-to-mouth ritual of smoking may find the nicotine inhaler to be an appealing option. Patients with underlying bronchospastic conditions should use the nicotine inhaler with caution because the nicotine vapor may be irritating and provoke bronchospasm.

### **Bupropion SR**

Bupropion SR was the first non-nicotine medication FDA-approved for smoking cessation. Clinical trials involving enrolling nearly 10,000 patients over the past 16 years have confirmed its effectiveness as an aid for smoking cessation.<sup>45</sup> A recent meta-analysis found that bupropion SR treatment doubles long-term (>6 months) abstinence rates when compared to placebo (Table 85-4).<sup>7</sup>

### **Pharmacokinetics**

Animal data suggest the absolute bioavailability of bupropion ranges from 5% to 20%. It undergoes extensive hepatic metabolism to three active metabolites; one of the metabolites, hydroxybupropion, is formed by the cytochrome P450 isoenzyme CYP2B6. Bupropion and its metabolites are eliminated in urine (87%) and feces (10%), with less than 1% being excreted unchanged in the urine. The half-life for bupropion is 21 hours, and its metabolites have a half-life range of 20 to 27 hours; steady-state plasma concentrations are reached within 5 and 8 days, respectively.<sup>69</sup>

### **Dosing**

Treatment with bupropion SR should be initiated while the patient is still smoking because approximately 1 week of treatment is necessary to achieve steady-state blood levels. Patients should set a target quit date that falls within the first 2 weeks of treatment, generally in the second week. The starting dose of bupropion SR is one 150-mg tablet each morning for the first 3 days. If the initial dose is tolerated, the dosage should be increased on the fourth day to the recommended maximum dosage of 300 mg/day (150 mg BID). Therapy should be continued for 7 to 12 weeks after the quit date; however, some patients might benefit from extended treatment. Whether to continue treatment with bupropion SR for periods longer than 12 weeks for smoking cessation must be determined for individual patients.<sup>69</sup> For patients experiencing side effects with the 300 mg/day regimen, Swan et al suggest that 150 mg/day is better tolerated and exhibits comparable long-term efficacy.<sup>70</sup> Similarly, Hurt and colleagues found no significant difference in long-term (>6 months) abstinence rates between subjects randomized to 150 mg/day or 300 mg/day.<sup>71</sup>

### **Patient Education**

Patients should be instructed to follow the dosing regimen described previously. Advise patients experiencing insomnia to avoid taking the second dose close to bedtime. Inform patients that bupropion might cause dizziness, drowsiness, or reduced alertness, and caution should be exercised when driving or

operating machinery. Because alcohol use might increase the likelihood of seizures, patients should avoid or drink alcohol only in moderation while taking bupropion. Patients who consume alcohol regularly should be advised to talk with a health care provider about their alcohol use before initiating bupropion therapy because abrupt cessation of alcohol use while taking bupropion might increase the risk of seizure. Patients should also be advised not to take Zyban and Wellbutrin or generic bupropion formulations concomitantly to avoid dose-related adverse effects, including seizures.

### **Adverse Reactions**

Adverse effects associated with bupropion therapy include insomnia (35%–40%) and dry mouth (10%)<sup>7</sup>; these usually lessen with continued use. Taking the second daily dose in the early evening, but no sooner than 8 hours after the first dose, might reduce insomnia. Less common side effects include headache, nausea, tremors, and rash. Seizures are a dose-related toxicity associated with bupropion therapy. For this reason, bupropion is contraindicated in patients with underlying seizure disorders and those receiving concurrent therapy with other forms of bupropion (Wellbutrin, Wellbutrin SR, and Wellbutrin XL). Bupropion also is contraindicated in patients with anorexia or bulimia nervosa, patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines), and patients currently taking monoamine oxidase inhibitors due to the increased potential for seizures in these populations. In clinical trials for smoking cessation, the frequency of seizures with bupropion SR is <0.1% (seven seizures among 8,000 bupropion-treated patients),<sup>45</sup> which is comparable to the reported incidence of seizures (0.1%) with the sustained-release formulation (Wellbutrin) when used for the treatment of depression.<sup>72</sup> For this reason, bupropion should be used with extreme caution in patients with a history of seizure, cranial trauma, patients receiving medications known to lower the seizure threshold, and patients with underlying severe hepatic cirrhosis. Animal studies suggest that seizures may be related to the peak plasma concentration of bupropion,<sup>73</sup> and as a precautionary measure, the manufacturer recommends that patients space the doses at least 8 hours apart and limit the total daily dose to no more than 300 mg.

### **Product Selection Considerations**

Bupropion SR may be the drug of choice for patients who prefer to take oral medications (an alternative oral option is varenicline, described as follows). Because bupropion SR is simple to use (twice daily oral dosing), this agent may be preferable for patients with regimen compliance concerns (e.g., those unable to consistently use short-acting NRT formulations that require multiple daily doses). Bupropion SR may be particularly beneficial for use in patients with coexisting depression or in individuals with a history of depressive symptoms during a previous quit attempt. Finally, bupropion SR can be used safely in conjunction with NRT, and data suggest that this combination might be slightly more effective than monotherapy with either agent.<sup>7,74</sup> Disadvantages of bupropion SR include a high prevalence of insomnia and the need to screen patients carefully to prevent the rare complication of seizures.

### **Varenicline**

Varenicline is the most recent agent approved by the FDA for smoking cessation. Data from meta-analyses indicate that

varenicline significantly increases long-term abstinence rates relative to placebo and bupropion SR,<sup>7</sup> with a pooled odds ratio of 3.1 for varenicline versus placebo for continuous abstinence at 6 months follow-up (Table 85-4). In clinical trials comparing varenicline with bupropion, varenicline was shown to be significantly superior at 52 weeks with an odds ratio of 1.7 (95% CI, 1.3–2.2).<sup>75</sup>

### Pharmacokinetics

Varenicline absorption is virtually complete after oral administration, and oral bioavailability is unaffected by food or time-of-day dosing. Once absorbed, varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination is primarily through glomerular filtration, along with active tubular secretion, possibly via the organic cation transporter, OCT2.<sup>76</sup> The half-life is approximately 24 hours, and following administration of multiple oral doses, steady-state conditions are reached within 4 days.<sup>77</sup>

### Dosing

Treatment with varenicline should be initiated 1 week before the patient stops smoking. This dosing regimen allows for gradual titration of the dose to minimize treatment-related nausea and insomnia. The recommended dose of varenicline is 1 mg BID (taken as one 1-mg tablet in the morning and one 1-mg tablet in the evening) following a 1-week titration: 0.5 mg daily days 1 to 3, 0.5 mg twice daily days 4 to 7, and 1 mg twice daily weeks 2 to 12. For patients who have successfully quit smoking at the end of 12 weeks, an additional course of 12 weeks may be appropriate to increase the likelihood of long-term abstinence. Varenicline is excreted largely unchanged in the urine, and as such, should be used with caution in patients with severe renal dysfunction (<30 mL/minute). Dosage adjustments may be necessary.

### Patient Education

The tablets are to be taken orally, after eating, with a full glass of water. Nausea and insomnia are side effects that are usually temporary. However, if these symptoms persist, patients should notify their provider so dosage reduction can be considered. The typical regimen is a 12-week course of therapy, and patients should be advised to comply with the prescribed dosage for the recommended duration.

### Adverse Reactions

Varenicline is generally well tolerated. Common side effects ( $\geq 5\%$  and twice the rate observed in placebo-treated patients) include nausea (30%), sleep disturbance (insomnia 18%; abnormal dreams 13%), constipation (8%), flatulence (6%), and vomiting (5%). Per the manufacturer's prescribing information, nausea was the most common adverse event associated with varenicline treatment. Nausea was dose dependent and generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. Initial dose titration was beneficial in reducing the occurrence of nausea. Approximately 3% of subjects receiving varenicline 1 mg BID discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.<sup>76</sup>

Post marketing, there have been case reports of neuropsychiatric symptoms (behavior changes, agitation, depressed mood,

suicidal ideation or behavior) as well as reports of worsening of pre-existing psychiatric illness among patients being treated with varenicline. These reports are rare in comparison to the total number of patients using the medication, but nonetheless warrant ongoing surveillance. In 2008, the FDA alerted health care providers to advise patients and caregivers that patients should stop taking varenicline and contact their health care provider immediately if agitation, depressed mood, or changes in behavior that are not typical for them are observed, or if the patient develops suicidal ideation or suicidal behavior.<sup>78</sup> Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of varenicline, and as such, the safety and efficacy of the medications in these populations have not been established.<sup>76</sup>

### Product Selection Considerations

Varenicline is a first-line agent for the treatment of tobacco use and dependence.<sup>7</sup> It offers a convenient oral dosing regimen and a new mechanism of action that might be particularly appealing for patients who have failed quit attempts with other first-line agents (e.g., NRT or bupropion SR). Its use has not been recommended in combination with other agents and therefore is currently limited to monotherapy. As with any of these medications, varenicline should be combined with behavioral counseling in order to maximize chances for a successful, long-term quit attempt. Given its potential for inducing negative neuropsychiatric effects, varenicline might not be the optimal choice for patients with a current or past history of psychiatric illness.

P.J. has tried the nicotine gum and transdermal patch during previous quit attempts. Because he was intolerant to the nicotine gum (it stuck to his dental work), this form of NRT is not appropriate. P.J.'s experience with the transdermal patch suggests he may benefit from a short-acting NRT formulation that allows for active administration and titration of drug as needed to alleviate symptoms of withdrawal. Other first-line therapies include the nicotine nasal spray, inhaler, and lozenge; bupropion SR; or varenicline. P.J. should not use the nicotine nasal spray because he has allergic rhinitis and may be more susceptible to the irritant effects of the spray. In addition, some data suggest that the bioavailability of nicotine is reduced in patients with rhinitis.<sup>79</sup> Furthermore, the safety and efficacy of the nasal spray in patients with chronic nasal disorders have not been adequately studied. Reasonable choices for P.J. therefore include bupropion SR, nicotine lozenge, nicotine inhaler, or varenicline. Any of these options are reasonable, and the choice of therapy should be dictated by P.J.'s individual preference. Alternatively, it is reasonable to consider combination therapy (see question 10).

## Safety of Nicotine Replacement Therapy in Patients With Cardiovascular Disease

**9.** P.J. would like to try the nicotine inhaler. Is NRT safe for use in patients with cardiovascular disease?

Nicotine activates the sympathetic nervous system leading to an increase in heart rate, blood pressure, and myocardial contractility. Nicotine may also cause coronary artery vasoconstriction.<sup>80</sup> These known hemodynamic effects of

nicotine have led to doubts about the safety of using NRT in patients with established cardiovascular disease, particularly those with serious arrhythmias, unstable angina, or MI.

Soon after the nicotine patch was approved, anecdotal case reports in the lay press linked NRT (patch and gum) with adverse cardiovascular events (i.e., arrhythmias, MI, stroke). Since then, several randomized, controlled trials have evaluated the safety of NRT in patients with cardiovascular disease, including angiographically documented coronary artery stenosis, MI, stable angina, and previous coronary artery bypass surgery or angioplasty.<sup>81-83</sup> The results of these trials suggest no significant increase in the incidence of cardiovascular events or mortality among patients receiving the nicotine patch when compared with placebo. However, because these trials specifically excluded patients with unstable angina, serious arrhythmias, and recent MI, the manufacturers of NRT products recommend that these agents be used with caution among patients in the immediate (within 2 weeks) post-MI period, those with serious arrhythmias, and those with unstable angina.<sup>7</sup> It is notable, however, that NRTs (patch, nasal spray) have been shown to have fewer effects on biomarkers of cardiovascular risk than does smoking,<sup>84</sup> and smoking cessation has been shown to improve cardiovascular parameters with no negation of these improvements with use of NRT.<sup>85</sup>

Although one methodologically weak case-control study raised questions regarding NRT use in intensive care settings,<sup>86</sup> NRT use in patients with cardiovascular disease has been the subject of numerous reviews, and it is widely believed by experts in the field that the risks of NRT in this patient population are small in relation to the risks of continued tobacco use.<sup>44,59,80,87,88</sup> The 2008 Clinical Practice Guideline concludes that there is no evidence of increased cardiovascular risk with these medications.<sup>7</sup> Although the use of NRT may pose some theoretical risk in a patient like P.J., cigarette smoking is far more hazardous to his health. Cigarettes, unlike NRT, deliver numerous toxins that induce a hypercoagulable state, reduce the oxygen-carrying capacity of hemoglobin, and adversely affect serum lipids. The amount of nicotine that P.J. would receive using the recommended dose of any NRT product will not exceed the amount he previously obtained from his 1.5–2 PPD smoking habit. The clinician should strongly encourage pharmacotherapy during P.J.'s current quit attempt. P.J. is 10 lb overweight; the additional risk imposed by a modest weight gain after smoking cessation likely will not be of clinical significance, compared with that of continued smoking.

## Combination Therapy

**10.** J.B. is a 60-year-old man referred to the pulmonary clinic for further evaluation and management of his chronic obstructive pulmonary disease (COPD). He complains of decreased exercise tolerance and has noted increasing shortness of breath (SOB) with minimal exertion (e.g., while golfing or climbing stairs). He currently uses an albuterol inhaler (90 mcg/puff), 2 puffs Q 4 hr regularly for SOB. His medical history is otherwise unremarkable except for osteoarthritis controlled with acetaminophen 1 g TID. He has smoked approximately 1.5 to 2 PPD for more than 40 years. J.B. indicates he has made several quit attempts over the past year. On the first attempt (quitting “cold turkey”), J.B.

relapsed within 2 days. J.B. was smoke free for nearly 2 weeks on his second quit attempt (using the 4-mg nicotine lozenge), but he found it difficult to adhere to the frequent dosing schedule and relapsed shortly, discontinuing the lozenge. His most recent quit attempt was 6 months ago using varenicline (1 mg BID). After 1 month of abstinence, J.B. self-terminated varenicline (“I thought I didn’t need it anymore”) and relapsed within 2 weeks. On further questioning, J.B. states that he did not enroll in a behavioral counseling program or seek additional assistance (other than pharmacotherapy) during any of his quit attempts. He expresses an interest in smoking cessation but is discouraged by his inability to quit. On physical examination, coarse breath sounds that clear after coughing are noted. His chest x-ray results are normal. Spirometry reveals a forced expiratory volume in 1 second (FEV<sub>1</sub>) of 2.8 L (72% of predicted) and a forced vital capacity (FVC) of 4.1 L (81% of predicted). His FEV<sub>1</sub>/FVC ratio is 68%. He weighs 76 kg and is 72 in. tall. J.B. is concerned about his worsening pulmonary function and is committed to making another effort to quit. What treatment options are appropriate for J.B.?

Tobacco smoking is the single most important risk factor for the development of COPD, and most patients diagnosed with COPD are current or former smokers.<sup>89</sup> Medications (e.g., bronchodilators, anti-inflammatory agents) used to treat the symptoms of COPD have not been shown to alter the disease progression.<sup>89</sup> J.B.'s pulmonary function tests indicate he has stage II (moderate) COPD<sup>89</sup>; given his worsening pulmonary symptoms, it is imperative that he stop smoking as soon as possible. J.B. should be advised that medications for COPD offer only limited symptomatic relief; the most important component of his treatment is smoking cessation.<sup>89,90</sup> The clinician should commend J.B. for his interest in quitting and help him devise a patient-specific treatment plan.

In addition to monotherapy with any of the first-line agents, the 2008 Clinical Practice Guideline identified selected combinations of medications that can be considered in the initial treatment of tobacco dependence. Medication combinations that significantly increase long-term (>6 months) cessation rates relative to placebo and are recommended as first-line treatments include combination NRT and the nicotine patch in combination with bupropion SR (Table 85-4).<sup>7</sup>

### Combination Nicotine Replacement Therapy

Combination NRT involves the use of a long-acting formulation (patch) in combination with a short-acting formulation (gum, lozenge, inhaler, or nasal spray). The long-acting formulation, which delivers relatively constant levels of drug, is used to prevent the onset of severe withdrawal symptoms, whereas the short-acting formulation, which delivers nicotine at a faster rate, is used as needed to control withdrawal symptoms that may occur during potential relapse situations (e.g., after meals, when stressed, or around other smokers). A recent meta-analysis found that the nicotine patch in combination with a short-acting NRT formulation (gum, inhaler, or nasal spray) was significantly more effective than single-agent NRT. The odds of long-term (>6 months) cessation was 1.4 with combination NRT compared to NRT monotherapy (95% CI, 1.1–1.6).<sup>44</sup>

### Nicotine Patch and Bupropion SR in Combination

The combination of bupropion SR and NRT has been evaluated in three long-term controlled trials. Patients receiving

combination therapy with bupropion SR and the nicotine patch in standard dosages were significantly more likely to quit than were patients randomized to the nicotine patch alone.<sup>7</sup> The odds of long-term (>6 months) abstinence were 1.3, with the combination compared to nicotine patch monotherapy (95% CI, 1.0–1.8).<sup>7</sup>

### TREATMENT SELECTION

Given the severity of J.B.'s condition and his willingness to quit now, the clinician should initiate treatment as soon as possible. His treatment should consist of pharmacotherapy in conjunction with behavioral counseling and appropriate follow-up.

#### Pharmacotherapy

The clinician should work with J.B. to select the most appropriate pharmacotherapy. As noted previously, appropriate options would include the various NRT formulations, bupropion SR, varenicline, or an effective combination of first-line agents. The choice of therapy is dictated by considerations such as individual patient preference for a given agent, previous experience with cessation medications, current medical conditions, previous levels of smoking, medication adherence issues, and the patient's out-of-pocket cost. For patients reporting a positive experience with a given medication, retreatment with the same agent or a combination of agents might be appropriate, with consideration given to increasing the dose, frequency, or duration of therapy. For patients reporting a negative experience with pharmacotherapy (e.g., poor adherence, side effects, palatability issues, cost), an alternative agent should be considered. Given J.B.'s previous adherence issues with the nicotine lozenge as monotherapy, it might be preferable to use a long-acting cessation medication such as the nicotine patch, bupropion SR, or varenicline. Combination therapy with the nicotine patch and a short-acting NRT formulation (used as needed) or bupropion SR would also be appropriate.

#### Behavioral Counseling

Although medications are effective alone in helping patients quit smoking, maximizing patients' chances for a long-term, successful quit attempt requires the use of one or more medications in combination with behavioral counseling. J.B.'s previous 1-month quit attempt highlights the successful impact of varenicline in this patient; however, the relapse is likely attributable to a shortened course of therapy and the absence of a behavioral counseling program. J.B. should be advised that the medications are designed to make patients more comfortable while quitting and that behavioral counseling is needed to address the "habit" of smoking by helping him cope with difficult situations and triggers for relapse. J.B. should be advised to (a) call the tollfree tobacco quitline at 1-800-QUIT NOW, (b) call the tollfree number that accompanies the selected medication (all medications include a free counseling program), (c) enroll in a local group program, (d) join an online quitting program such as Quitnet.com, or (e) request individualized counseling from a health professional with expertise in tobacco cessation. In addition, J.B. should be reminded that compliance with the medication regimen—daily compliance, as well as duration of therapy—will increase his chances of quitting for good. Clinician-delivered counseling might also include a personalized message to further enhance his motivation to quit. For example, the clinician could translate J.B.'s spirometry results

into an effective "lung age" (e.g., the age of the average healthy individual with similar spirometry values). Given J.B.'s height (72 in.) and FEV<sub>1</sub> (2.8 L), his estimated "lung age" is almost 80 years.<sup>91</sup> This educational approach has been found to significantly increase long-term (12-month) quit rates in a recent controlled trial.<sup>91</sup>

### Complementary Therapies

**11. J.B. is worried about "taking more drugs" and asks whether one of the natural herbal products might be better for him than "prescription drugs."**

Although many herbal and homeopathic products are available to help people quit smoking, data that support their safety and effectiveness are lacking. Most herbal preparations for smoking cessation contain lobeline, an herbal alkaloid with partial nicotine agonist activity. Although direct-to-consumer advertisements suggest that lobeline-containing preparations are safe and effective, a meta-analysis found no evidence to support the role of lobeline as an effective aid for smoking cessation.<sup>92</sup> Likewise, nicobrevin (an herbal product not available in the United States that contains quinine, menthyl valerate, camphor, and eucalyptus oil),<sup>93</sup> hypnosis,<sup>94</sup> and acupuncture<sup>95</sup> have not been found to be effective treatments for smoking cessation.<sup>7</sup> Furthermore, patients should be cautioned that herbal cigarettes are not safe alternatives because they result in the inhalation of other toxins present in smoke. J.B. should be advised that the efficacy of the herbal therapies are not well established, and use of these agents cannot be recommended at this time.

**12. K.M. is a 47-year-old female who has been smoking cigarettes (2 PPD) for almost 30 years. She admits to numerous failed attempts over the past 10 years. K.M. states, "I've tried just about everything to help me quit, but nothing seems to work." K.M. has tried NRT (transdermal patch, lozenge, and inhaler), bupropion SR, varenicline, acupuncture, and hypnotherapy. On questioning, K.M.'s treatment regimens have been appropriate (e.g., correct dosages, duration of therapy). K.M. has enrolled in several worksite cessation classes throughout the years but admits to sporadic attendance due her stressful and unpredictable schedule (she is a paralegal in a busy law firm). Her medical history is significant for TMJ syndrome secondary to nocturnal bruxism (teeth grinding). K.M. is ready to quit now and states, "I want to go to my 30-year high school reunion [4 months from now] as a nonsmoker." What treatment options exist for patients failing first-line therapies?**

For most smokers, the quitting process is characterized by a series of quit attempts and subsequent relapses. On average, former smokers report 10.8 quit attempts over a period of 18.6 years before achieving long-term cessation.<sup>96</sup> Most quit attempts are undertaken without assistance, and approximately 95% of attempts end in relapse.<sup>7</sup> As emphasized in the 2008 Clinical Practice Guideline, clinicians should approach the treatment of tobacco dependence in a manner similar to the treatment of other chronic medical conditions such as diabetes, asthma, hyperlipidemia, and hypertension. By acknowledging the chronic nature of tobacco dependence, clinicians will appreciate the need for ongoing care (which includes patient education, behavioral counseling, and pharmacotherapy) rather than episodic care (e.g., a single treatment course or

periodic/occasional interventions).<sup>7</sup> K.M. should be congratulated on her renewed interest in quitting, and the clinician should work with her to design an individualized treatment plan.

### Second-Line Agents

#### CLONIDINE

Clonidine is a centrally acting  $\alpha_2$ -adrenergic agonist that reduces sympathetic outflow from the central nervous system. Clonidine is approved for use as an antihypertensive agent, but it is also effective in reducing the autonomic symptoms of both opioid and alcohol withdrawal. Studies of clonidine for smoking cessation have been inconsistent, but a recent meta-analysis concluded that clonidine treatment doubles long-term (>6 month) abstinence rates relative compared to placebo (Table 85-4).<sup>7</sup> Dosages for tobacco cessation have ranged from 0.15 to 0.75 mg/day PO and 0.1 to 0.3 mg/day transdermally. The recommended starting dose is 0.1 mg BID or 0.1 mg/day transdermally, increasing by 0.10 mg/day/week as tolerated for up to 10 weeks.<sup>7</sup> The high incidence of side effects, including dry mouth, sedation, dizziness, and constipation, relegate clonidine as a second-line agent reserved for individuals who have failed or are intolerant of first-line agents.

#### NORTRIPTYLINE

Nortriptyline, a tricyclic antidepressant, has demonstrated efficacy for smoking cessation, approximately doubling long-term (6-month) abstinence rates compared with placebo (Table 85-4).<sup>7</sup> The regimen used for treating tobacco dependence is 25 mg/day, increasing gradually to a target dosage of 75 to 100 mg/day, for approximately 12 weeks.<sup>7</sup> Because the half-life of nortriptyline is prolonged (up to 56 hours), therapy should be initiated at least 10 days before the quit date to allow it to reach steady-state concentrations at the target dose. The side effects most commonly observed with nortriptyline include sedation, dry mouth, blurred vision, urinary retention, lightheadedness, and tremor. This drug should be used with caution in patients with underlying cardiovascular conditions because of the risk of arrhythmias and postural hypotension.

### High-Dose Nicotine Replacement Therapy

Plasma levels of nicotine achieved with NRT are generally much lower than those observed during regular smoking.<sup>64,97</sup> Given this incomplete level of nicotine replacement, standard doses of NRT may be insufficient for some individuals, and in particular, for moderate-to-heavy smokers. Studies using transdermal nicotine in doses up to 44 to 63 mg/day suggest that high-dose NRT is safe.<sup>98-102</sup> However, trials evaluating higher doses of NRT have yielded conflicting results. Some studies suggest higher doses of NRT may be more effective in heavy smokers,<sup>100,101,103</sup> whereas others have demonstrated slight but not statistically significant improvements in cessation rates<sup>104,105</sup> or no difference.<sup>106,107</sup> When the results of six studies were pooled, the odds ratio for abstinence was 1.2 for high-dose NRT compared to conventional dose NRT (95% CI, 1.0-1.3), suggesting that high-dose NRT therapy may be advantageous in some patients.<sup>44</sup> This approach should be reserved for patients not able to quit using conventional doses of transdermal NRT.

### Extended Use of Medications

In a minority of patients, extended duration medication therapy appears to be safe and effective. Long-term follow-up data from the Lung Health Study have found that approximately 15% of long-term quitters continued nicotine gum therapy with no serious side effects.<sup>108</sup> The 2008 Clinical Practice Guideline states that extended use of medications might be beneficial in individuals who report persistent withdrawal symptoms during treatment, those who have relapsed shortly after medication discontinuation, or those who are interested in long-term therapy.<sup>7</sup> Clinicians should be aware that many of the medications (bupropion SR, varenicline, nicotine nasal spray and inhaler) are FDA approved for long-term (6-month) use.<sup>69,76,109,110</sup> Although the goal should be complete abstinence from all nicotine-containing products, continued use of medicinal nicotine is substantially safer than any level of smoking.<sup>7,111</sup>

K.M. has relapsed following appropriate treatment with several first-line agents, and the clinician should evaluate K.M.'s previous quit attempts, including the dates, methods used (behavioral and pharmacotherapy), and her perceptions of why these methods were ineffective. If K.M. believes a particular medication was more effective than others, it might be reasonable to use the same agent during her next quit attempt.<sup>7</sup> Alternative approaches include the use of a different medication (including second-line agents) or a combination of medications<sup>7</sup> (see question 10). Given that K.M. has TMJ, the nicotine gum formulation should not be used.

### Drug Interactions With Smoking

**13.** M.K. is a new patient presenting to the pharmacy with a new prescription for Ortho Tri-Cyclen (norgestimate/ethinyl estradiol). The new patient history form completed by M.K. reveals that she is 32 years old, weighs 65 kg, and is 70 in. tall. She takes no prescription medications but occasionally uses loratadine 10 mg PRN for allergies and ibuprofen 400 mg PRN for dysmenorrhea. She has no significant medical history. Her father has hypertension and suffered an MI last year. Her mother has type 2 diabetes and dyslipidemia. Her social history is significant for tobacco use (1 PPD for 15 years), alcohol (1 glass of wine per night), and caffeine (5-6 cups of coffee daily). Are there any potential interactions with M.K.'s new prescription?

### Smoking and Combined Hormonal Contraceptives

One of the most important, but often unrecognized, precautions to consider with oral contraceptive use is the potential interaction between tobacco smoke and estrogens in combination hormonal contraceptives. Estrogens are known to promote coagulation by altering clotting factor levels and increasing platelet aggregation. As described in question 7, substances present in tobacco smoke, including oxidant gases and other products of combustion, induce a hypercoagulable state increasing the risk of acute cardiovascular events. Exposure to both factors (smoking and high levels of estrogen) greatly increases the risk of thromboembolic and thrombotic disorders. Considerable epidemiologic evidence indicates that cigarette smoking substantially increases the risk of adverse cardiovascular events, including stroke, MI, and thromboembolism in women who use oral combination hormonal contraceptive agents.<sup>112,113</sup> This

risk is age related, in that the absolute risk of death from cardiovascular disease in oral contraceptive users who smoke is 3.3 per 100,000 women ages 15 to 34 years compared with 29.4 per 100,000 women ages 35 to 44 years. To put this in perspective, the corresponding risk of death from cardiovascular disease in *nonsmoking* women who use oral contraceptives is much lower, with a death rate of 0.65 per 100,000 women ages 15 to 34 years and 6.21 per 100,000 women ages 35 to 44 years.<sup>114</sup> Because of the increase risk of adverse cardiovascular events, current guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the World Health Organization (WHO) state that combination estrogen-progestin contraceptives should not be used in women who are older than 35 years of age and smoke.<sup>115,116</sup> These organizations recommend the use of progestin-only contraceptives (oral and injectable formulations) and intrauterine devices in this population.<sup>115,116</sup>

M.K. is 32 years of age, and despite her heavy smoking status (20 cigarettes per day), oral contraceptive use is not contraindicated at this time. However, the clinician should strongly advise M.K. to quit smoking and assess her readiness to do so. M.K. should be informed that if she continues to smoke while using oral combined hormonal contraceptives, her risk of developing a blood clot, stroke, or heart attack will continue to increase over time. Her family history (father with recent MI and mother with diabetes and hyperlipidemia) suggests that she may be genetically predisposed to cardiovascular disease, and thus, efforts to minimize preventable risk factors should be encouraged to reduce the likelihood that she will develop cardiovascular-related complications in the future.

**14. M.K. is not considering quitting smoking at this time and does not want to discontinue her oral contraceptives because she is sexually active and needs a reliable form of birth control. She wonders if the new low-dose birth control pills or other formulations (e.g., patch, vaginal ring) are safer for smokers.**

Combined oral contraceptives available in the United States contain estrogen in doses ranging from 20 to 50 mcg of ethinyl estradiol. The results of *in vitro* studies have shown that oral contraceptives containing  $\geq 50$  mcg of ethinyl estradiol induce greater procoagulatory effects than do preparations containing either 30 mcg or 35 mcg of ethinyl estradiol; formulations containing 20 mcg of ethinyl estradiol appear to have little or no adverse effects on coagulation.<sup>117,118</sup> Early epidemiologic reports linking oral contraceptive use and severe cardiovascular events were largely observed in women using oral contraceptives containing  $> 50$  mcg of ethinyl estradiol.<sup>119</sup> Since then, manufacturers have reduced the dose of estrogen in oral contraceptives such that the majority of preparations available in the United States contain 20 to 35 mcg of ethinyl estradiol.<sup>120</sup>

In 2001, the U.S. Surgeon General stated that lower-dose oral contraceptives may be associated with a reduced risk for coronary heart disease (CHD), compared with higher-dose formulations. Despite this conclusion, the report cautioned that heavy smokers who use oral contraceptives still have a greatly elevated risk for CHD.<sup>121</sup> Consistent with the Surgeon General's cautionary statement, a recent study found that women who smoked  $> 25$  cigarettes per day had a 20-fold higher risk of MI than nonsmoking women who used oral contraceptives.

Interestingly, the elevated risk was independent of the dose of estrogen in the oral contraceptive; women using preparations containing  $> 50$  mcg of estrogen were no more likely to experience an MI than were women using preparations containing  $< 50$  mcg of estrogen. There was only one case involving the use of a preparation containing 20 mcg of estrogen, and thus, the safety of this dose could not be evaluated.<sup>122</sup>

Serum estrogen levels obtained with the vaginal ring are significantly lower than those achieved with either transdermal or oral combined contraceptive formulations,<sup>123</sup> and theoretically, the contraceptive vaginal ring might be a safer formulation for women who smoke. However, because the contraceptive patch and vaginal ring are relatively new, and their safety has not been established among women who smoke, guidelines issued by the ACOG state that the same precautions for the use of oral combined contraceptives should apply to these newer formulations as well.<sup>116</sup>

M.K.'s prescribed oral contraceptive agent (Ortho Tri-Cyclen) is a triphasic formulation containing 35 mcg of ethinyl estradiol in combination with weekly increasing doses of norgestimate (0.18, 0.215, and 0.25 mg) throughout each monthly cycle. Although some clinicians recommend the use of low-dose (20-mcg) estrogen preparations in smokers, the available evidence suggests that the prescribed regimen poses no additional risk in M.K. However, if M.K. increases her smoking levels to  $> 25$  cigarettes per day, some data suggest that her risk for an MI is increased.<sup>122</sup> The clinician should inform M.K. that there are currently no studies demonstrating a reduced risk of adverse cardiovascular events in smokers using oral contraceptives containing low doses (e.g., 20 mcg) of estrogen or the newer transdermal and vaginal ring formulations. In the absence of data, only smoking cessation can be advocated to definitively reduce the risk of stroke, MI, and thromboembolism in women who use combined hormonal contraceptives.

### Behavioral Counseling

Although M.K. is not considering quitting at this time, it is appropriate for the clinician to apply the 5 R's (Table 85-5) to promote motivation to quit. This counseling should be *relevant* to M.K.'s situation and should highlight the *risks* of continued tobacco use, such as her elevated risk for thromboembolic and thrombotic disorders (associated with continued use of oral contraceptives). M.K. should be asked to think about the *rewards* of quitting and any potential *roadblocks* to quitting. At subsequent encounters, the clinician should sensitively assess M.K.'s tobacco use status and motivation to quit, and offer assistance with quitting when M.K. is ready. If M.K. decides to quit, it would be important to reassess her caffeine intake because caffeine levels have been reported to increase by 56% in patients who quit smoking.<sup>30</sup>

## NONCIGARETTE FORMS OF TOBACCO

### Smokeless Tobacco

#### Classification

**15. T.M. is a 29-year-old man who presents to the clinic for evaluation of a painless "white patch" along his lower left gumline, which he noted several weeks ago while flossing his teeth. His social history is significant for the use of smokeless tobacco (consumes**

one can of Copenhagen moist snuff every 2–3 days), cigarettes (1 pack per week), and alcohol (one to two beers daily). T.M. reports he has “dipped” for the past 10 years but only recently started smoking “socially” in the evenings when out with friends. He is in otherwise excellent health and takes no medications. What is smokeless tobacco?

Smokeless tobacco is a term used to describe forms of tobacco that are not burned and inhaled but rather held in the mouth to allow absorption of nicotine across the oral (buccal) mucosa. Smokeless tobacco products in the United States are broadly categorized as either chewing tobacco or snuff. Chewing tobacco, which is generally available in loose-leaf, plug, and twist formulations, is chewed or held in the cheek or lower lip. Snuff, which is commonly available as loose particles or sachets resembling mini tea bags, has a much finer consistency and is generally held in the mouth and not chewed. Most snuff formulations in the United States are classified as moist snuff, and users place a small amount (a “pinch”) between the cheek and gum (also known as dipping) and suck on the moist mass of tobacco for 30 minutes or longer. Dry snuff, which is generally sniffed or inhaled through the nostrils, is less commonly used. Newer formulations including “spitless” moist snuff (e.g., Snus), and lozenges containing compressed tobacco powder are being marketed as cigarette substitutes for situations where smoking is prohibited.<sup>124</sup>

### Epidemiology

According to the U.S. Department of Health and Human Services, in 2006, an estimated 8.2 million Americans ages 12 years and older (3.3%) had used smokeless tobacco in the past month. Males (6.6%) were more likely than females (0.3%) to be current users.<sup>125</sup> The prevalence of smokeless tobacco use is highest among individuals between the ages of 18 and 25 and is substantially higher among American Indians, Alaskan Natives, residents of the southern United States, and persons living in rural areas.<sup>125,126</sup>

### Pharmacokinetics

Absorption of nicotine from chewing tobacco and snuff is pH dependent, with more nicotine absorbed across the buccal mucosa under alkaline conditions. Smokeless tobacco manufacturers manipulate the nicotine content and pH of their products by adding alkaline buffering agents and changing the tobacco processing methods to control the delivery of nicotine. For example, a “starter” formulation such as Skoal Bandits has a lower nicotine content and is more acidic (pH = 5.4) to increase tolerability. Once dependence has been established, users generally advance to more alkaline, higher nicotine content products such as Skoal Fine Cut (pH = 7.6) and Copenhagen (pH = 8.6), which are capable of delivering higher levels of nicotine.<sup>126</sup> As depicted in Figure 85-3, the nicotine from smokeless tobacco is absorbed less rapidly than from cigarette smoke, and the peak levels generally occur after 20 to 30 minutes. Plasma levels of nicotine decline slowly even after removal of tobacco from the mouth because of the gradual release of nicotine from mucous membranes and the possible intestinal absorption of nicotine from swallowed tobacco.<sup>127</sup> Although the rate of nicotine absorption from cigarettes exceeds that from smokeless tobacco, the extent of absorption does not. In fact, regular smokeless tobacco users experience

comparable exposure to nicotine and are as likely to develop physical dependence as are regular smokers.<sup>126,128</sup>

**16.** On examination, a superficial whitish lesion with moderate wrinkling of the tissue adjacent to the mandibular left canine and premolars is noted. In addition, there is localized gingival recession and moderate brown staining of the enamel surfaces. T.M. reports that he routinely places snuff between his lower left cheek and gum. He asks if the lesion might be cancerous and wonders if it is related to his snuff use. What are the health consequences of smokeless tobacco use?

Users of smokeless tobacco are often under the mistaken impression that these formulations are a “safe” alternative to smoking cigarettes because it is not inhaled. In addition to the cosmetic concerns (e.g., halitosis, staining of teeth), the use of smokeless tobacco is associated with numerous adverse health effects,<sup>128</sup> including the following:

#### *Soft Tissue Alterations/Leukoplakia*

Smokeless tobacco users commonly develop an oral soft tissue condition called leukoplakia or “snuff dipper’s lesion.” These white-colored patches or plaques, which are observed in approximately 15% of chewing tobacco users and 60% of snuff users, generally develop at mucosal sites in contact with the tobacco.<sup>128,129</sup> Of concern is the fact that a small percentage of these lesions may transform into squamous cell carcinomas.<sup>126,130</sup> Following cessation, the oral leukoplakia appears to regress or completely disappear in the majority of cases.<sup>130,131</sup>

#### *Periodontal Effects*

In addition to the soft tissue alterations noted previously, regular users of smokeless tobacco are at significant risk for the development of gingival recession (complete or partial loss of the tissue covering the root of the tooth), caries, and tooth abrasion. The loss of gingival tissue, observed in up to 27% of smokeless tobacco users, generally occurs at sites constantly exposed to tobacco.<sup>129</sup> The high sugar content found in many smokeless tobacco products in contact with exposed tooth root tissue might account for the increased incidence of dental caries in smokeless tobacco users.<sup>126,128,129</sup>

#### *Cancer*

The most serious consequence of smokeless tobacco use is an increased risk of developing oral and pharyngeal cancers; the risk appears to be dose related with heavy, long-time users being more likely to develop oral cancer compared with nonusers.<sup>128</sup> Smokeless tobacco contains 28 known carcinogens, including tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and radioactive polonium-210, all of which are in direct contact with mucosal tissues for prolonged periods.<sup>132</sup>

Although smokeless tobacco products do not yield many of the risks associated with the inhalation of combusted tobacco (e.g., pulmonary disease, lung cancer), these products impose harm and should not be recommended as aids for smoking cessation, particularly because safer, more effective products (i.e., medications labeled for smoking cessation) are available.<sup>124,128,133</sup>

T.M. is presenting with an oral mucosal lesion commonly observed in smokeless tobacco users. His long-standing history

of snuff use and characteristic white, wrinkled lesion appearing at a site where he habitually places snuff are consistent with leukoplakia. T.M. should be informed that the lesion is most likely caused by his chronic snuff use, and he should be strongly advised to quit. With continued exposure to carcinogens present in smokeless tobacco, there is an increased risk that the leukoplakia will undergo malignant transformation. The presence of an identifiable tobacco-induced oral lesion might serve as a powerful motivator for a quit attempt. If he is able to quit snuff use, the gum tissue will likely normalize over a period of 6 weeks.<sup>131</sup> If the lesion persists, he should be referred for biopsy and further diagnostic evaluation. Finally, T.M. already has evidence of localized gingival recession, which increases his risk for serious periodontal disease and further dental-related complications. These periodontal problems will progress as long as he continues to use smokeless tobacco.

### Treatment

**17.** T.M. relates that his new girlfriend is a “militant” non-smoker who is likely to stop dating him if he does not quit. He is aware that tobacco is “bad for him” and is worried about developing oral cancer. He believes it will not be difficult to quit smoking because he smokes so little. He is more worried about stopping the use of snuff and wants to know if there are any medications to help him quit.

Despite the known health risks and high prevalence of smokeless tobacco use, there are limited evidence-based recommendations to guide clinicians in the treatment use smokeless tobacco use.<sup>7</sup> In a recent meta-analysis, Ebbert et al.<sup>134</sup> reviewed the results of 20 randomized, controlled trials evaluating behavioral counseling and pharmacotherapy interventions for smokeless tobacco use, and their findings are summarized as follows.

#### BEHAVIORAL THERAPY

Behavioral interventions, including the use of self-help materials (written manuals, pamphlets, videotapes), brief (15- to 20-minute) counseling sessions, telephone support, oral examination with feedback, computerized gradual reduction of tobacco, and use of non-tobacco oral substitutes (herbal and mint snuff, chewing gum), have been shown to significantly increase long-term (>6 month) cessation rates (OR 1.6; 95% CI, 1.4–1.8) compared with control interventions. Interventions that appear to be particularly effective in promoting abstinence among smokeless tobacco users compared to control interventions include telephone support (OR 2.1; 95% CI, 1.7–2.6) or oral examination with clinician-delivered feedback (OR 1.9; 95% CI, 1.1–3.2).<sup>134</sup>

#### NICOTINE REPLACEMENT THERAPY

To date, the nicotine patch and gum are the only NRT formulations that have been evaluated in randomized controlled trials for smokeless tobacco cessation. A pooled analysis of trials evaluating long-term (>6-month) quit rates did not find a statistically significant improvement with the nicotine patch (OR 1.2; 95% CI, 0.9–1.5) or nicotine gum (OR 1.0; 95% CI, 0.6–1.6) when compared to placebo.<sup>134</sup> Encouraging results from a small open-label trial suggest the nicotine lozenge may

be effective for cessation of smokeless tobacco use, but these findings are preliminary.<sup>135</sup> Overall, data from controlled trials suggest NRT is not effective in the treatment of smokeless tobacco use, but further studies are necessary.<sup>7,134</sup>

#### BUPROPION SR

Bupropion SR for smokeless tobacco cessation has been evaluated in two small randomized, controlled trials with a follow-up duration of at least 6 months. A pooled analysis of these trials failed to find a statistically significant improvement in cessation rates relative to placebo (OR 0.9; 95% CI, 0.5–1.6).<sup>134</sup>

The 2008 Clinical Practice Guideline recommends that smokeless tobacco users receive counseling interventions similar to those recommended for smokers.<sup>7</sup> Based on the available evidence, it appears that behavioral interventions are effective in the treatment of smokeless tobacco use. Limited data suggest that pharmacotherapy with bupropion SR or NRT is ineffective. However, more research is necessary to determine whether combination pharmacotherapy and counseling will provide improved cessation rates in smokeless tobacco users. T.M. should be provided with behavioral counseling tailored to his stage of readiness to quit—if he is ready to quit in the next 30 days, a treatment plan should be devised. If he is not ready to quit in the next 30 days, motivational counseling should be applied using the 5 R’s (Table 85-5). Because oral examination with patient feedback appears to promote quitting, T.M. should be referred to a dental provider for additional monitoring and follow-up. T.M. has specifically asked about the use of pharmacotherapy as a cessation aid, and although data do not support the use of bupropion SR or NRT because of insufficient evidence of effectiveness, these agents might be considered. T.M. should also be informed that a non-tobacco oral substitute (herbal and mint snuff) in combination with behavioral counseling is also effective.<sup>134</sup>

### Cigars

**18.** R.N., a 40-year-old man who currently smokes 1 PPD of cigarettes, would like to know whether cutting down to one to two cigars per day is a safe alternative to cigarette smoking.

Cigars are conventionally defined as “any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco.”<sup>136</sup> The types of cigars available in the United States vary and include *little* cigars (shaped like cigarettes and weighing <1.3 g); *small* cigars or cigarillos (some with a plastic mouthpiece and weighing between 1.2 and 2.5 g); *regular* cigars (usually rolled to a tip on one end and banded; generally weighing between 5 and 17 g); and *premium* cigars (expensive, generally hand rolled, and weighing >22 g).<sup>136,137</sup> Cigar tobacco is generally air cured and produces smoke with a more alkaline pH, which allows for buccal absorption of nicotine.<sup>138</sup>

Cigar consumption has significantly increased over the past decade.<sup>139</sup> According to the U.S. Department of Health and Human Services, in 2006, an estimated 13.7 million Americans ages 12 years or older (5.6%) had smoked one or more cigars in the past month. The prevalence of cigar use was highest among individuals ages 18 to 25 years (12.1%); males (9.3%) were more likely than females (2.1%) to be current

cigar smokers.<sup>125</sup> Some data suggest that the increased consumption is due to a greater prevalence of occasional cigar smoking by previous nonsmokers, particularly among those of higher socioeconomic status.<sup>136</sup> This trend is likely the result of enhanced marketing and promotional efforts by the tobacco industry; cigar advertisements often depict celebrities or athletes associating cigar smoking with glamour, affluence, and success.<sup>136,140</sup> Increasing numbers of former cigarette smokers switching to cigars and experimentation among adolescents with cigar smoking may also play a role.<sup>136</sup>

Exactly how much nicotine an individual might obtain from a single cigar is difficult to determine or generalize because cigar weight and nicotine content vary widely from brand to brand and from cigar to cigar. Most cigars range in weight from about 1 to 22 g; a typical cigarette weighs less than 1 g. The nicotine content of ten commercially available cigars studied in 1996 ranged from 10 to 444 mg. In comparison, U.S. cigarettes have a relatively narrow total nicotine content range (mean = 13.5 ± 0.1 mg) per cigarette.<sup>141</sup> Relating these data, Henningfield et al. concluded that it is possible for one large cigar to contain as much tobacco as an entire pack of cigarettes and deliver enough nicotine to establish and maintain dependence.<sup>138</sup>

The adverse health effects of cigar smoking have been well described and include an increased risk of cancer of the lung, oral cavity, larynx, esophagus, and pancreas. In addition, cigar smokers who inhale deeply are at increased risk for developing cardiovascular disease and COPD.<sup>136</sup> Cigarette smokers who switch to smoking only cigars decrease their risk of developing lung cancer, but their risk is markedly higher than if they were to quit smoking altogether.<sup>136</sup>

R.N. should be counseled that switching from cigarette smoking to low-level daily cigar smoking will not reduce his risk for developing a tobacco-related disease. The amount of nicotine delivered by one to two cigars per day is capable of sustaining his dependence on nicotine. In addition, former cigarette smokers are more likely to inhale deeply, which further increases the risk of cancer and cardiovascular and pulmonary disease. The clinician should strongly advise R.N. to quit smoking cigarettes and that switching to cigars is not a safe alternative.

## Bidis and Clove Cigarettes

**19.** K.K. is a 16-year-old male who has been suspended from school after his third offense for smoking on campus. K.K. began experimenting with bidis and kreteks a few years ago and then started smoking cigarettes “socially” with his friends. For the past year, he has been smoking about a half-pack of cigarettes per day. What are bidis and kreteks?

### Bidis

Bidis are small, hand-rolled cigarettes imported to the United States primarily from India and other Southeast Asian countries. They consist of finely ground tobacco wrapped in a brown tendu or temburni leaf. Bidis, which are similar in appearance to marijuana cigarettes, are readily available in tobacco shops and ethnic stores and via Internet retailers in a variety of flavors (e.g., chocolate, vanilla, strawberry, cherry, mango, orange) and tend to be more popular among younger smokers.<sup>142</sup> In a

U.S. survey of nearly 64,000 adults (≥18 years) in 15 states, young adults (18–24 years) reported the highest rates of ever (16.5%) and current (1.4%) bidi use.<sup>143</sup> In 2006, an estimated 2.3% of 12th graders had smoked bidis in the past year.<sup>125</sup> In a previous survey in Massachusetts, reasons cited by urban adolescents for smoking bidis were that they were better tasting, less expensive, safer, and easier to buy than traditional cigarettes.<sup>144</sup>

Although bidis contain less tobacco than standard cigarettes, studies have shown they produce substantial amounts of tar, nicotine, and carbon monoxide.<sup>145,146</sup> A study using standardized smoking machine testing methods found that bidis deliver three times the amount of carbon monoxide and nicotine and nearly five times the amount of tar found in standard cigarettes.<sup>145</sup> Because of the low combustibility of the tendu leaf wrapper, bidis must be puffed constantly to remain lit. As a result, bidi smokers inhale more frequently and more deeply, thereby markedly increasing the delivery of tar and other toxins.<sup>144</sup> Most bidis do not have a traditional filter tip, which further increases exposure to toxic constituents present in smoke. However, a filter does not confer added safety, as evidenced by a study that found that bidi cigarettes containing a filter actually delivered higher levels of tar, nicotine, and carbon monoxide when compared with unfiltered bidi brands. In this study, the filtered bidi cigarettes contained a small wad of cotton instead of the usual cellulose acetate filter found in American cigarettes. The investigators speculated that the inefficient cotton filter and the slightly larger size of the filtered bidi brands led to the observed higher yields of inhaled toxins.<sup>146</sup>

Although by law all packages of bidis sold in the United States must contain the Surgeon General warning about the hazards of smoking, spot-checks in various retail outlets have shown that many of these products are not labeled with health warnings.<sup>147</sup> The absence of federally mandated warning labels may lead to the false impression that these products are safer than other forms of tobacco. However, studies in India have shown that bidi smokers have a comparable or greater risk of developing tobacco-related respiratory, cardiovascular, and neoplastic disease than cigarette smokers. Even low levels of bidi smoking (1–7 bidis/day) are associated with an elevated risk of death (risk ratio estimate, 1.3) compared to nonsmokers. Higher levels of bidi smoking (≤8 bidis/day) incur an even higher risk of death (risk ratio estimate, 2.2).<sup>148</sup>

### Clove Cigarettes

Clove cigarettes or “kreteks” are cigarettes imported from Indonesia containing a mixture of approximately 60% to 70% tobacco and 30% to 40% minced cloves.<sup>142</sup> Although usage data in adults are not available, in 2006, an estimated 6.2% of 12th graders had smoked kreteks in the past year.<sup>125</sup> Data from smoking machine tests have found that clove cigarettes deliver twice as much nicotine and carbon monoxide and three times as much tar as conventional cigarettes.<sup>149</sup> In addition to the hazards associated with smoking, clove cigarette use has been implicated in causing rare cases of hemorrhagic pulmonary edema, pneumonia, bronchitis, and hemoptysis.<sup>150–152</sup> It has been speculated that eugenol, a compound possessing local anesthetic properties and present in large quantities in clove cigarette smoke, might be toxic to pulmonary tissue. The anesthetic effects of eugenol might also place users at an increased

risk of pulmonary aspiration resulting from an impaired gag reflex.<sup>152</sup>

There is concern among some experts that experimentation with noncigarette tobacco (kreteks, bidis, cigars) provides an alternative form of nicotine exposure to individuals who might not otherwise smoke cigarettes. This concern is heightened by recent data that suggests susceptible youth can become addicted to nicotine shortly (within 1–2 days) after smoking initiation.<sup>153</sup> K.K. began experimenting with bidis and clove cigarettes before he smoked cigarettes socially. It is difficult to know whether K.K.'s previous use of bidis and clove cigarettes led to regular cigarette smoking, but these products can deliver nicotine levels capable of inducing and sustaining dependence.

## Water Pipes

**20.** L.B.C. is a 19-year-old college freshman who resides in an on-campus dormitory. She has been invited by several of her hallmates to “hang-out” at a local hookah bar for the evening. What is hookah, and is this form of tobacco “safe”?

Hookah or water pipe smoking is an ancient method of tobacco use whereby users inhale smoke that is passed through water. Water pipe nomenclature is region specific and includes names such as “hookah” (Africa and Indian subcontinent); “narghile” (Israel, Jordan, Lebanon, Syria); “shisha,” “boory,” or “goza” (Egypt, Saudi Arabia); and “hubble bubble” (many regions).<sup>154</sup>

A water pipe is a multicomponent apparatus consisting of a mouthpiece, hose, water bowl, body, and head. Maassel (a mixture of tobacco, dried fruit pulp, honey, and molasses in a variety of flavors) is placed in the head and then covered with perforated aluminum foil. Small pieces of burning charcoal are placed on top of the foil. Following inhalation, heat emanating from the burning charcoal is drawn through the tobacco mixture generating smoke. A vacuum created in the water bowl causes the smoke to “bubble” through the water and collect in the air space above the water. The cooled smoke is then transported to the user through the hose and mouthpiece during inhalation.<sup>154</sup>

Hookah bars and cafes, many of which are in close proximity to college campuses, have been emerging throughout the United States,<sup>155</sup> and data suggest this form of tobacco use is becoming increasingly popular among young adults.<sup>156,157</sup> Recent surveys estimate a 13% to 20% prevalence of current water pipe smoking (use within the previous 30 days) among U.S. college students.<sup>156,158</sup> Although many water pipe users assume that the water will filter out toxins and believe this form of smoking is less harmful than cigarette smoking,<sup>156,157,159</sup> data are lacking to substantiate this belief. Indeed, studies have found that water pipe smokers who inhale are exposed to nicotine and other toxins in levels that are comparable to or exceed those found in cigarette smoke,<sup>160–162</sup> suggesting that water pipe smoking is not “safe.” Furthermore, preliminary data suggest that water pipe smokers are at risk for developing dependence and other adverse health-related conditions associated with smoking.<sup>154</sup>

## REFERENCES

- Doll R et al. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;328:1519.
- U.S. Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A report of the Surgeon General. DHHS Publication No. (PHS) 88-8406. Washington, DC: Government Printing Office; 1988.
- U.S. Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. Washington, DC: 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; 2004.
- WHO Report on the Global Tobacco Epidemic, 2008. The MPOWER package. Geneva, Switzerland: World Health Organization; 2008.
- Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and economic costs—United States, 1997–2001. *MMWR Morb Mortal Wkly Rep* 2005;54:625.
- U.S. Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
- Fiore MC et al. Treating tobacco use and dependence: 2008 update. Clinical practice guideline. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service; May 2008.
- Leshner AI. Drug abuse and addiction are biomedical problems. *Hosp Pract* 1997;2.
- U.S. Department of Health and Human Services. Preventing tobacco use among young people: a report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1994.
- Gilpin EA et al. Smoking initiation rates in adults and minors: United States, 1944–1988. *Am J Epidemiol* 1994;140:535.
- U.S. Department of Health and Human Services. Healthy people 2010. Washington, DC: U.S. Department of Health and Human Services; 2000.
- Centers for Disease Control and Prevention. Cigarette use among high school students—United States, 1991–2005. *MMWR Morb Mortal Wkly Rep* 2006;55:724.
- Johnston LD. Teen smoking resumes decline. Press release. Ann Arbor: University of Michigan News Service; December 11, 2007. Available at: www.monitoringthefuture.org. Accessed June 15, 2008.
- Centers for Disease Control and Prevention. Cigarette smoking among adults—United States, 2006. *MMWR Morb Mortal Wkly Rep* 2007;56:1157.
- Centers for Disease Control and Prevention. State-specific prevalence of current cigarette smoking among adults and quitting among persons aged 18–35 years—United States, 2006. *MMWR Morb Mortal Wkly Rep* 2007;56:993.
- Lasser K et al. Smoking and mental illness: a population-based study. *JAMA* 2000;284:2606.
- Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clin Pharmacol Ther* 2008;83:531.
- Benowitz NL. Neurobiology of nicotine addiction: implications for smoking cessation treatment. *Am J Med* 2008;121:S3.
- Li MD et al. A meta-analysis of estimated genetic and environmental effects on smoking behavior in male and female adult twins. *Addiction* 2003;98:23.
- Sullivan PF, Kendler KS. The genetic epidemiology of smoking. *Nicotine Tob Res* 1999;1(Suppl 2):S51.
- Xian H et al. The heritability of failed smoking cessation and nicotine withdrawal in twins who smoked and attempted to quit. *Nicotine Tob Res* 2003;5:245.
- Benowitz NL. Cigarette smoking and nicotine addiction. *Med Clin North Am* 1992;76:415.
- Taylor P. Agents acting at the neuromuscular junction and autonomic ganglia. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. New York: McGraw-Hill; 2006.
- Hukkanen J et al. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev* 2005;57:79.
- Kessler DA. The control and manipulation of nicotine in cigarettes. *Tob Control* 1994;3:362.
- Perry DC et al. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. *J Pharmacol Exp Ther* 1999;289:1545.
- Hughes JR et al. Symptoms of tobacco withdrawal: a replication and extension. *Arch Gen Psychiatry* 1991;48:52.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2000.

29. Hughes JR, Hatsukami D. Errors in using tobacco withdrawal scale [letter to the editor]. *Tob Control* 1998;7:92.
30. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999;36:425.
31. Kroon LA. Drug interactions with smoking. *Am J Health Syst Pharm* 2007;64:1917.
32. Rx for Change: Clinician-Assisted Tobacco Cessation. San Francisco: The Regents of the University of California, University of Southern California, and Western University of Health Sciences; 1999–2008.
33. Centers for Disease Control and Prevention. Cigarette smoking-attributable morbidity—United States, 2000. *MMWR Morb Mortal Wkly Rep* 2003; 52:842.
34. American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.
35. California Environmental Protection Agency. Proposed identification of environmental tobacco smoke as a toxic air contaminant: executive summary. January 26, 2006. Available at: [www.arb.ca.gov/regact/ets2006/ets2006.htm](http://www.arb.ca.gov/regact/ets2006/ets2006.htm). Accessed June 6, 2008.
36. U.S. Department of Health and Human Services. The health benefits of smoking cessation: a report of the Surgeon General. DHHS Publication No. (CDC) 90-8416. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention and Health Promotion, Office on Smoking and Health; 1990.
37. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;1:1645.
38. Peto R et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *Br Med J* 2000;321:323.
39. Bjartveit K, Tverdal A. Health consequences of smoking 1–4 cigarettes per day. *Tob Control* 2005; 14:315.
40. Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette consumption. *Tob Control* 2006;15:472.
41. Zhu S et al. Smoking cessation with and without assistance: a population-based analysis. *Am J Prev Med* 2000;18:305.
42. Prochaska JO, DiClemente CC. The Transtheoretical Approach: Crossing Traditional Boundaries of Therapy. Homewood, IL: Dow Jones-Irwin; 1984.
43. Severson HH et al. A self-help cessation program for smokeless tobacco users: comparison of two interventions. *Nicotine Tob Res* 2000;2:363.
44. Stead LF et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008;CD000146.
45. Hughes JR et al. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007; CD000031.
46. Coe JW et al. Varenicline: an  $\alpha 4\beta 2$  nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005;48:3474.
47. Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. *Int J Clin Pract* 2006;60:571.
48. Palmer KJ et al. Transdermal nicotine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an aid to smoking cessation. *Drugs* 1992;44:498.
49. Gore AV, Chien YW. The nicotine transdermal system. *Clin Dermatol* 1998;16:599.
50. Benowitz NL et al. Determinants of nicotine intake while chewing nicotine polacrilex gum. *Clin Pharmacol Ther* 1987;41:467.
51. Henningfield JE et al. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *JAMA* 1990;264:1560.
52. Choi JH et al. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tob Res* 2003;5:635.
53. Shiffman S et al. Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 2002;162: 1267.
54. Heatherton TF et al. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict* 1989;84:791.
55. O'Hara P et al. Early and late weight gain following smoking cessation in the Lung Health Study. *Am J Epidemiol* 1998;148:821.
56. Perkins KA et al. Acute effects of tobacco smoking on hunger and eating in male and female smokers. *Appetite* 1994;22:149.
57. Hatsukami D et al. Effects of tobacco abstinence on food intake among cigarette smokers. *Health Psychol* 1993;12:499.
58. Kawachi I et al. Can physical activity minimize weight gain in women after smoking cessation?. *Am J Public Health* 1996;86:999.
59. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. *Prog Cardiovasc Dis* 2003;46:91.
60. Adamopoulos D et al. New insights into the sympathetic, endothelial and coronary effects of nicotine. *Clin Exp Pharmacol Physiol* 2008;35:458.
61. Bazzano LA et al. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. *Ann Intern Med* 2003; 138:891.
62. Tonstad S, Johnston JA. Cardiovascular risks associated with smoking: a review for clinicians. *Eur J Cardiovasc Prev Rehabil* 2006;13:507.
63. Rigotti NA et al. Interventions for smoking cessation in hospitalised patients. *Cochrane Database Syst Rev* 2007;CD001837.
64. Benowitz NL et al. Sources of variability in nicotine and cotinine levels with use of nicotine nasal spray, transdermal nicotine, and cigarette smoking. *Br J Clin Pharmacol* 1997;43:259.
65. Roth MT, Westman EC. Asthma exacerbation after administration of nicotine nasal spray for smoking cessation. *Pharmacotherapy* 2002;22:779.
66. Schneider NG et al. The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet* 2001;40:661.
67. Bergstrom M et al. Regional deposition of inhaled <sup>11</sup>C-nicotine vapor in the human airway as visualized by positron emission tomography. *Clin Pharmacol Ther* 1995;57:309.
68. Molander L et al. Dose released and absolute bioavailability of nicotine from a nicotine vapor inhaler. *Clin Pharmacol Ther* 1996;59:394.
69. GlaxoSmithKline. Zyban package insert. Research Triangle Park, NC; August 2007.
70. Swan GE et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: a randomized trial. *Arch Intern Med* 2003;163:2337.
71. Hurt RD et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195.
72. Dunner DL et al. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. *J Clin Psychiatry* 1998;59: 366.
73. Johnston AJ et al. Pharmacokinetic optimisation of sustained-release bupropion for smoking cessation. *Drugs* 2002;62(Suppl 2):11.
74. Jorenby DE et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685.
75. Cahill K et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2007;CD006103.
76. Pfizer, Inc. Chantix package insert. New York, NY; June 2008.
77. Faessel HM et al. Multiple-dose pharmacokinetics of the selective nicotinic receptor partial agonist, varenicline, in healthy smokers. *J Clin Pharmacol* 2006;46:1439.
78. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Information for Healthcare Professionals Varenicline (marketed as Chantix). February 1, 2008. Available at: [www.fda.gov/cder/drug/InfoSheets/HCP/vareniclineHCP.htm](http://www.fda.gov/cder/drug/InfoSheets/HCP/vareniclineHCP.htm). Accessed June 15, 2008.
79. Lunell E et al. Relative bioavailability of nicotine from a nasal spray in infectious rhinitis and after use of a topical decongestant. *Eur J Clin Pharmacol* 1995;48:71.
80. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol* 1997;29:1422.
81. Joseph AM et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996;335:1792.
82. Tzivoni D et al. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovasc Drugs Ther* 1998;12:239.
83. Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients With Coronary Artery Disease. *Arch Intern Med* 1994; 154:989.
84. Benowitz NL et al. Cardiovascular effects of nasal and transdermal nicotine and cigarette smoking. *Hypertension* 2002;39:1107.
85. Haustein KO et al. Effects of cigarette smoking or nicotine replacement on cardiovascular risk factors and parameters of haemorrhology. *J Intern Med* 2002;252:130.
86. Lee AH, Afessa B. The association of nicotine replacement therapy with mortality in a medical intensive care unit. *Crit Care Med* 2007;35:1517.
87. Joseph AM, Fu SS. Safety issues in pharmacotherapy for smoking in patients with cardiovascular disease. *Prog Cardiovasc Dis* 2003;45:429.
88. McRobbie H, Hajek P. Nicotine replacement therapy in patients with cardiovascular disease: guidelines for health professionals. *Addiction* 2001;96: 1547.
89. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007. Available from: [www.goldcopd.org](http://www.goldcopd.org). Accessed June 15, 2008.
90. Anthonisen NR. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV<sub>1</sub>. The Lung Health Study. *JAMA* 1994;272:1497.
91. Parkes G et al. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomized controlled trial. *BMJ* 2008;336:598.
92. Stead LF, Hughes JR. Lobeline for smoking cessation. *Cochrane Database Syst Rev* 2000; CD000124.
93. Stead LF, Lancaster T. Nicobrevin for smoking cessation. *Cochrane Database Syst Rev* 2006; CD005990.
94. Abbot NC et al. Hypnototherapy for smoking cessation. *Cochrane Database Syst Rev* 2000; CD001008.
95. White AR et al. Acupuncture for smoking cessation. *Cochrane Database Syst Rev* 2006;CD000009.
96. Hazelden Foundation. Survey on Current and Former Smokers—1998. Available at: [www.hazelden.org/web/public/smokers1998.page](http://www.hazelden.org/web/public/smokers1998.page). Accessed June 6, 2008.
97. Lawson GM et al. Application of serum nicotine and plasma cotinine concentrations to assessment of nicotine replacement in light, moderate, and heavy smokers undergoing transdermal therapy. *J Clin Pharmacol* 1998;38:502.
98. Fredrickson PA et al. High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels. *Psychopharmacology* 1995;122:215.
99. Benowitz NL et al. Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. *J Pharmacol Exp Ther* 1998;287:958.
100. Dale LC et al. High-dose nicotine patch therapy: percentage of replacement and smoking cessation. *JAMA* 1995;274:1353.
101. Bars MP et al. "Tobacco free with FDNY": the New York City Fire Department World Trade Center Tobacco Cessation Study. *Chest* 2006;129:979.
102. Hurt RD et al. Nicotine patch therapy based on smoking rate followed by bupropion for prevention of relapse to smoking. *J Clin Oncol* 2003;21:914.

103. Tonnesen P et al. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. *Eur Respir J* 1999;13:238.
104. Jorenby DE et al. Varying nicotine patch dose and type of smoking cessation counseling. *JAMA* 1995;274:1347.
105. Hughes JR et al. Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tob Res* 1999;1:169.
106. Killen JD et al. Do heavy smokers benefit from higher dose nicotine patch therapy? *Exp Clin Psychopharmacol* 1999;7:226.
107. Paoletti P et al. Importance of baseline cotinine plasma values in smoking cessation: results from a double-blind study with nicotine patch. *Eur Respir J* 1996;9:643.
108. Murray RP et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Lung Health Study Research Group. *Chest* 1996;109:438.
109. Pfizer Consumer Healthcare. Nicotrol inhaler prescribing information. Morris Plains, NJ; February 2005.
110. Pfizer Consumer Healthcare. Nicotrol nasal spray prescribing information. Morris Plains, NJ; February 2005.
111. Steinberg MB et al. The case for treating tobacco dependence as a chronic disease. *Ann Intern Med* 2008;148:554.
112. Seibert C et al. Prescribing oral contraceptives for women older than 35 years of age. *Ann Intern Med* 2003;138:54.
113. Burkman R et al. Safety concerns and health benefits associated with oral contraception. *Am J Obstet Gynecol* 2004;190:S5.
114. Schwingl PJ et al. Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States. *Am J Obstet Gynecol* 1999;180(1 Pt 1):241.
115. World Health Organization. Medical Eligibility Criteria for Contraceptive Use. 3rd ed. Geneva, Switzerland: World Health Organization; 2004.
116. ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 73: use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol* 2006;107:1453.
117. Fruzzetti F. Hemostatic effects of smoking and oral contraceptive use. *Am J Obstet Gynecol* 1999;180(6 Pt 2):S369.
118. Aldrich JM et al. Effect of a combined oral contraceptive containing 20 mcg ethinyl estradiol and 75 mcg gestodene on hemostatic parameters. *Gynecol Endocrinol* 2006;22:1.
119. U.S. Department of Health and Human Services. Women and smoking: a report of the Surgeon General. Atlanta: 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; 2001.
120. Kiley J, Hammond C. Combined oral contraceptives: a comprehensive review. *Clin Obstet Gynecol* 2007;50:868.
121. U.S. Department of Health and Human Services. The health consequences of smoking: cancer. A report of the Surgeon General. DHHS Publication No. (PHS) 82-50179. Rockville, MD: Public Health Service, Office on Smoking and Health; 1982.
122. Rosenberg L et al. Low-dose oral contraceptive use and the risk of myocardial infarction. *Arch Intern Med* 2001;161:1065.
123. van den Heuvel MW et al. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005;72:168.
124. Hatsukami DK et al. Changing smokeless tobacco products: new tobacco-delivery systems. *Am J Prev Med* 2007;33:S368.
125. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration. Results from the 2006 national survey on drug use and health: national findings (Office of Applied Studies, NSDUH Series H-32, DHHS Publication No. SMA 07-4293). Rockville, MD; 2007.
126. Hatsukami DK, Severson HH. Oral spit tobacco: addiction, prevention and treatment. *Nicotine Tob Res* 1999;1:21.
127. Fant RV et al. Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tob Control* 1999;8:387.
128. Ebbert JO et al. Smokeless tobacco: an emerging addiction. *Med Clin North Am* 2004;88:1593.
129. Taybos G. Oral changes associated with tobacco use. *Am J Med Sci* 2003;326:179.
130. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med* 2008;37:1.
131. Martin GC et al. Oral leukoplakia status six weeks after cessation of smokeless tobacco use. *J Am Dent Assoc* 1999;130:945.
132. Hecht SS et al. Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers. *Cancer Epidemiol Biomarkers Prev* 2007;16:1567.
133. Henley SJ et al. Tobacco-related disease mortality among men who switched from cigarettes to spit tobacco. *Tob Control* 2007;16:22.
134. Ebbert JO et al. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev* 2007;4:CD004306.
135. Ebbert JO et al. Nicotine lozenges for the treatment of smokeless tobacco use. *Nicotine Tob Res* 2007;9:233.
136. National Cancer Institute. Cigars: health effects and trends. Smoking and Tobacco Control Monograph No. 9. NIH Publication No. 98-4302. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 1998.
137. Baker F et al. Health risks associated with cigar smoking. *JAMA* 2000;284:735.
138. Henningfield JE et al. Nicotine concentration, smoke pH and whole tobacco aqueous pH of some cigar brands and types popular in the United States. *Nicotine Tob Res* 1999;1:163.
139. U.S. Department of Agriculture, Economic Research Service. Tobacco outlook. Report TBS-263. October 24, 2007. Available at: <http://usda.mannlib.cornell.edu/usda/current/TBS/TBS-10-24-2007.pdf>. Accessed June 15, 2008.
140. Wenger LD et al. Cigar magazines: using tobacco to sell a lifestyle. *Tob Control* 2001;10:279.
141. Connolly GN et al. Trends in nicotine yield in smoke and its relationship with design characteristics among popular US cigarette brands, 1997–2005. *Tob Control* 2007;16:e5.
142. Deckers SK et al. Tobacco and its trendy alternatives: implications for pediatric nurses. *Crit Care Nurs Clin North Am* 2006;18:95.
143. Delnevo CD et al. Bidi cigarette use among young adults in 15 states. *Prev Med* 2004;39:207.
144. Centers for Disease Control and Prevention. Bidi use among urban youth—Massachusetts, March–April 1999. *MMWR Morb Mortal Wkly Rep* 1999;48:796.
145. Malson JL et al. Comparison of the nicotine content of tobacco used in bidis and conventional cigarettes. *Tob Control* 2001;10:181.
146. Watson CH et al. Determination of tar, nicotine, and carbon monoxide yields in the smoke of bidi cigarettes. *Nicotine Tob Res* 2003;5:747.
147. Taylor TM, Biener L. Bidi smoking among Massachusetts teenagers. *Prev Med* 2001;32:89.
148. Jha P et al. A nationally representative case-control study of smoking and death in India. *N Engl J Med* 2008;358:1137.
149. Malson JL et al. Clove cigarette smoking: biochemical, physiological, and subjective effects. *Pharmacol Biochem Behav* 2003;74:739.
150. Centers for Disease Control and Prevention. Illnesses possibly associated with smoking clove cigarettes. *MMWR Morb Mortal Wkly Rep* 1985;34:297.
151. American Medical Association. Evaluation of the health hazard of clove cigarettes. Council on Scientific Affairs. *JAMA* 1988;260:3641.
152. Guidotti TL et al. Clove cigarettes: the basis for concern regarding health effects. *West J Med* 1989;151:220.
153. DiFranza JR et al. Symptoms of tobacco dependence after brief intermittent use: the Development and Assessment of Nicotine Dependence in Youth-2 study. *Arch Pediatr Adolesc Med* 2007;161:704.
154. Maziak W et al. Tobacco smoking using a waterpipe: a re-emerging strain in a global epidemic. *Tob Control* 2004;13:327.
155. Lewin T. Collegians smoking hookahs . . . filled with tobacco. *New York Times*, April 19, 2006. Available at: [www.nytimes.com/2006/04/19/education/19hookah.html?ei=5070&em=e29cc03a601b322a&ex=1190001600&pagewanted=print](http://www.nytimes.com/2006/04/19/education/19hookah.html?ei=5070&em=e29cc03a601b322a&ex=1190001600&pagewanted=print). Accessed June 6, 2008.
156. Eissenberg T et al. Waterpipe tobacco smoking on a U.S. college campus: prevalence and correlates. *J Adolesc Health* 2008;42:526.
157. Ward KD et al. Characteristics of U.S. waterpipe users: a preliminary report. *Nicotine Tob Res* 2007;9:1339.
158. Smith SY et al. Harm perception of nicotine products in college freshmen. *Nicotine Tob Res* 2007;9:977.
159. Smith-Simone S et al. Waterpipe tobacco smoking: knowledge, attitudes, beliefs, and behavior in two U.S. samples. *Nicotine Tob Res* 2008;10:393.
160. Sepetdjian E et al. Measurement of 16 polycyclic aromatic hydrocarbons in narghile waterpipe tobacco smoke. *Food Chem Toxicol* 2008;46:1582.
161. Shihadeh A, Saleh R. Polycyclic aromatic hydrocarbons, carbon monoxide, “tar”, and nicotine in the mainstream smoke aerosol of the narghile water pipe. *Food Chem Toxicol* 2005;43:655.
162. Neergaard J et al. Waterpipe smoking and nicotine exposure: a review of the current evidence. *Nicotine Tob Res* 2007;9:987.