Cigarette smoking is the single most preventable cause of premature death in the United States, responsible for one in every five deaths. Smoking harms nearly every organ of the body, causing many diseases (including, but not limited to, cardiovascular disease, pulmonary disease, and cancer) and reducing the health of smokers in general. Quitting smoking has immediate as well as long-term benefits, reducing risks for diseases caused by smoking and improving health in general.

Tobacco products are effective delivery systems for the drug nicotine. Nicotine is a highly addictive drug that activates the dopamine reward pathway in the brain that reinforces continued tobacco use. Nicotine withdrawal symptoms (e.g., irritability, anxiety, difficulty concentrating, restlessness, depressed mood, insomnia, impaired performance, increased appetite or weight gain, cravings) generally occur when nicotine is discontinued.

Constituents in tobacco smoke are associated with a number of clinically significant drug interactions.

Tobacco dependence, a chronic disease that often requires repeated intervention and multiple attempts to quit, is characterized by physiological dependence (addiction to nicotine) and behavioral habit of using tobacco.

Numerous effective medications, as delineated in the Clinical Practice Guideline, are available for treating tobacco use and dependence. Most patients should be encouraged to use one or more first-line agents, which include the nicotine patch, nicotine gum, nicotine lozenge, nicotine nasal spray, nicotine oral inhaler, sustained-release bupropion, and varenicline. All first-line agents approximately double quit rates, and therefore the choice of therapy is based largely on contraindications, precautions, patient preference, and tolerability of the available dosage forms. In some cases, medications can be combined or used for extended durations. Although complementary therapies are available, these are not recommended because of insufficient evidence of efficacy.

Comprehensive counseling, as defined by the Clinical Practice Guideline, includes asking about tobacco use, advising patients to quit, assessing readiness to quit, assisting patients with quitting, and arranging follow-up. This approach is referred to as "The 5 A's." Counseling and support can be provided a variety of ways, such as through individual counseling, group programs, telephone, or the Internet. Two components of counseling are especially effective and should be applied when assisting patients with quitting: practical counseling (problem solving or skills training) and social support delivered as part of treatment. Relapse is common, and clinicians should work with patients throughout the quit attempt to increase the chances for long-term abstinence.

continued
In Patients with psychiatric disorders exhibit a higher prevalence of tobacco use and a disproportionately high level of tobacco-related morbidity and mortality. An estimated

During the 20th century, 100 million deaths were caused by tobacco, and currently, an estimated 5.4 million deaths occur annually. 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. Experimentation with cigarettes and the development of regular smoking typically occur during adolescence. In 2007, 59.7% of new smokers were younger than the age of 18 when they smoked their first cigarette. Because most teens who smoke at least monthly continue to smoke in adulthood, tobacco use trends among youth are a key indicator of the overall health trends for the nation. According to the 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, identifying an urgent need for tobacco prevention and cessation programs focused on younger age groups. Subsequent decreases occurred, but overall the rate of decline has slowed substantially in recent years. In 2009, an estimated 25.2% of 12th graders had smoked one or more cigarettes in the past 30 days, combining grades 9 through 12, the prevalence of current smoking was highest among males (19.4%) than among females (14.7%).

Despite tobacco control efforts at the state and national levels, only a few subgroups have met the Healthy People 2010 target goal of ≤12% smoking prevalence. In 2009, the highest statewide median prevalence of current smoking was evident in West Virginia and Kentucky (25.0%), and the lowest prevalence was evident in Utah (9.8%). Although much of tobacco control is coordinated through the states, the extent to which tobacco control is addressed in states’ cancer control plans is highly variable, and there is significant room for improvement in compliance with the CDC’s tobacco-related recommendations.

EPIEMIOLOGY OF TOBACCO USE AND DEPENDENCE

In the United States, cigarettes are the most common form of tobacco that is consumed, but other forms are also prevalent: smokeless tobacco (chewing tobacco, oral snuff), pipes, cigars, clove cigarettes, bidis, hookah, and electronic cigarettes (“e-cigarettes”). Among adults, smoking prevalence varies by sociodemographic factors, including sex, race or ethnicity, education level, age, and poverty level. The Centers for Disease Control and Prevention (CDC) reported that in 2009, 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 20.6% (23.5% of men and 17.9% of women). Table 88-1 summarizes the smoking prevalence estimates for various population subgroups, stratified by sex. An estimated 44.3% of cigarettes smoked in the United States are among persons with mental illness, with the prevalence of smoking being 2 to 4 times higher among patients with psychiatric and substance use disorders.
Factors Contributing to Tobacco Use

Tobacco addiction is maintained by nicotine dependence.18,19 Nicotine induces a variety of pharmacologic effects, described as follows, that lead to dependence.20 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).21 Physiological factors, such as pre-existing medical conditions (e.g., psychiatric comorbidities),20,21 and one’s genetic profile, also can predispose individuals to tobacco use.20,21 Notably, it has been estimated in twin studies that 40% to 60% of smoking is heritable.18,19

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.18 As such, smokers experience nearly immediate onset of the positive effects of nicotine, including pleasure, relief of anxiety, improved task performance, improved memory, mood modulation, and skeletal muscle relaxation.20 These effects, mediated by alterations in neurotransmitter levels, reinforce continued use of nicotine-containing products.18,19

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 with a pK₂ of 8.0.22 In acidic media, nicotine is ionized and poorly absorbed; conversely, in alkaline media, nicotine is nonionized and well absorbed. Under physiological conditions (pH = 7.4), a large proportion of nicotine is nonionized and readily crosses cell membranes.22 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 therapy (NRT) products to maximize the absorption potential of nicotine.22,23

Once absorbed, nicotine induces a variety of central nervous system, cardiovascular, and metabolic effects. Nicotine stimulates the release of several neurotransmitters, including 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 (β-endorphin and γ-aminobutyric acid [GABA]).22 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.22,23

T A B L E 88-1

| Characteristic | Category | Men (n = 12,193) | Women (n = 15,410) | Total (n = 27,603)
|---------------|----------|-----------------|--------------------|-----------------
| Race/ethnicity | White, non-Hispanic | 24.5 | 19.8 | 22.1 |
|               | Black, non-Hispanic | 23.9 | 19.2 | 21.3 |
|               | Hispanic | 19.0 | 9.8 | 14.5 |
|               | American Indian/Alaska Native, non-Hispanic | 20.7 | 23.2 |
|               | Asian, non-Hispanic | 16.9 | 7.5 | 12.0 |
|               | Multiple race, non-Hispanic | 33.7 | 24.8 | 29.5 |
| Education     | 0–12 years (no diploma) | 30.5 | 22.2 | 26.4 |
|               | GED | 53.2 | 44.7 | 49.1 |
|               | High school graduate | 29.0 | 21.5 | 25.1 |
|               | Some college (no degree) | 26.1 | 21.0 | 23.3 |
|               | Associate degree | 20.6 | 19.1 | 19.7 |
|               | Undergraduate degree | 12.4 | 9.9 | 11.1 |
|               | Graduate degree | 6.9 | 6.3 | 6.6 |
| Age group (years) | 18–24 | 28.0 | 15.6 | 21.8 |
|               | 25–44 | 26.5 | 21.5 | 24.0 |
|               | 45–64 | 24.5 | 19.5 | 21.9 |
|               | 65 and older | 9.5 | 9.5 | 9.5 |
| Poverty status | At or above poverty level | 22.2 | 16.7 | 19.4 |
|               | Below poverty level | 34.2 | 28.7 | 31.1 |
|               | Unknown | 22.3 | 13.2 | 17.3 |
| Total         | 21.5 | 17.9 | 20.6 |

*Data for women not reported because of unstable percentages; relative standard error ≥ 30%.

1. Percent of persons reporting having smoked ≥100 cigarettes during their lifetime and who, at the time of interview, reported smoking every day or some days. Excludes 128 respondents whose smoking status was unknown.
2. Includes 3 respondents of unknown race.
3. Data are for women not reported because of unstable percentages; relative standard error ≥ 10%.
4. Data are for women not reported because of unstable percentages; relative standard error ≥ 10%.
5. Percentages may not add to total due to rounding.
6. GED, general educational development certificate.
Chronic administration of nicotine has been shown to result in an increased number of nicotine receptors in specific regions of the brain, 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. Chronic administration also leads to tolerance of the behavioral and cardiovascular effects of nicotine during the course of the day; however, tobacco users regain sensitivity to the effects of nicotine after overnight abstinence from nicotine, as shown in Figure 88-1. After smoking the first cigarette of the day, the smoker experiences marked pharmacologic effects, particularly pleasure and arousal. No other cigarette throughout the day produces the same degree of pleasure or 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 or 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 or arousal; instead, smoking primarily alleviates 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. Withdrawal symptoms, which include anger, anxiety, depression, difficulty concentrating, impatience, insomnia, and restlessness, typically manifest within a few days after quitting, peak within a week, and subside within 2 to 4 weeks. 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. The rapid metabolism of nicotine (half-life \( t_{1/2} = 18–20 \) 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 a marker of tobacco use as well as a marker for exposure to secondhand smoke. Measurement of 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 crosses the placenta and accumulates in breast milk.

**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. PAHs, which are the products of incomplete 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 acetonitrile, pyridines, benzo(a)pyrene, 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 88-2 summarizes key interactions with smoking. Patients who begin smoking, quit smoking, or dramatically alter their level of smoking might require dosage adjustments for some medications.

**Health Consequences of Tobacco Use**

All forms of tobacco are harmful, and there is no safe level of exposure to tobacco products. Smoking has a causal or contributory role in the development of a variety of medical conditions (Table 88-3). In the United States, tobacco use accounts for an estimated 443,595 deaths each year, and millions suffer from chronic conditions attributable to smoking. Among current smokers, emphysema is the most common condition (49.1%), followed by chronic bronchitis (41.1%). Overall, an estimated
**Table 88-2**

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Mechanism of Interaction and Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic Interactions</strong></td>
<td></td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>- Conflicting data on significance of a PK interaction, but possible ↓ plasma concentrations (up to 50%); ↓ half-life</td>
</tr>
<tr>
<td>Bendamustine (Trevanda)</td>
<td>- Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers because of likely ↓ bendamustine concentrations, with ↑ concentrations of its two active metabolites.</td>
</tr>
<tr>
<td>Caffeine</td>
<td>- ↓ Metabolism (induction of CYP1A2); ↓ clearance (36%).</td>
</tr>
<tr>
<td>Chlorpropamide (Thorazine)</td>
<td>- ↓ AUC, 36%; and serum concentrations (24%); ↓ sedation and hypotension possible in smokers; smokers may need ↑ dosages.</td>
</tr>
<tr>
<td>Clopidogrel (Plaxil)</td>
<td>- ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (22%).</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>- ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (51%).</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>- ↑ Clearances (24%); ↓ trough serum concentrations (twofold).</td>
</tr>
<tr>
<td>Flucloxacillin (Voxcin)</td>
<td>- ↑ Clearance (61%); ↓ trough serum concentrations (13%).</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>- ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ plasma concentrations (32%).</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>- ↑ Clearance (44%); ↓ serum concentrations (70%).</td>
</tr>
<tr>
<td>Heparin</td>
<td>- Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects.</td>
</tr>
<tr>
<td>Insulin, subcutaneous</td>
<td>- Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance.</td>
</tr>
<tr>
<td>Iomotecan (Camptosar)</td>
<td>- ↑ Clearance (18%); ↓ serum concentrations of active metabolite SN-38 (70–80%); via induction of glucuronidation; ↓ systemic exposure resulting in lower hematologic toxicity and may reduce efficacy.</td>
</tr>
<tr>
<td>Methadone (Methadone)</td>
<td>- ↑ Clearance (25%); via oxidation and glucuronidation; ↓ half-life (36%).</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>- ↑ Metabolism (induction of CYP1A2); ↑ clearance (94%); ↓ serum concentrations (72%).</td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>- ↑ Clearance (77%, via side-chain oxidation and glucuronidation).</td>
</tr>
<tr>
<td>Ropinirole (Requip)</td>
<td>- ↑ Clearance (54%); ↓ trough serum concentrations (55%).</td>
</tr>
<tr>
<td>Saxagliptin (Januvia)</td>
<td>- ↑ Clearance (54%); ↓ trough serum concentrations (54%).</td>
</tr>
<tr>
<td>Theophylline (Theo-Dur, etc.)</td>
<td>- ↑ Metabolism (induction of CYP1A2); ↑ clearance (58–100%); ↓ half-life (68%).</td>
</tr>
<tr>
<td>Tyrosine (Meptate)</td>
<td>- ↑ Metabolism (induction of CYP1A2); ↓ clearance (58–100%); ↓ half-life (68%).</td>
</tr>
<tr>
<td>Tryptic aminepropanes (e.g., imipramine, nortriptyline)</td>
<td>- Possible interaction with tryptic aminepropanes in the direction of ↓ blood levels, but the clinical significance is not established.</td>
</tr>
<tr>
<td>Trazodone (Zaleplon)</td>
<td>- ↓ AUC (30–40%) and ↓ half-life (15%) observed in male smokers.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>- ↑ Metabolism (induction of CYP1A2) of R-enantiomer; however, S-enantiomer is more potent and effect on INR is microchiral. Consider monitoring INR on smoking cessation.</td>
</tr>
<tr>
<td><strong>Pharmacodynamic Interactions</strong></td>
<td></td>
</tr>
<tr>
<td>Benazepril (Lotensin)</td>
<td>- ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>- Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation.</td>
</tr>
<tr>
<td>Corticosteroids, inhaled</td>
<td>- Smokers with asthma may lose some response to inhaled corticosteroids.</td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>- ↑ 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 twofold ↑ risk of venous thromboembolism compared with oral contraceptive users, likely as a result of ↑ estrogen exposure (80% higher).</td>
</tr>
<tr>
<td>Nsaid (propoxyphene, pentazocine)</td>
<td>- Mechanism unknown.</td>
</tr>
<tr>
<td>Nsaid</td>
<td>- Smokers may need ↑ opioid dosages for pain relief.</td>
</tr>
</tbody>
</table>

Shaded rows indicate the most clinically significant interactions.

AUC, area under the curve; Cmax, maximal concentration; INR, international normalized ratio; PD, pharmacodynamic; PK, pharmacokinetic.

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Helicobacter pylori

Acute respiratory illnesses

Major conclusions of the 2006

Reduced fertility in women

Similarly, more recent data suggest that smokers who

10.875in Top: 0.373in Gutter: 0.664in

On average, cigarette smokers

37

Persons who quit before

report are: (a) many millions of Americans,

Pregnancy and pregnancy outcomes

Cataract

Coronary heart disease (angina pectoris, ischemic
cardiac disease, myocardial infarction)

Cerebrovascular disease (transient ischemic attacks, stroke)

Peripheral arterial disease

Acute respiratory illnesses

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

Pregnancy and pregnancy outcomes

Premature, premature rupture of membranes

Placenta previa

Placental abruption

Premature delivery

Low infant birth weight

Infant mortality

Sudden infant death syndrome

Cataract

Osteoporosis (reduced bone density in
postmenopausal women, increased risk of hip fracture)

Periodontitis

Peptic ulcer disease (in patients who are infected
with Helicobacter pylori)

Surgical outcomes

Poor wound healing

TABLE 88-3
Health Consequences of Smoking

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Acute myeloid leukemia</th>
<th>Bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>Abdominal aortic aneurysm</td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Coronal heart disease (angina pectoris, ischemic heart disease, myocardial infarction)</td>
<td></td>
</tr>
<tr>
<td>Reproductive effects</td>
<td>Reduced fertility in women</td>
<td></td>
</tr>
<tr>
<td>Other effects</td>
<td>Cataract</td>
<td></td>
</tr>
</tbody>
</table>

36.9% of current smokers and 26.0% of former smokers live with a smoking-related chronic disease. In the United States, lung cancer is the leading cause of cancer-related mortality for men and women and is a disease for which the 5-year survival rate is approximately 16%.

SECON DHAND SMOKE EXPOSURE
Exposure to secondhand smoke, which includes the smoke emanating from burning tobacco and that inhaled by the smoker, affects an estimated 88 million nonsmokers older than the age of 3 in the United States, resulting in an estimated 50,000 deaths annually. In addition to contributing to numerous diseases among nonsmoking children and adults. Major conclusions of the 2006 Surgeon General's Health Effects of Involuntary Exposure to Tobacco Smoke report are: (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 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. In 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.

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. Benefits incurred soon after quitting (e.g., within 2 weeks to 3 months) include improvements in pulmonary function, circulation, and ambulation. Smoking cessation results in measurable improvements in lung function (see Chapter 24, Chronic Obstructive Pulmonary Disease). 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. Similarly, more recent data suggest that smokers who quit for good over a sustained period have an overall mortality rate and death rate associated with cardiovascular disease, ischemic heart disease, and stroke that is similar to individuals who have never smoked. In contrast, individuals who had success fully quit, but later resumed smoking, had mortality risks that were significantly higher than lifetime nonsmokers.

Quitting at ages 10, 40, 50, and 60 results in 10, 9, 6, and 3 years of life gained, respectively. On average, cigarette smokers die approximately 10 years younger than do nonsmokers, and of those who continue smoking, at least half will eventually die as a result of a tobacco-related disease. Persons who quit before age 35 add 10 years of life and have a life expectancy similar to men who had never smoked. In addition to losing years of life because of smoking, a 26-year prospective study of smoking in middle showed a dose-dependent reduction in the health-related quality of life in old age among men. Never smokers live longer than heavy smokers, and their extra years are of higher quality. A 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, and therefore, decreasing the number of cigarettes smoked per day should be viewed as a positive step toward quiting, 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. In summary, there is no safe level of tobacco use, and although it is never too late to incur benefits of quitting, there are substantial benefits associated with quitting at a younger age.
**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. 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 US 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, specifies that clinicians can have an important impact on their patients’ ability to quit. A meta-analysis of 29 studies estimated that compared with patients who did not receive an intervention from a clinician, patients who receive a tobacco-cessation intervention from a physician clinician or a nonphysician 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, more intensive counseling yields more dramatic increases in quit rates. Other effective methods for delivery of counseling include group programs and telephone counseling. Internet-based interventions have become more prevalent in recent years, but a recent meta-analysis of 20 trials revealed inconsistent results. 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). 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 88-4. Clinicians can have a significant impact on a patient’s likelihood of success by recommending pharmacotherapy agents.

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**Table 88-4: Efficacy of Treatment Methods for Tobacco Use and Dependence**

<table>
<thead>
<tr>
<th>Behavioral Interventions</th>
<th>Estimated Odds Ratioa (95% CI)</th>
<th>Estimated Abstinenceb (Rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advice to quit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No advice to quit</td>
<td>1.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Physician advice to quit</td>
<td>1.3 (1.1–1.6)</td>
<td>10.2 (8.5–12.0)</td>
</tr>
<tr>
<td>Clinician intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No counseling by a clinician</td>
<td>1.0</td>
<td>10.2</td>
</tr>
<tr>
<td>Counseling by a nonphysician clinician</td>
<td>1.7 (1.3–2.1)</td>
<td>15.8 (12.8–18.8)</td>
</tr>
<tr>
<td>Counseling by a physician</td>
<td>2.2 (1.5–3.2)</td>
<td>19.9 (13.7–26.2)</td>
</tr>
<tr>
<td>Format of smoking cessation counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No format</td>
<td>1.0</td>
<td>10.8</td>
</tr>
<tr>
<td>Self-help</td>
<td>1.2 (1.0–1.3)</td>
<td>12.3 (10.9–13.6)</td>
</tr>
<tr>
<td>Proactive telephone counseling</td>
<td>1.2 (1.1–1.4)</td>
<td>13.1 (11.4–14.8)</td>
</tr>
<tr>
<td>Group counseling</td>
<td>1.3 (1.1–1.6)</td>
<td>13.9 (11.6–16.1)</td>
</tr>
<tr>
<td>Individual counseling</td>
<td>1.7 (1.4–2.0)</td>
<td>16.8 (14.7–19.1)</td>
</tr>
<tr>
<td>Pharmacotherapy Interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>1.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Nicotine gum (6–14 weeks)</td>
<td>2.0 (1.8–2.2)</td>
<td>24.2 (22.2–26.4)</td>
</tr>
<tr>
<td>Nicotine lozenge (2 mg)</td>
<td>2.1 (1.5–2.9)</td>
<td>24.8 (18.1–31.6)</td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>2.0 (1.4–2.8)</td>
<td>24.2</td>
</tr>
<tr>
<td>Nicotine patch (6–14 weeks)</td>
<td>1.9 (1.7–2.2)</td>
<td>24.8 (23.3–25.8)</td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>2.3 (1.7–3.0)</td>
<td>26.7 (21.5–32.7)</td>
</tr>
<tr>
<td>Varenicline (2 mg/day)</td>
<td>3.1 (2.5–3.8)</td>
<td>33.2 (28.9–37.8)</td>
</tr>
<tr>
<td>Nicotine gum (6–14 weeks)</td>
<td>2.0 (1.8–2.2)</td>
<td>24.2 (22.2–26.4)</td>
</tr>
<tr>
<td>Nicotine lozenge (2 mg)</td>
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<td>3.1 (2.5–3.8)</td>
<td>33.2 (28.9–37.8)</td>
</tr>
</tbody>
</table>

---

aEstimated relative to referent group.

bAbstinence percentages for specified treatment method.

cA 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.

dSustained-release bupropion.

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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, six key components constitute 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 follow-up care. These steps are referred to as the “5 A’s” and are described, in brief, as follows. Figure 88-2 can be used as a guide for structuring counseling interactions.

* 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, patients should be asked about exposure to secondhand smoke. Before imparting advice, consider asking the patient for permission to do so: “Mu, Crosby, may I talk to you about this concern?”

* Advise: Tobacco users should be advised to consider quitting. 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, “I’m concerned because you are on two different inhalers for your emphysema. Quitting smoking is the single most important treatment to improve your breathing. I strongly encourage you to quit. Would you be interested in having me help you with this?”

* 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.

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. Malikin, what are your thoughts about quitting, and would you consider quitting sometime in the next 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 endpoint being sustained abstinence from all nicotine-containing products.

When counseling patients who are not ready to quit, an important first step is to foster 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 involve enhancing motivation to quit,

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**FIGURE 88-2 Tobacco-cessation counseling guide sheet.** (Reprinted with permission from Rx for Change: Clinician-Assisted Tobacco Cessation. Copyright © 1999–2012. The Regents of the University of California. All rights reserved.)
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, & heart attacks) and chronic risks (promoting smoking among children by being a negative role model, effects of secondhand 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 88-6) for addressing each barrier. Common barriers include nicotine withdrawal symptoms, 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 prepare for the quit attempt, including mental preparation, alterations in physical and social environment, and should work with patients in selecting the quitting methods patients’ opinions about the different medications 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 medications 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 pharmacological 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.

Patients should be advised to select a quit date. Ideally, this date will be within the next 2 weeks to allow 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.

and this can be accomplished by applying the “5 R’s” (Table 88-5) 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 in the next 10 days, encourage them to seriously consider quitting and ask the following questions:

1. **Do you ever plan to quit?**
   - If the patient responds “no,” the clinician should ask, “What would have to change for you to decide to quit?” If the patient responds “nothing,” then offer to assist, if or when the patient changes his or her mind. If the patient responds “yes,” the clinician should continue with question 2.

2. **What might be some benefits of quitting now, instead of later?**
   - The longer a patient smokes, quitting generally becomes more difficult. 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 would have to change for you to decide to quit soon?**
   - This question probes patients’ perceptions of quitting, which reveals some of the barriers to quitting that can then be discussed.

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 88-2. The first steps are to discuss the patient’s tobacco use history, inquiring about levels of smoking, number of years smoked, methods 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 medications 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 pharmacological 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.

Patients should be advised to select a quit date. Ideally, this date will be within the next 2 weeks to allow 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 88-6. Patients should be counseled about withdrawal symptoms, medication use, and 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. 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 and cravings or temptations to use tobacco. A list of strategies for key triggers or temptations for tobacco use is provided in Table 88-6. 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.

**PHARMACOTHERAPY OPTIONS**

All smokers who are trying to quit should be encouraged to use one or more US 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). Currently, the FDA-approved first-line agents that have been shown to be effective in promoting smoking cessation include five NRT dosage forms, sustained-release bupropion, and varenicline. Dosing information, precautions, and adverse effects for the first-line agents are shown in Table 88-7. Pharmacologic agents that have not...
received an approval from the FDA for smoking cessation but are recommended as second-line agents include clonidine and nortriptyline.

**FIRST-LINE AGENTS**

**NICOTINE REPLACEMENT THERAPY**

NRT improves cessation rates 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 nicotine. 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. Figure 88.3 depicts the concentration-time curves for the various NRT formulations, compared with a cigarette and moist snuff (a smokeless form of 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

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**Table 88.6 Cognitive and Behavioral Strategies for Tobacco Cessation**

**Cognitive Strategies**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focus on the way a patient thinks.</td>
<td>Often, patients 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.</td>
</tr>
<tr>
<td>Review commitment to quit, focus on downtime of tobacco</td>
<td>Reminding oneself that cravings and temptations are temporary and will pass. Announce, either silently or aloud, “I want to be a nonsmoker and the temptation will pass.”</td>
</tr>
<tr>
<td>Distractive thinking</td>
<td>Deliberate, immediate refocusing of thinking when cues about tobacco are used.</td>
</tr>
<tr>
<td>Positive self-talk, “pop talk”</td>
<td>Saying “I can do this” and reminding oneself of previous difficult situations in which tobacco use was avoided with success.</td>
</tr>
<tr>
<td>Relaxation through imagery</td>
<td>Centering of mind toward positive, relaxing thoughts.</td>
</tr>
<tr>
<td>Mental rehearsal, visualization</td>
<td>Preparing for situations that might arise by envisioning how best to handle them. For example, envision what would happen if offered a cigarette by a friend—mentally craft and rehearse a response, and perhaps even practice it by saying it aloud.</td>
</tr>
</tbody>
</table>

**Behavioral Strategies**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involve specific actions to reduce risk for relapse.</td>
<td>For maximal effectiveness, these should be considered before quitting, after determining patient-specific triggers for tobacco use. Here, we list some behavioral strategies for several common cues or triggers for relapse.</td>
</tr>
<tr>
<td>Stress</td>
<td>Anticipate upcoming challenges at work, school, or in personal life. Develop a substitute plan for tobacco use during times of stress (e.g., breathe deeply several times, take a break or leave the situation, call a supportive friend or family member, perform self-massage, or use nicotine replacement therapy to manage situational cravings).</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Drinking alcohol can lead to relapse. Consider limiting or abstaining from alcohol during the early stages of quitting.</td>
</tr>
<tr>
<td>Other tobacco users</td>
<td>Quitting is more difficult when around other tobacco users. This is especially difficult if there is another tobacco user in the household. When possible during the early stages of quitting, limit prolonged contact with individuals who are using tobacco. Ask coworkers, friends, and housemates not to smoke or use tobacco in your presence.</td>
</tr>
<tr>
<td>Oral gratification needs</td>
<td>Have nontobacco oral substitutes (e.g., gum, sugarless candy, straws, toothpicks, lip balm, toothbrush, nicotine replacement therapy, bottled water) readily available.</td>
</tr>
<tr>
<td>Automatic smoking routines</td>
<td>Anticipate routines that are associated with tobacco use and develop an alternative plan.</td>
</tr>
<tr>
<td>Morning coffee</td>
<td>Morning coffee with cigarettes: change morning routine, drink tea instead of coffee, take shower before drinking coffee, take a brisk walk shortly after awakening.</td>
</tr>
<tr>
<td>Smoking while driving</td>
<td>Smoking while driving: remove all tobacco from car, have car interior detailed, listen to an audio book or talk radio, use oral substitute.</td>
</tr>
<tr>
<td>Smoking at the phone</td>
<td>Smoking while at the phone: stand while talking, limit call duration, change phone location, keep hands occupied by doodling or sketching.</td>
</tr>
<tr>
<td>Postcessation weight gain</td>
<td>The majority of tobacco users gain weight after quitting. Most quitters gain &lt;10 pounds, but there is a broad range of weight gain reported, with up to 10% of quitters gaining as much as 30 pounds. Do not attempt to modify multiple behaviors at one time. If weight gain is a barrier to quitting, 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., nicotine gum, lozenges, or sustained-release bupropion).</td>
</tr>
<tr>
<td>Cravings for tobacco</td>
<td>Cravings for tobacco are temporary and usually pass within 5–10 minutes. Handle cravings through distractive thinking, take a break, change activities or tasks, take deep breaths, perform self-massage, or use nicotine replacement therapy.</td>
</tr>
</tbody>
</table>
## TABLE 88-7
Pharmacotherapy Options: Products; Precautions, Warnings, and Contraindications; Dosing; and Adverse Effects

### NRT Formulations

<table>
<thead>
<tr>
<th>Product</th>
<th>Gum</th>
<th>Lozenge</th>
<th>Transdermal Patch</th>
<th>Nasal Spray</th>
<th>Oral Inhaler</th>
<th>Bupropion SR</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicorette, a Generic</td>
<td>Nicorette standard and mini, a Generic</td>
<td>Nicorette CQ, b Generic</td>
<td>Nicorette CQ, c Generic</td>
<td>Nicorette CQ</td>
<td>Nicotrol NS, c Nicotrol Inhaler</td>
<td>Zyban, a Generic</td>
<td>Chantix, c</td>
</tr>
<tr>
<td>OTC 2 mg, 4 mg</td>
<td>OTC 2 mg, 4 mg</td>
<td>Ra Metered spray</td>
<td>Ra Metered spray</td>
<td>Ra 10 mg cartridge</td>
<td>Delivers mg of inhaled nicotine vapor</td>
<td>Ra 150 mg extended-release tablet</td>
<td>Ra 0.5 mg, 1 mg tablet</td>
</tr>
<tr>
<td>Original, cinnamon, fruit, mint, orange</td>
<td>Cherry, mint</td>
<td>7 mg, 12 mg, 21 mg (24-hour release)</td>
<td>0.5 mg of nicotine in 50-μL aqueous nicotine solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Precautions, Warnings, and Contraindications

- Recent (≤2 weeks) myocardial infarction
- Serious underlying arrhythmias
- Serious or worsening angina pectoris
- Pregnancy and breast-feeding
- Adolescents (<18 years)
- Recent (≤2 weeks) myocardial infarction
- Serious underlying arrhythmias
- Recent or worsening angina pectoris
- Pregnancy and breast-feeding
- Adolescents (<18 years)
- Recent (≤2 weeks) myocardial infarction
- Recent underlying arrhythmias
- Recent or worsening angina pectoris
- Pregnancy (category D) and breast-feeding
- Adolescents (<18 years)
- Recent (≤2 weeks) myocardial infarction
- Recent underlying arrhythmias
- Recent or worsening angina pectoris
- Pregnancy (category D) and breast-feeding
- Adolescents (<18 years)
- Recent (≤2 weeks) myocardial infarction
- Recent underlying arrhythmias
- Recent or worsening angina pectoris
- Pregnancy (category D) and breast-feeding
- Adolescents (<18 years)
- Severe reactive airway disease
- Severe hepatic cirrhosis
- Seizure disorder
- Concomitant bupropion (e.g., Wellbutrin) therapy
- Current or prior diagnosis of bulimia or anorexia nervosa
- Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
- Monoamine oxidase inhibitor therapy in previous 14 days
- Severe renal impairment (dosage adjustment is necessary)
- Pregnancy (category C) and breast-feeding
- Adolescents (<18 years)
- Severe reactive airway disease
- Seizure disorder
- Concomitant bupropion (e.g., Wellbutrin) therapy
- Current or prior diagnosis of bulimia or anorexia nervosa
- Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
- Monoamine oxidase inhibitor therapy in previous 14 days
- Severe renal impairment (dosage adjustment is necessary)
- Pregnancy (category C) and breast-feeding
- Adolescents (<18 years)
- Severe reactive airway disease
- Seizure disorder
- Concomitant bupropion (e.g., Wellbutrin) therapy
- Current or prior diagnosis of bulimia or anorexia nervosa
- Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
- Monoamine oxidase inhibitor therapy in previous 14 days
- Severe renal impairment (dosage adjustment is necessary)
- Pregnancy (category C) and breast-feeding
- Adolescents (<18 years)
- Severe reactive airway disease
- Seizure disorder
- Concomitant bupropion (e.g., Wellbutrin) therapy
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- Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
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- Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
- Monoamine oxidase inhibitor therapy in previous 14 days
- Severe renal impairment (dosage adjustment is necessary)
- Pregnancy (category C) and breast-feeding
- Adolescents (<18 years)

(continued)
### Pharmacotherapy Options: Products; Precautions, Warnings, and Contraindications; Dosing; and Adverse Effects (Continued)

#### TABLE 88-7

<table>
<thead>
<tr>
<th>NRT Formulations</th>
<th>Gum</th>
<th>Lozenge</th>
<th>Transdermal Patch</th>
<th>Nasal Spray</th>
<th>Oral Inhaler</th>
<th>Bupropion SR</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>First cigarette: 30 minutes after waking</td>
<td>4 mg</td>
<td>30 minutes after waking</td>
<td>2 mg</td>
<td>30 minutes after waking</td>
<td>1–2 pieces every 2–4 hours</td>
<td>1–2 doses/hour</td>
</tr>
<tr>
<td></td>
<td>First cigarette: &gt;30 minutes after waking</td>
<td>2 mg</td>
<td>60 minutes after waking</td>
<td>2 mg</td>
<td>60 minutes after waking</td>
<td>1–2 pieces every 4–6 hours</td>
<td>1–2 doses/hour</td>
</tr>
<tr>
<td></td>
<td>Weeks 1–6: 1 piece every 1–2 hours</td>
<td>6 mg</td>
<td>144 mg/day</td>
<td>3 mg</td>
<td>144 mg/day</td>
<td>1–2 doses/hour</td>
<td>7 mg/day</td>
</tr>
<tr>
<td></td>
<td>Weeks 7–9: 1 piece every 2–4 hours</td>
<td>12 mg</td>
<td>72 mg/day</td>
<td>5 mg</td>
<td>72 mg/day</td>
<td>2–4 doses/hour</td>
<td>14 mg/day</td>
</tr>
<tr>
<td></td>
<td>Weeks 10–12: 1 piece every 4–6 hours</td>
<td>24 mg</td>
<td>288 mg/day</td>
<td>10 mg</td>
<td>288 mg/day</td>
<td>4–6 doses/hour</td>
<td>28 mg/day</td>
</tr>
<tr>
<td>Precautions, Warnings, and Contraindications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Headache</td>
<td>Tearing</td>
<td>Duration: 3–6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>Constipation</td>
<td>Dry mouth</td>
<td>Duration: 6–12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>Nausea</td>
<td>Dry mouth</td>
<td>Duration: up to 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>Nervousness or difficulty concentrating</td>
<td>Rash</td>
<td>Duration: 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>Seizures</td>
<td>Insomnia</td>
<td>Duration: up to 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Adverse Effects

- **Gums/Lozenges**
  - Headache
  - Tearing
  - Flatulence
  - Dry mouth
  - Insomnia
  - Occasional difficulty swallowing

- **Transdermal Patches**
  - Rash
  - Rash
  - Tearing
  - Flatulence
  - Dry mouth
  - Queasy sensation

- **Nasal Sprays**
  - Headache
  - Nasal congestion
  - Numbness of the nasal mucosa

- **Oral Inhalers**
  - Headache
  - Insomnia
  - Occasional difficulty swallowing

- **Bupropion SR**
  - Headache
  - Insomnia
  - Occasional difficulty swallowing

- **Varenicline**
  - Headache
  - Insomnia
  - Occasional difficulty swallowing

*Marked by GlaxoSmithKline

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Cigarette Moist snuff Nasal spray Inhaler Lozenge (2 mg)

Time (minutes)

Gum (2 mg) Patch

0 1 2 3 4 5 6

0 1 2 3 4 5 6

Plasma Nicotine (μg/L)

0 5 10 15 20 25


has the slowest onset, but offers more consistent blood levels of nicotine for a sustained period.

SUSTAINED-RELEASE BUPROPION

Sustained-release bupropion 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.

Use of sustained-release bupropion approximately doubles the long-term abstinence rate when compared with placebo.8

VARENICLINE

Varenicline, a cytisine analog, is a partial agonist that binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors. 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, which attenuates the symptoms of nicotine withdrawal. In addition, by blocking the ability of nicotine to activate α4β2 nicotinic acetylcholine receptors, varenicline inhibits the surges of dopamine release that are believed to be responsible for the reinforcement and reward associated with smoking.55 Use of varenicline more than doubles the long-term abstinence rate when compared in clinical trials with placebo.55,56

SECOND-LINE AGENTS

Although not FDA-approved specifically for smoking cessation, the prescription medications clonidine and nortriptyline are recommended as second-line agents. Lack of an FDA-approved indication for smoking cessation and less desirable side-effect profiles currently prohibit these agents from achieving first-line classification.8
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. Fewer than 5% of patients discontinue therapy because of skin reactions.

T.B. appears to be experiencing a mild skin reaction and should be reassured that it is common 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 (0.1%), or she can take an oral antihistamine for symptomatic treatment. 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 before bedtime and apply a new patch as soon as possible after waking the following morning. 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 88-6) and schedule a future follow-up call. The clinician should commend T.B. for her decision to quit, congratulate her for remaining free of cigarettes 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. 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.

**CASE 88-1, QUESTION 3:** T.B. would like to discontinue the nicotine transdermal patch. She would like to purchase a nonprescription smoking-cessation medication and wants to know whether the gum or lozenge is an effective alternative.

**Nicotine Gum**

Nicotine polacrilex gum is a resin complex of nicotine and polacrilin in a chewing gum base that provides slow release and absorption of nicotine across the oral mucosa. The product is available in 2- and 4-mg strengths, and in multiple flavors (regular, cinnamon, fruit, mint, and orange). The gum has a distinct, tobaccolike, 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 when used properly, approximately 1.6 mg and 2.2 mg of nicotine is absorbed from each 2 mg and 4 mg piece of gum, respectively. Peak plasma concentrations of nicotine are achieved approximately 30 minutes after chewing a single piece of gum and then slowly decline thereafter (Fig. 88-3). Patients using short-term (6–14 weeks) or long-term (>14 weeks) treatment with nicotine gum are significantly more likely to remain abstinent compared with those receiving placebo (Table 88-4).

**DOsing**

Table 88-7 outlines the manufacturers’ recommended dosing schedule for the nicotine gum. The recommended dosage of the nicotine gum is based on the “time to first cigarette” (TTFC) of the day. Having a strong desire or need to smoke soon after waking is viewed as a key indicator of nicotine dependence. Therefore, patients who smoke their first cigarette of the day within 30 minutes of waking are likely to be more highly dependent on nicotine and require higher dosages than those who delay smoking for more than 30 minutes after waking (Table 88-7).
Specifcally, if the TTFC is 30 minutes or less, therapy should be initiated with the 4-mg gum. If the TTFC is more than 30 minutes, therapy should be initiated with the 2-mg gum. 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 polacrilin 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 during 1 to 3 months rather than using it as needed to control cravings.6

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 and 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 the effectiveness of nicotine gum might be reduced by acidic beverages (e.g., coffee, juices, wine, soft drinks), 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.

ADVERSE REACTIONS

The most common side effects associated with use of the nicotine gum include unpleasant taste, mouth irritation, jaw muscle soreness or fatigue, hypersalivation, hiccups, and dyspepsia. Many of these side effects can be minimized or prevented by using proper chewing technique.7 Patients should be warned that chewing the gum too rapidly may result in excessive release of nicotine, leading to lightheadedness, nausea, vomiting, irritation of the throat and mouth, hiccups, and indigestion.

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.8 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.

Nicotine Lozenge

The nicotine polacrilex lozenge is a resin complex of nicotine and polacrilin in a sugar-free, 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 23% more nicotine than does an equivalent dose of nicotine gum.8 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. 88-3). 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%).8,9 A meta-analysis of five studies using either the nicotine lozenge (nicotine polacrilin) 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 or lozenge relative to placebo (95% CI, 1.6–2.5).10

DOING

Table 88-7 outlines the manufacturers’ recommended dosing schedule for the nicotine lozenge. Like the nicotine gum, the lozenge is dosed based on the TTFC. 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 polacrilin 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,8,9 and patients can self-titrerate 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.

T.B. has expressed interest in either the nicotine gum or lozenge formulation for her quit attempt. Both agents are effective, and the choice of therapy is dependent on the patient’s perceptions and expectations regarding treatment, including the ability to comply with the regimen, previous experience with cessation medications, and other concerns (e.g., adverse effects, weight gain, cost of medications). T.B. would be a candidate for either agent provided she is able to comply with the frequent dosing schedule (one lozenge or piece of gum every 1–2 hours while she is awake). T.B. smokes her first cigarette of the day immediately after waking in the morning and she smokes approximately 30 cigarettes/day; this smoking pattern suggests a higher degree of nicotine dependence, and therefore T.B. would benefit from a higher dose of NRT. T.B. should initiate treatment with the 4-mg strength of either the nicotine lozenge or nicotine gum dosed every 1 to 2 hours while she is awake and tapered according to the schedule outlined in Table 88-7.

**CASE 88-1, QUESTION 4:** T.B. is very concerned 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.8 For nearly all patients, the health risks associated with postcessation weight gain are negligible compared with the risks of continued smoking. Studies suggest that most quitters gain fewer than 10 pounds, but there is a broad range of weight gain reported, with up to 10% of quitters gaining as much as 30 pounds.8 In general, women tend to gain more weight than men. In a study of nearly 6,000 smokers who were followed for 5 years after quitting, the average weight gain during the follow-up period was 19.2 and 16.7 pounds among women and men, respectively.9 For men and women, subgroups that are more likely to gain weight after quitting are African Americans, younger tobacco users (younger than 51 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.10 Increased postcessation caloric intake might 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 most patients, strict deterting to prevent weight gain, especially during the early stages of quitting, is generally not recommended.8 T.B. should be counseled that the average weight gain of fewer than 10 pounds is less detrimental to her overall health than is continued smoking. Although exercise interventions have not been shown to reduce weight gain among quitters,8 it should not be ruled out as a recommendation for T.B. because she expresses significant concern about weight gain, and this might be a barrier to her quitting. As such, it is reasonable for the clinician to recommend that T.B. engage in some form of physical activity, such as walking 30 minutes daily. Even small changes, such as taking the stairs instead of the elevator, or parking toward the end of a parking lot instead of in the closest spot, can make a difference. Furthermore, T.B. should be advised to plan her meals in advance to avoid binge eating, increase her water intake to create a feeling of fullness, chew sugarless gum, and limit alcohol consumption. T.B. may consider pharmacotherapy options that have been shown to delay weight gain—according to the Clinical Practice Guideline, this would include the 4-mg nicotine gum or lozenge or sustained release bupropion.8 It is important to note, however, that once the medication is terminated, most quitters gain, on average, an amount of weight that is comparable to that which would have been gained in the absence of medication.8

**CASE 88-1, QUESTION 5:** 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 more than a month. How should the clinician respond?

The clinician should thank T.B. for being honest about her smoking and ask whether she is comfortable discussing 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 is also important to focus on the “positive,” such as T.B.’s ability to have remained tobacco free for more than 1 month. Four weeks after quitting, 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 informative 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 88-6).

**CASE 88-2**

**QUESTION 1:** 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 (2 PPD) and alcohol (3–4 drinks/day). He is approximately 10 pounds overweight. His preoperative laboratory results are significant for a total cholesterol of 270 mg/dL (desirable, <200), low-density lipoprotein cholesterol (LDL-C) of 163 mg/dL...
A wealth of evidence suggests that cigarette smoking is a major cause of cardiovascular disease and is responsible for approximately 128,000 premature cardiovascular-related deaths each year. 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. In addition, smoking substantially 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. There are numerous plausible pathophysiological mechanisms by which 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 substantially increases the risk of MI and sudden death. 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. Smoking may accelerate atherosclerosis through effects on serum lipids; smokers tend to have higher levels of 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 (e.g., hypertension, dyslipidemia, which might contribute to the development and progression of atherosclerosis). Finally, smoking stimulates the release of neurotransmitters (e.g., epinephrine, norepinephrine) that increase myocardial workload and induce coronary vasodilation, leading to ischemia, arrhythmias, and sudden death. 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 (e.g., hypertension, dyslipidemia) have synergistically increased his risk for serious cardiovascular disease. 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. A meta-analysis of 20 studies determined that smoking cessation is associated with a 36% reduction in the risk of death among patients with established coronary heart disease. The reduced mortality risk associated with quitting smoking is comparable to that observed with other established secondary preventative approaches such as therapies for hypertension and dyslipidemia. The clinician should approach this hospitalization as an opportunity to assist P.J. with quitting smoking. Furthermore, published data suggest that initiation of intensive cessation counseling interventions for hospitalized patients is effective in achieving long-term abstinence.

CASE 88-2, QUESTION 3: 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 inadequately responded to treatment with the transdermal patch and experienced intolerable jaw soreness with the nicotine gum. Newer formulations of the nicotine gum are less viscous, and therefore easier to chew, than earlier formulations of the gum; however, other options are available. First-line treatment options that he has not tried include the nicotine lozenge (see Case 88-1, Question 3), nicotine nasal spray, nicotine inhaler, sustained-release bupropion, varenicline, or an effective combination of first-line agents (see Case 88-3, Question 1).

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-μg spray
Nasal congestion and most patients rated cough and mouth and throat irritation and then slowly decline thereafter. Use of the nicotine nasal spray more than doubles long-term abstinence rates when compared with placebo (Table 88-4).6-8

DOISING

Table 88-7 outlines the manufacturers’ recommended dosing schedule for the nicotine nasal spray. 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 during 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 tube 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. The spray increases the likelihood of tearing, coughing, and sneezing, so patients should wait 5 minutes before driving or operating heavy machinery.

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; 84% of patients still reported mild to moderate nasal irritation after 3 weeks of therapy.8 Nasal congestion and transient changes in taste and smell have also been reported.6 Despite the high incidence of local adverse effects, most patients become tolerant to the irritant effects of the spray during the first week.8

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 is rapidly absorbed across the buccal mucosa, 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.8

Nicotine Inhaler

The nicotine oral inhaler consists of a plastic mouthpiece and a disposable cartridge containing a porous plug containing 10 mg of nicotine and 1 mg of menthol. Menthol is added to reduce the irritant effect of nicotine.6

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 psychological factors that are important to many patients who smoke.8

As a patient inhales through the mouthpiece, nicotine vapor is released from the cartridge and is distributed throughout the oral cavity. When the inhaler is used correctly, approximately 4 mg of nicotine vapor is released from the cartridge, and 2 mg is absorbed across the buccal mucosa.8 Peak plasma nicotine concentrations with the inhaler are achieved after approximately 30 minutes of use20 and then slowly decline thereafter (Fig. 88-3). Use of the nicotine inhaler approximately doubles long-term abstinence rates when compared with placebo (Table 88-4).8,60

DOISING

Table 88-7 outlines the manufacturers’ recommended dosing schedule for the nicotine inhaler. During the initial 3 to 6 weeks of treatment, the patient should use 1 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 for 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 during the following 6 to 12 weeks.

PATIENT EDUCATION

To minimize the likelihood of throat irritation, patients should be instructed to inhale shallowly (as if puffing a pipe). When used correctly, 100 shallow puffs from one cartridge during 20 minutes approximate 10 puffs from one cigarette during 5 minutes.6 The release of nicotine from the inhaler is temperature dependent and significantly reduced at temperatures less than 40° F.11 In cold conditions, patients should store the inhaler and cartridges in a warm place (e.g., inside pocket). 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.8

As with all forms of NRT that are absorbed across the buccal mucosa, the effectiveness of the nicotine inhaler is 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 or throat irritation (40%) and cough (32%).6 Most patients rated cough and mouth and throat irritation symptoms as mild, decreasing with continued use. Other less common side effects are rhinitis, dyspepsia, hiccup, 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 inhaled or can be used in the absence of tobacco 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 can be irritating and might induce bronchospasm.
Sustained-Release Bupropion

Sustained-release bupropion was the first nonnicotine medication to receive FDA approval for smoking cessation. Clinical trials involving more than 11,000 patients have confirmed its effectiveness as an aid for smoking cessation, and meta-analyses estimate that sustained-release bupropion treatment approximates double the long-term abstinence rates relative to placebo (Table 88.4).8,9

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.10

DOsing

Treatment with sustained-release bupropion (Table 88.7) 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 sustained-release bupropion 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 maximal dosage of 300 mg/day (150 mg BID). Therapy should be continued for 7 to 12 weeks after the quit date.

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 be advised not to take Zydoban and Wellbutrin or generic bupropion formulations concomitantly to avoid dose-related adverse effects, including seizures.

ADVERSE REACTIONS

The most common adverse effects associated with bupropion therapy include insomnia (35%-40%) and dry mouth (10%),8,9 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 a history of seizures or cranial trauma, in individuals taking medications that may lower the seizure threshold, and in patients with underlying severe hepatic cirrhosis. Animal studies suggest that seizures may be related to the peak plasma concentration of bupropion, 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. In July 2011, the FDA mandated that the prescribing information for all bupropion-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide.10 These additional warnings were based on postmarketing adverse-event surveillance reports received by the FDA.

PRODUCT SELECTION CONSIDERATIONS

Sustained-release bupropion may be the drug of choice for patients who prefer to take oral medications (an alternative oral option is varenicline, described below). Because sustained-release bupropion tablets are easy to dose (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). Sustained-release bupropion might be beneficial for use in patients with depression or in individuals with a history of depressive symptoms during a previous quit attempt. Finally, sustained-release bupropion has been found to reduce postcessation weight gain during treatment,8,9 and this might be of short-term benefit in selected patients with concerns about weight gain after quitting. Disadvantages of sustained-release bupropion include a high prevalence of insomnia and several contraindications and precautions that preclude use in some patients.

Varenclline

Varenclline is the most recent agent approved by the FDA for smoking cessation. Clinical trials involving nearly 5,000 patients treated with varenclline have confirmed its effectiveness as an aid for smoking cessation. Data from meta-analyses indicate that varenclline significantly increases long-term abstinence rates relative to placebo, and sustained-release bupropion.11 The pooled risk ratio for long-term abstinence (26 months) for varenclline compared with placebo was 2.3 (95% CI, 1.9-2.9). The pooled risk ratio for varenclline versus sustained-release bupropion and the nicotine patch at 1-year follow-up was 1.5 (95% CI, 1.2-1.9) and 1.3 (95% CI, 1.0-1.7), respectively.11

PHARMACOKINETICS

Varenclline absorption is virtually complete after oral administration, and oral bioavailability is unaffected by food. Once absorbed, varenclline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination is primarily through glomerular filtration, along with active tubular secretion. The half-life is approximately 24 hours, and following administration of multiple oral doses, steady-state conditions are reached within 4 days.11

DOsing

Treatment with varenclline (Table 88.7) should be initiated 1 week before the patient stops smoking. This dosing regimen
Furthermore, the safety and efficacy of varenicline has not been established in these populations.88 Recently the prescribing information for varenicline was revised to include warning for a possible increased risk of cardiovascular events (MI, ischemic and hemorrhagic stroke) in patients with stable cardiovascular disease.89

**PRODUCT SELECTION CONSIDERATIONS**

Varenicline is a first-line agent for the treatment of tobacco use and dependence. 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 sustained-release bupropion). As with any of these medications, varenicline should be combined with behavioral counseling to maximize chances for a successful, long-term quit attempt. Given its potential for inducing negative neuropsychiatric effects, varenicline should be used with extreme caution in 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 gradual titration of the dose to minimize treatment-related nausea and insomnia. The recommended dosage titration for varenicline is as follows: 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 considered to increase the likelihood of long-term abstinence. Varenicline should be used with caution in patients with impaired renal function. For patients with severe renal dysfunction (estimated creatinine clearance <30 mL/minute) the recommended maximal dose of varenicline is 0.5 mg twice daily. In patients with end-stage renal disease undergoing hemodialysis, a maximal dose of 0.5 mg daily is recommended.88

**ADVERSE REACTIONS**

Varenicline is generally well tolerated. Common side effects (≥3% and twice the rate observed in placebo-treated patients) include nausea (30%), sleep disturbance (insomnia 18%; abnormal dreams 13%), constipation (9%), flatulence (6%), and vomiting (5%). Per the manufacturer’s prescribing information, nausea was the most common adverse event associated with varenicline treatment. Nausea dose was dose dependent and generally described as mild or moderate and often transient; however, for some patients, it was persistent for 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.84

In July 2009, the FDA mandated that the prescribing information for varenicline include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicidal-related events including ideation, behavior, and attempted suicide.85 These additional warnings were based on continued postmarketing adverse event surveillance reports received by the FDA. As such, the warnings and precautions sections of the medication’s prescribing information have been updated, and the FDA recommends that (a) patients tell their health care providers about any history of psychiatric illness before starting varenicline, and (b) clinicians and patients monitor for changes in mood and behavior during treatment with varenicline.88 Because patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of varenicline, the safety and efficacy of varenicline has not been established in these populations.88 Recently the prescribing information for varenicline was revised to include warning for a possible increased risk of cardiovascular events (MI, ischemic and hemorrhagic stroke) in patients with stable cardiovascular disease.89

**PATIENT EDUCATION**

The tablets are to be taken after eating and with 8 ounces of water. Nausea and insomnia are side effects that are usually temporary. Patients should be advised to discontinue varenicline and contact their health care provider immediately if they experience agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them (see adverse reactions below).

**ADVERSE REACTIONS**

Varenicline is generally well tolerated. Common side effects (≥3% and twice the rate observed in placebo-treated patients) include nausea (30%), sleep disturbance (insomnia 18%; abnormal dreams 13%), constipation (9%), flatulence (6%), and vomiting (5%). Per the manufacturer’s prescribing information, nausea was the most common adverse event associated with varenicline treatment. Nausea dose was dose dependent and generally described as mild or moderate and often transient; however, for some patients, it was persistent for 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.84

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**PRODUCT SELECTION CONSIDERATIONS**

Varenicline is a first-line agent for the treatment of tobacco use and dependence. 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 sustained-release bupropion). As with any of these medications, varenicline should be combined with behavioral counseling to maximize chances for a successful, long-term quit attempt. Given its potential for inducing negative neuropsychiatric effects, varenicline should be used with extreme caution in 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 sug
Given his escalating 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, and the most important component of his treatment is smoking cessation. The clinician should commend J.B. for his interest in quitting and help him devise a patient-specific treatment plan. Although the use of first- and second line medications approximately double the likelihood that a patient will successfully quit smoking, data from clinical trials suggest that only 15% to 25% of patients remain abstinent for more than 6 months. 

Given these modest success rates, clinicians and researchers have explored modified approaches to standard therapies, including the use of combination therapy. Plasma levels of nicotine achieved with standard doses of NRT are generally much lower than those attained with regular smoking. 

As such, conventionally dosed NRT may pose some theoretical risk in a patient like J.B., 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 J.B. would receive using the recommended dose of any NRT product will not exceed the amount he previously obtained from his 2 PPD smoking habit.

The clinician should strongly encourage pharmacotherapy during P.J.’s current quit attempt. P.J. is 10 pounds 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 for Tobacco Dependence**

**CASE 88.3**

**QUESTION 1** 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 going or climbing stairs). He currently uses an albuterol inhaler (90 mcg/puff), 2 puffs every 4 hours 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 during the past year. On the first attempt (quitting “cold turkey”), J.B. relapsed within 2 days. J.B. successfully quit for nearly 2 weeks on his second attempt (using the 4-mg nicotine lozenge), but he found it difficult to adhere to the frequent dosing schedule and relapsed shortly after discontinuing the lozenge. His most recent quit attempt was 6 months ago using varenicline. After 1 month of abstinence, J.B. self-terminated varenicline (“I thought I didn’t need it anymore”) and relapsed within 1 week. 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 prior lack of success. On physical examination, coarse breath sounds that clear after coughing are noted. A chest radiograph obtained in the office shows no infiltrates. Spirometry reveals a forced expiratory volume in 1 second (FEV1) of 2.8 L (72% of predicted) and a forced vital capacity (FVC) of 4.1 L (81% of predicted). His FEV1/FVC ratio is 68%. He weighs 76 kg and is 72 inches 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 nearly all patients diagnosed with COPD are current or former smokers. Medications (e.g., bronchodilators, anti-inflammatory agents) used to treat the symptoms of COPD have not been shown to slow disease progression. J.B.’s pulmonary function tests indicate he has stage II (moderate) COPD. Given his escalating 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, and the most important component of his treatment is smoking cessation. The clinician should commend J.B. for his interest in quitting and help him devise a patient-specific treatment plan. Although the use of first- and second line medications approximately double the likelihood that a patient will successfully quit smoking, data from clinical trials suggest that only 15% to 25% of patients remain abstinent for more than 6 months.

Given these modest success rates, clinicians and researchers have explored modified approaches to standard therapies, including the use of combination therapy. Plasma levels of nicotine achieved with standard doses of NRT are generally much lower than those attained with regular smoking. As such, conventionally dosed NRT may pose some theoretical risk in a patient like J.B., 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 J.B. would receive using the recommended dose of any NRT product will not exceed the amount he previously obtained from his 2 PPD smoking habit.

The clinician should strongly encourage pharmacotherapy during P.J.’s current quit attempt. P.J. is 10 pounds 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.
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, sustained-release bupropion, varenicline, or an effective combination of first-line agents. The choice of therapy is dictated by considerations such as 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 costs. For patients reporting a positive experience with a given medication, treatment 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, sustained-release bupropion, or varenicline. Combination therapy with the nicotine patch and sustained-release bupropion or a short-acting NRT formulation (e.g., nicotine gum, lozenge, or inhaler used as needed) 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 medica
tions in combination with behavioral counseling. J.B.’s previous 1-month-long quit attempt highlights the successful impact of varenicline in this patient; however, J.B.’s relapse likely is attributable to a shortened course of therapy and the absence of a behavioral change 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 toll-free tobacco quitline at 1-800-QUIT NOW (see Case 88-5, Question 1); (b) call the toll-free number that accompanies the selected medication (most 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 adherence with the medication regimen—daily adherence, 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 perform pulmonary function testing and 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 inches) and FEV1 (2.8 L), his estimated lung age is almost 80 years.106 This educational approach has been found to significantly increase long-term (12-month) quit rates in a recent controlled trial.107

Drug Interactions With Smoking

CASE 88-4

QUESTION 1: M.K. is a new patient requesting Ortho Tri-Cyclen (noregestimale/ethinyl estradiol). The new patient history form completed by M.K. reveals that she is 32 years old, weighs 65 kg, and is 70 inches tall. She takes no prescription medications but occasionally uses loratadine 10 mg as needed for allergies, and ibuprofen 400 mg as needed 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 (3–4 cups of coffee daily). Are there any potential drug 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 (see Chapter 47, Contraception). Estrogens are known to promote coagulation by altering clotting factor levels and increasing platelet aggregation. As described in Case 88-2, Question 1, substances present in tobacco smoke, including oxidant gases and other products of combustion, induce a hypercoagu
gable 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 cardio
diovascular events, including stroke, MI, and thrombembolism in women who use oral combination hormonal contraceptive agents.108,109 This risk is age-related, in that the absolute risk of death as a result of 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 as a result of 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.108 Because of the increased risk of adverse cardiovascular events, current guidelines from the American Col
gle 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, and progestin-only con
traceptives (oral and injectable formulations) and intrauterine devices are recommended for use in this population.107,108 M.K. is 32 years of age, and despite smoking 20 cigarettes per day, oral contraceptive use is not contraindicated, per drug manufacturer recommendations, 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 with time. Risk factors associated with her family his
tory (hyper tension, MI, diabetes, and hyperlipidemia) suggest a genetic predisposition to cardiovascular disease, and thus efforts to minimize preventable risk factors should be encouraged.

COMPLEMENTARY THERAPIES

CASE 88-4, QUESTION 2: M.K. asks whether any of the natural herbal products for cessation that she “hears about on the radio” are effective.

Although many herbal and homeopathic products are available to help people quit smoking, data that support their safety and efficacy are lacking. Most herbal preparations for smok
ing cessation contain lobeline, an herbal alkaloid with partial
nicotine agonist activity. Although direct-to-consumer advertise-
ments suggest that lobeline-containing preparations are safe and
effective, a meta-analysis106 and recent controlled trial107 found
no evidence to support the role of lobeline as an effective aid for
smoking cessation. Likewise, St. John’s wort (an herbal product
with antidepressant properties),108 nicobelin (an herbal prod-
uct not available in the United States that contains quinine,
menthol valerate, camphor, and eucalyptus oil),109 hypnosis,110
and acupuncture111 have not been found to be effective treat-
ments for smoking cessation.4 Furthermore, patients should be
cautions that herbal cigarettes are not safe alternatives because
they result in the inhalation of other toxins present in smoke.
M.K. should be advised that the efficacy of the herbal therapies
is not well established, and use of these agents cannot be recom-
manded at this time.

**CASE 88-4, QUESTION 3:** M.K. is not considering quitting
smoking in the next 30 days. She cannot discontinue her
oral contraceptives because she is sexually active and needs
a reliable form of birth control. She wonders whether 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 at least 10 mcg of ethinyl estradiol
induce greater procoagulatory effects than do preparations con-
taining either 30 mcg or 35 mcg of ethinyl estradiol; formulations
containing 20 mcg of ethinyl estradiol appear to have little or no
adverse effect.112113 Early epidemiologic reports linking oral contraceptive use and severe cardiovascular events
were largely observed in women using oral contraceptives con-
taining more than 50 mcg of ethinyl estradiol.114115 Since then,
manufacturers have reduced the dose of estrogen in oral contra-
ceptives such that the majority of preparations available in the
United States contain 20 to 35 mcg of ethinyl estradiol.116

In 2001, the US 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.117

Serum estrogen levels obtained with the vaginal ring are sig-
nificantly lower than those achieved with either transdermal or
oral combined contraceptive formulations.118119 and theoretically,
the contraceptive patch and vaginal ring are relatively new, and their safety has not been
established among 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 in 2006
by the ACOG state that the same precautions for the use of oral
combined contraceptives should apply to these newer formula-
tions as well.120 M.K.’s prescribed oral contraceptive agent (Ortho Tri-Cyclen)
is a triphasic formulation containing 15 mcg of ethinyl estradiol in
combination with weekly increasing doses of norgestrel (0.18,
0.215, and 0.25 mg) throughout each monthly cycle. Although
some clinicians recommend the use of low-dose (20-mcg) estro-
gen 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 more than 25 cigarettes
per day, some data suggest that her risk for an MI is increased.121

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 published data, only smok-
ing 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 appro-
priate for the clinician to apply the 5 R’s (Table 88-5) 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 thrombotic 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 58% in patients who quit smoking.122

**Brief Interventions to Promote Tobacco Cessation**

**CASE 115**

**QUESTION 1:** J.C. is a 52-year-old man with a history of
asthma requesting a refill of his albuterol inhaler pre-
scription. This is the third request for an albuterol inhaler
(purchase 200 doses/inhaler) during the past 2 months. Before this
period, his last refill was more than a year ago. J.C. reports
that he has been using albuterol on most days of the week for
coughing and SOB. He has no other medical conditions and
takes no other medications. His social history is signific-
ificant for tobacco use (smokes 1.5 PPD; he recently started
smoking again after starting a new job where “everyone
smokes”). J.C. previously quit smoking 20 years ago using
the “cold turkey” approach (e.g., no medications or coun-
seling), and although he was successful, he was miserable
for weeks and he expresses reluctance to “go through this
again” during a stressful job transition.

The clinician is running behind schedule and does
not have the time to provide comprehensive smoking-
cessation counseling during this patient encounter. What
brief smoking-cessation interventions can the clinician pro-
vide to J.C. to assist him with quitting?

**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 comprehen-
sive tobacco-cessation counseling during a patient visit, cli-
nicians are encouraged to apply a truncated 5 A’s model, whereby
they ask about tobacco use, advise tobacco users to quit, and
refer patients who are ready to quit to a telephone quitline.
Effective brief interventions can generally be accomplished in
fewer than 3 minutes. 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 finan-
cial 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,9 and these positive results have been shown to trans-
late into real world effectiveness.14 The addition of medication
to quitline counseling significantly improves abstinence rates
compared with medication alone. In addition, preliminary evi-
dence suggests that quitlines are also effective for smokeless
tobacco cessation. The telephone number for the toll-free
tobacco quitline is 1-800-QUIT NOW. In some states, clinicians
can submit a fax referral form, on behalf of a patient, to the quit-
line. This form initiates a process whereby a quitline counselor
then contacts the patient directly.

J.C.’s asthma is not well controlled (e.g., he has been using a
short-acting bronchodilator 2–3 days/week for SOB and cough-
ing). The change in J.C.’s asthma control is temporally related
to his recent job change and relapse to daily smoking. Exposure
to tobacco smoke is a potent trigger for asthma exacerbations
and an important cause of poor asthma control. Given that the
clinician is unable to provide comprehensive smoking cessation
counseling at this time, a brief intervention is appropriate. The
clinician should strongly advise J.C. to quit as a key component
of his asthma management plan and refer him to a free telephone
quitline or to other resources that are available within the com-
munity (e.g., local individual or group counseling programs). Time
permitting, the clinician could educate J.C. on the benefits of
medications in reducing nicotine withdrawal symptoms given
his previous negative experience with quitting.

For a video demonstration of a brief counseling intervention for J.C. delivered by a health care provider, go to
http://thepoint.lww.com/AT10e.

**Smoking Among Individuals With Mental Illness**

**CASE 88-6**

**QUESTION 1:** J.D. is a 42-year-old woman presenting to
clinic for follow-up of her depression management. Nine
months ago, she was started on venlafaxine XR 75 mg daily.
At her 3-month follow-up visit, she was stable on venlafax-
ine XR 150 mg daily, and her depressive symptoms had
improved. She also reported that she was sleeping much
better. J.D. has no other significant past medical history, and
she takes no other medications. Her social history is positive
for current tobacco use (1 PPD for 25 years) and caffeine use
(1–2 Diet Cokes a day). She does not drink alcohol. During
the appointment J.D. indicates that she would like to quit
smoking because she is feeling better about herself, and
she knows that her overall health will improve if she quits.
She also states that the last time she attempted to quit (sev-
eral years ago, using the nicotine gum), she felt “down and
had difficulty concentrating and couldn’t sleep.” She now is
fearful that her depression will return if she quits. Is smok-
ing cessation appropriate for J.D. at this time, and what are
her treatment options?

Although persons with mental illness constitute 22% of the US
population, they consume an estimated 44% of the cigarettes, and
incur nearly half of the tobacco-related deaths. Tobacco use and
dependency is more common among people with more serious mental illness, with schizophrenia being the high-
est: 9 of 10 persons with schizophrenia smoke. On average,
patients with mental illness die 25 years earlier than the gen-
eral population, and smoking is a key contributor to prema-
ture death. In the past, the mental health community has not
addressed smoking cessation with their patients, but increas-
ing evidence suggests that quitting is possible and should be
promoted. For patients with mental illness to achieve wellness,
smoking cessation intervention is an essential component of the
overall care plan.

Given that J.D. is currently willing to quit, and her depression
has been stabilized for more than 4 months in the continuation
phase of depression treatment, it is appropriate for the clinician
to discuss a quitting plan with J.D. and initiate therapy. The ther-
apeutic approach should include counseling and pharmacother-
y, with ongoing monitoring of progress toward quitting and
depressive symptoms.

**TREATMENT SELECTION**

**PHARMACOTHERAPY**

Because no contraindications are present, any of the FDA-
approved medications for cessation are appropriate. Although
sustained-release bupropion and varenicline both possess black-
boxed warnings highlighting the risk of serious neuropsychiatric
symptoms, this does not preclude use of these products for J.D. Recen-
tly completed and ongoing studies are examining the risks in
greater detail, and many of these trials include patients with various levels of severity and types of psychiatric
disorders. Regardles of whether sustained-release bupropion, vareni-
cline, or NRT product(s) are selected, the clinician should mon-
itor J.D. closely to assess incidence of depressive symptomatol-
gy. If sustained-release bupropion or varenicline is selected, J.D.
should be advised to stop taking the medication and contact
the clinician immediately if she experiences agitation, depressed
mood, and any changes in behavior that are not typical of nicotine
withdrawal, or if she experiences suicidal thoughts or behavior.

**BEHAVIORAL COUNSELING**

Because J.D. has indicated that she is ready to quit, the clinician
should commend her for making the important decision that
will positively impact her overall health. J.D. should be advised
that quitting is a process, and it will be important for them to
work closely together to address the physiological as well as
psychological aspects of quitting during the upcoming months.
As outlined in Figure 88-2, the clinician should review with J.D.
her primary reasons for wanting to quit, assess her confidence in
her ability to quit, determine key triggers for tobacco use, assess
and address any concerns related to quitting, and determine a
quit date.

**CASE 88-6, QUESTION 2:** After discussing the various treat-
ment options with the clinician, J.D. decides that she would
like to add sustained-release bupropion to her regimen
because the nicotine gum by itself didn’t help her much last
time. She also thinks that the combination of venlafaxine with
bupropion might help to “keep her depression more stable” while she is quitting. She confides in the clinician
that her biggest fear is the ability to avoid smoking when
she is stressed because of her job. She is a survey researcher
and must meet client-induced deadlines. How can J.D. cope
with stressful situations?

A variety of coping mechanisms can be applied to alleviate
the need to smoke during stressful situations or when exposed
to other triggers for smoking (Table 88-6). The clinician should
encourage J.D. to think about strategies that would be effec-
tive for her in these situations, such as deep breathing or calling
a supportive friend. Additionally, the clinician should consider sug-
gest use of a short-acting NRT product (e.g., nicotine gum,
lozenge, inhaler, or nasal spray) as needed to alleviate situational
cravings to smoke. The clinician should also describe the dosing of sustained-release bupropion and the need to begin therapy 1 to 2 weeks before the quit date (Table 88-7). A follow-up appointment should be scheduled for approximately 3 months after the quit date, and the patient should be advised to contact the clinician if she encounters any difficulties before then.

CASE 88-6, QUESTION 3: Four weeks later, J.D. calls and reports that she has a dry mouth, is having difficulty sleeping, and feels jittery and anxious. She also is currently using nicotine gum (2 mg), approximately four pieces daily. How should J.D. be managed?

As noted above, insomnia and dry mouth are commonly associated with sustained-release bupropion therapy and usually lessen with continued use.7 The nicotine gum dose is low and not likely contributing to this condition. To address insomnia, J.D. can be advised to take the second dose of the day earlier, but not less than 8 hours after the first dose of the day. Alternatively, the clinician could consider reducing the daily dose to 150 mg in the morning and omitting the evening dose. Although the manufacturer recommends 500 mg per day, the 150-mg dose has been shown to have comparable outcomes with those of the 300-mg dose135,136 and is better tolerated.135 The clinician also should assess J.D.’s caffeine consumption patterns and, if appropriate, suggest that she reduce her caffeine intake by 50% and not drink caffeinated beverages after 12 noon so her system is clear of its stimulatory properties before sleep.137

Extended-Use Medications for Cessation

CASE 88-6, QUESTION 4: J.D. returns to the clinician’s office 3 months later, and indicates that she is doing well but had a few “slips” and smoked four times, most recently last week when she learned that her best friend was diagnosed with ovarian cancer. Other than feeling down about her friend, she has not felt depressed and has been handling her stress at work through deep-breathing exercises. Because she is not taking smoke breaks every few hours, she is able to accomplish more during the day, and meeting deadlines has not been a problem. She uses the nicotine gum a few times a week, and does not feel ready to discontinue the sustained-release bupropion. She wonders whether it is possible to continue the therapy for a bit longer, until she feels more stable as a nonsmoker.

Extended-duration medication therapy appears to be safe and effective. Long-term follow-up data from the Lung Health Study indicate that approximately 15% of long-term quitters continued nicotine gum therapy with no serious side effects.137 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.9

Clinicians should be aware that although many of the medications (sustained-release bupropion, varenicline, nicotine nasal spray, and inhaler) are approved by the FDA for long-term (6-month) use, the effectiveness of additional weeks on therapy is not well established. A recent meta-analysis of eight trials found that extended treatment with varenicline might prevent relapse, extended treatment with bupropion is unlikely to have a clinically important effect, and studies of extended treatment with nicotine replacement are needed.134 Given J.D.’s current depression and because she recently encountered a difficult situation with her friend’s diagnosis, it is reasonable for the clinician to recommend continuation of therapy for an additional 12 weeks and reassess progress at that time.

KEY REFERENCES AND WEBSITE

A full list of references for this chapter can be found at http://rxforchange.ucsf.edu/. Below are the key references and websites for this chapter, with the corresponding reference number in this chapter found in parentheses after the reference.

Key References

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Key Website