in the clinic

Smoking Cessation

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According to the U.S. Centers for Disease Control and Prevention (1), 21% of American adults (44.5 million people) and 22% of American high school students (3.75 million people) smoke cigarettes. Although per capita tobacco use in the United States has decreased dramatically since the 1950s, it is unlikely that the United States will reach the Healthy People 2010 objectives of reducing smoking prevalence to less than 12% in adults and less than 16% in youth (2). Tobacco use is an even bigger public health threat in many regions outside of the United States. Many people who smoke wish that they could stop, but quitting is difficult and failure is common. Some, of course, do succeed in quitting permanently. In 2004, the CDC estimated that 45.6 million American adults were former smokers, representing half of all people who had ever smoked. Physicians play a critical role in reducing the burden of tobacco-related health problems by helping their patients who smoke to quit and by motivating their nonsmoking patients to remain nonsmokers. Unfortunately, many physicians report inadequate training in smoking cessation, and many smokers who see physicians do not receive assistance to quit.

Health Consequences of Smoking

Which health problems have definite links to tobacco use? Smoking increases the risks of numerous diseases and associated illness and death. In general, smokers have a mortality rate approximately twice that of nonsmokers (3–5). Good evidence links smoking to cancer, cardiopulmonary disease, and complications of pregnancy. The risk for smoking-related disease increases with the amount a person smokes.

In a cohort study of 34,439 British male physicians, it was found after 40 years of follow-up that smokers had a mortality rate twice that of nonsmokers (40% vs. 20%). 13 times the risk for chronic obstructive lung disease, 15 times the risk for lung cancer, and 1.6 times the risk for ischemic heart disease (3).

In a study that followed 24,505 women and 25,034 men born between 1925 and 1941, 9% of female and 14% of male never smokers and 26% of female and 41% of male heavy smokers died in middle age. Smoking cessation decreased the risk of death during middle age (5).

Tobacco use accounts for 25% to 30% of all cases of cancer and approximately 170,000 cancer deaths every year in the United States. The types of cancer associated with tobacco use include those that affect the lung, mouth and pharynx, esophagus, stomach, pancreas, bladder, kidney, cervix, and possibly the colon in addition to acute myelogenous leukemia.

In particular, tobacco smoking has been linked to 90% of cases of lung cancer in males and 78% in females (6). Smoking is the most important risk factor for chronic obstructive pulmonary disease (COPD). Only 5% to 10% of patients with COPD have never smoked. An estimated 12.5% of current smokers and 9.4% of former smokers have COPD (2), and an estimated 20% of regular cigarette smokers develop progressive COPD. Smokers are at least 4 times more likely to develop acute lung injury and the acute respiratory distress syndrome than people who do not smoke.

Smoking is a major cause of coronary artery disease, cerebrovascular disease, peripheral vascular disease, and abdominal aortic aneurysm (AAA). An estimated 20% of all deaths from heart disease are attributable to cigarette smoking.

A case–control study of myocardial infarction that involved 27,809 participants in 52 countries found that current smokers were at substantially higher risk for nonfatal myocardial infarction than never-smokers (odds ratio [OR], 2.95 [95% CI, 2.77 to 3.14]) (7). Among 73,451 U.S. veterans aged 50 to 79 years without a history of AAA who were screened with ultrasound, smoking was strongly associated with an AAA (OR, 5.57 [CI, 4.24 to 7.31]) (8).
In a prospective analysis of 2174 patients over age 40, current smoking was highly correlated with an increased risk for peripheral arterial disease (OR, 4.5 [CI, 2.3 to 8.8]) after adjustment for confounding factors (9).

Babies born to women who smoke are more likely to have low birthweight and to be premature. Smoke exposure may increase the risk for miscarriage. Women, particularly those older than 35 years of age, who smoke and use birth control pills face an increased risk for heart attack, stroke, and venous thromboembolism.

Other conditions that affect smokers include cataract, chronic cough, respiratory infections, damage to skin, poor oral health, low bone density, gastroesophageal reflux, and fire-related injury or death (6).

**Which health problems are associated with second-hand smoke exposure?**

Second-hand smoke, also known as environmental tobacco smoke, presents a substantial health risk to nonsmokers. The National Cancer Institute considers any amount of exposure to second-hand smoke potentially unsafe, but nonsmokers who live or work with smokers in homes or workplaces where smoking is allowed are at the greatest risk.

Exposure to second-hand smoke is clearly linked to an increase in certain types of cancer among nonsmokers. Approximately 3000 lung cancer deaths per year among adult nonsmokers in the United States are linked to second-hand smoke (10). Research also suggests associations between environmental tobacco exposure and cancer of the nasal sinus, cervix, breast, and bladder.

Those exposed to second-hand smoke are at increased risk for cardiopulmonary problems, including decreased lung function, chronic cough, and ischemic heart disease. Research has indicated that as many as 60,000 annual heart disease deaths in adult nonsmokers result from second-hand smoke (11).

Exposed children are more likely to have severe lower respiratory tract infections, severe asthma, and middle ear infections (12). In addition, the risk for sudden infant death syndrome is higher among babies exposed to smoke, and babies born to women exposed to second-hand smoke are more likely to have low birthweight and to be premature.

**Prevention of Smoking-Related Disease**

**What are the health benefits that smokers who quit can anticipate?**

Smoking cessation provides meaningful health benefits, and people who quit smoking live longer on average than people who continue to smoke. Some benefits begin shortly after cessation (Figure 1). Smokers who quit decrease their risk for lung cancer and other types of cancer, heart attack, stroke, and chronic lung disease. The U.S. Surgeon General reports that people who quit smoking before age 50 have half the risk for dying within the next 15 years compared with those who continue to smoke (6).

After 10 years of smoking cessation, the risk for lung cancer in former smokers was 30% to 50% less than that of current smokers. Individuals who quit smoking for 5 years have half the risk for cancer of the oral cavity and esophagus compared with continuing smokers. Smoking cessation also results in a 50% reduction in bladder cancer. Former smokers have a reduced risk for cervical cancer within a few years of smoking cessation and a

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**Health Consequences of Smoking...** All people who smoke are at increased risk for several types of cancer (lung, esophageal, oral, bladder, cervical, pancreatic, and possibly others), coronary artery disease, peripheral vascular disease, aortic aneurysm, stroke, chronic lung disease, poor pregnancy outcomes, and premature death. Environmental tobacco puts exposed nonsmokers at risk for many of these same health problems and contributes to childhood morbidity and mortality from infections and respiratory illness. Smokers and those who live with them are at risk for fire-related injury and death.

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**CLINICAL BOTTOM LINE**

Smokers and those who live with them are at risk for fire-related injury and death. Environmental tobacco puts exposed nonsmokers at risk for many of these same health problems and others), coronary artery disease, peripheral vascular disease, aortic aneurysm, stroke, chronic lung disease, poor pregnancy outcomes, and premature death. Environmental tobacco puts exposed nonsmokers at risk for many of these same health problems and contributes to childhood morbidity and mortality from infections and respiratory illness. Smokers and those who live with them are at risk for fire-related injury and death.
reduced risk for pancreatic cancer after 10 years of smoking cessation.

Observational studies suggest that there is a 50% reduction in cardiac events in the first year following smoking cessation and that the level of risk approaches that of persons who have never smoked after 2 to 3 years (13, 14). Circulation improves within just a few weeks of quitting. Within 5 to 15 years, stroke risk is reduced to that of a nonsmoker.

The chronic cough associated with smoking resolves or markedly decreases in 94% to 100% of patients when they quit, and in about half of these patients, cough resolution occurs within a few weeks. Lung function improves within 3 months, and shortness of breath improves within 1 to 9 months as lung function returns to normal.

Smoking cessation during the first 3 to 4 months of pregnancy reduces the risk for having a low-birthweight baby to that of women who never smoked.

Other benefits from smoking cessation include elimination of the damaging effects of tobacco on skin, breath, teeth, and gums. Cessation improves the sense of smell and taste. Everyday activities like climbing stairs or walking are less tiring. Smoking cessation eliminates the expense of cigarettes, as well as the higher costs of health and life insurance charged to smokers.

Which patients have the greatest potential to benefit from smoking cessation?

Patients with established coronary artery disease, COPD, and pregnant women and their babies are at the highest risk from smoking and thus benefit the most from quitting. Children also benefit significantly when smokers who they are living with quit.

Why is it difficult for smokers to quit?

Quitting smoking is hard for many reasons, but mostly because nicotine is highly addictive. It produces a mood-elevating physiologic response. Nicotine withdrawal symptoms include mild depression, anxiety, headaches, nausea, shakes, cough, hunger, fatigue, and insomnia. Typically, symptoms are most intense in the first 72 hours after quitting and last from 2 to 8 weeks. The craving for nicotine can last much longer.

Quitting smoking also requires behavior change. The habit of smoking is comforting to many smokers, and the act of reaching for, lighting, and
smoking a cigarette becomes a routine part of life. Certain environments or social situations may cause relapse in people who quit smoking.

Is there an age after which smoking cessation fails to yield benefit?

Smoking cessation benefits people of all ages, regardless of the length of their smoking history.

Evidence for the benefits of smoking cessation in the elderly comes from a large study (4) involving men and women age 65 years or older. The study found that individuals who continued to smoke had significantly higher rates of mortality as well as cardiovascular and neoplastic disease than former smokers or nonsmokers after 5 years follow-up.

In a large, population-based study of Norwegian smokers 40 to 70 years of age (5), the mortality benefits of quitting were greatest for those who quit earliest, but benefits were clearly present for those who quit at age 60, the oldest age at which this study reported the effects of quitting.

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### Prevention of Smoking-Related Disease...

Doctors should send a clear message to their patients that no amount of tobacco is safe and ask all patients if they smoke regardless of age. Doctors should emphasize the importance of smoking cessation when counseling patients with coronary artery disease or chronic obstructive pulmonary disease, pregnant women, and those who live with children.

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### CLINICAL BOTTOM LINE

How should clinicians screen for tobacco use and when should they provide tobacco cessation counseling?

Clinicians should ask all patients if they smoke, regardless of age, sex, or medical history. Since most adults who have ever smoked daily became daily users at or before age 18 years, the opportunities for primary smoking prevention are less for clinicians who care for adults than for those who care for children. However, all clinicians should send a clear message to patients that any amount of smoking is unhealthy and the best prevention is never to start.

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### Treatment

Can smokers quit without any intervention?

Some smokers do successfully stop smoking without any health care provider intervention, but intervention improves the success rate. Evidence documents that an intervention as simple as a single message from a physician to quit increases quit rates.

In a systematic review examining smoking cessation therapies with at least 6 months of follow-up (15), 17 randomized clinical trials included 1 episode of advice and encouragement from a physician. The summary absolute reduction in the rate of smoking was 2% (CI, 1 to 3). Ten trials of frequent encouragement found a reduction of 5% (CI, 1 to 8).

Another review of randomized, controlled trials examining smoking cessation advice from a medical practitioner found that brief advice increased smoking cessation rates (16). The OR for cessation was 1.69 (CI, 1.45 to 1.98) in favor of brief advice.

More intensive interventions can improve the smoking cessation success rates. Both behavioral therapy and pharmacotherapy can provide effective assistance, and the likelihood of successful smoking cessation is increased when they are combined.

What behavioral interventions are effective in smoking cessation?

At every clinic visit, physicians should ask their patients about smoking, advise all smoking patients to quit, assess the smoking patients’ willingness to change, assist them in their attempts to quit, and arrange follow-up to reassess willingness of patients unwilling to quit or to evaluate and support those who attempt to quit (Table 1) (17).

Behavioral interventions can range from briefly asking patients about smoking habits to multiple counseling sessions. Individual therapy, group therapy, and self-help therapy have all been found to help people stop smoking (Table 2). There is no apparent advantage of group therapy over individual therapy, nonspecific behavior modification over brief advice, or gradual cessation over abrupt cessation (16). While even brief interventions can work, high-intensity counseling (more than 10 minutes) is more

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likely to succeed than low-intensity counseling (3 to 10 minutes), according to the Public Health Service (17). Additionally, programs with 8 or more sessions have provided greater benefit than those with 3 or fewer sessions.

Self-Help Therapy
Some patients may benefit from self-help therapy, but the magnitude of the benefit is likely to be small. Evidence suggests that standard self-help material provides no additional benefit when used with other interventions like clinician advice or nicotine replacement therapy (18). The Public Health Service guideline does not advocate the use of self-help interventions alone (17). There does not appear to be an advantage of group therapy over individual therapy, non-specific behavior modification over brief advice, or gradual cessation over abrupt cessation.

Individual Therapy
Evidence suggests that individualized counseling by health care providers improves quit rates. One review found insufficient evidence to suggest that more intensive counseling was better than brief counseling (16), but the Public Health Service guideline states that “There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness.” In their review of the evidence they found an OR of 1.6 (CI, 1.2 to 2.0) for cessation with low-intensity counseling (i.e., 3 to 10 minutes) and an OR of 2.3 (CI, 2.0 to 2.7) with high-intensity counseling (i.e., greater than 10 minutes). It was also determined that 8 or more sessions were more beneficial than programs with 3 or fewer sessions (17).

Some clinicians have reasoned that hospitalized individuals who smoke might be more responsive to smoking cessation interventions, but brief hospital smoking cessation programs have shown mixed results. Only intensive interventions consisting of inpatient contact plus follow-up for at least 1 month were associated with a higher quit rate than routine care (19). A brief intervention during hospital admission for smokers after myocardial infarction or bypass surgery, for instance, found no significant difference in abstinence at 6 weeks and 12 months (20).

Telephone Therapy
Consistent support and reminders to stay on track can be particularly helpful for people trying to quit. Individual telephone counseling is a popular way of administering such support and reinforcement. Research indicates that both proactive (initiated by patients) and reactive (arranged by clinicians) telephone counseling helps smokers interested in quitting (21). Quit rates are highest for those who receive more intensive therapy in the form of multiple sessions of call-back counseling.

A study of the effectiveness of the California Smokers Helpline (22) that randomized smokers to 7 telephone counseling sessions or to telephone counseling on an as-requested basis found a 2.2 increase in cessation in the intervention group at 1 year (P < 0.001).

A study of 837 smokers at Veterans Affairs medical centers (36) showed that telephone care, which combined phone counseling with provision of drug therapy, tripled long-term quit rates when compared with brief primary care intervention alone (13.0% vs. 4.1%; P < 0.001) (23).

Group Therapy
Group therapy provides smokers with mutual support as well as behavioral techniques for smoking cessation. Studies have found that group therapy

Table 1. U.S. Public Health Service Clinical Practice Guideline: 5-Step Brief Intervention for Smoking Cessation

<table>
<thead>
<tr>
<th>5-As: For Patients Willing to Quit</th>
<th>5-Rs: To Motivate Patients Unwilling to Quit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask about tobacco use</td>
<td>Encourage patient to think of Relevance of quitting to smoking</td>
</tr>
<tr>
<td>Advise to quit</td>
<td>Ask</td>
</tr>
<tr>
<td>Assess willingness to make a quit attempt</td>
<td>Assess the patient in identifying Risks of smoking</td>
</tr>
<tr>
<td>Assist in quit attempt</td>
<td>Discuss with patient Roadblocks or barriers to attempting cessation</td>
</tr>
<tr>
<td>Arrange follow-up</td>
<td>Repeat the motivational intervention at all visits</td>
</tr>
</tbody>
</table>

is more effective than self-help and about as effective as similar intensity individual therapy (24). Adding group therapy to other forms of treatment like nicotine replacement may provide additional benefit. Counseling that focuses on increasing cognitive and behavioral skills and on avoiding relapse appears to be most effective.

Exercise and Other Nondrug Therapies
Alternative behavioral interventions marketed for smoking cessation include exercise therapy, acupuncture, aversive smoking, and hypnosis. Systematic reviews have concluded that there is insufficient evidence to support their use. However, the Public Health Service acknowledges that some individuals might benefit from these techniques (17).

Which pharmacologic therapies are effective in smoking cessation?
Nicotine replacement therapies and bupropion are the most commonly used, effective forms of pharmacotherapy for smoking cessation. While smokers often use them alone for smoking cessation, combining pharmacotherapy with behavioral therapy increases success rates. Varenicline is a new drug for smoking cessation that received U.S. Food and Drug Administration approval in May 2006. Other pharmacologic therapies have limited evidence for benefit.

Nicotine Replacement
Nicotine replacement works by alleviating the symptoms of withdrawal. This therapy is available over-the-counter in gum, patch, and lozenge forms and by prescription in inhaler, nasal spray, and sublingual tablet forms. All forms increase the quit rate by about 1.5- to 2-fold at 6 months among motivated persons. This is equivalent to a smoking cessation rate of 17% among those using nicotine replacement compared with 10% among control groups (25). Nicotine therapy should not be used by people who continue to smoke. People planning to use nicotine medication should start using it on the day that they quit.

Given the lack of evidence that one form of nicotine replacement is more effective or safer than another, clinicians and patients should choose nicotine replacement therapy according to individual preferences, tolerability of the product, and financial cost (Table 3). When patients are paying out-of-pocket, the patch and gum are the least expensive nicotine replacement options and the nasal inhaler is the most expensive, costing as much as $15 per day. Side effects may be associated with the dose of nicotine, the duration of treatment, or the type of nicotine replacement used. For

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**Table 2. Behavioral Interventions for Smoking Cessation**

| Self-help | Materials that smokers can access to learn about strategies to quit  
|-----------|-------------------------------------------------------------------------------------------------------------------------------------|
| Individual therapy | Interventions that involve advice and encouragement that a provider (e.g., physician, nurse, psychologist, health educator) delivers to an individual smoker  
**Example:** Physician advice during an office visit, referral to a one-on-one visit with a nurse who delivers smoking cessation advice and follow-up |
| Group therapy | Interventions that involve advice and encouragement that a provider (e.g., physician, nurse, psychologist, health educator) delivers to a group of smokers  
**Example:** Employer or health plan–based classes on smoking cessation |
| Telephone therapy | Interventions that involve advice and encouragement delivered to an individual smoker during telephone calls  
**Example:** National smoking cessation hotline (1-800 QUIT NOW) |

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Smoking cessation typically spans the following stages of change:

- Precontemplative ("I don’t want to quit")
- Contemplative ("I am concerned but not ready to quit now")
- Preparation ("I am ready to quit")
- Action ("I just quit")
- Maintenance ("I quit 6 months ago")

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<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Effectiveness</th>
<th>Initial prescription</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine replacement gum*</td>
<td>Prevents nicotine withdrawal</td>
<td>Increases cessation rates about 1.5–2 times control at 6 months</td>
<td>1 piece (2 mg) whenever urge to smoke up to 30 pieces/day, continuous use for &gt;3 months not recommended</td>
<td>• Less expensive than other forms of nicotine replacement</td>
<td>• Some patients find taste unpleasant</td>
</tr>
<tr>
<td>Nicotine 24–hour patch†*</td>
<td>Prevents nicotine withdrawal</td>
<td>Increases cessation rates about 1.5–2 times control at 6 months</td>
<td>21-mg patch/day once daily for 4–8 weeks (remove and replace every 24 hours). Then 14-mg patch/day for 2–4 weeks followed by 7 mg patch/day for 2–4 weeks. (Adults weighing less than 100 pounds, smoking fewer than 10 cigarettes/day and/or with cardiovascular disease: 14 mg patch/day for 4–8 weeks. Then 7-mg patch/day for 2–4 weeks.)</td>
<td>• Fewer than 24 hours/day.</td>
<td>• More expensive than other forms of nicotine replacement</td>
</tr>
<tr>
<td>Nicotine spray*</td>
<td>Prevents nicotine withdrawal</td>
<td>Increases cessation rates about 1.5–2 times control at 6 months</td>
<td>1 spray [0.5 mg nicotine] into each nostril 1–2 times each hour as needed whenever the patient feels the need to smoke up to a maximum of 5 doses (total of 10 sprays)/hour or 40 doses (total of 80 sprays)/day. Initially, encourage use of at least 8 doses (16 sprays/day), the minimum effective dose. Recommended duration is 3 months.</td>
<td>• Some patients prefer this delivery method</td>
<td>• More expensive than other forms of nicotine replacement</td>
</tr>
<tr>
<td>Nicotine inhaler*</td>
<td>Prevents nicotine withdrawal</td>
<td>Increases cessation rates about 1.5–2 times control at 6 months</td>
<td>24 to 64 mg (6 to 16 cartridges) per day for up to 12 weeks followed by a gradual reduction in dosage over a period of up to 12 weeks</td>
<td>• Some patients prefer this delivery method</td>
<td>• More expensive than other forms of nicotine replacement</td>
</tr>
<tr>
<td>Nicotine lozenges*</td>
<td>Prevents nicotine withdrawal</td>
<td>Increases cessation rates about 1.5–2 times control at 6 months</td>
<td>1 lozenge every 1–2 hours for 6 weeks, then 1 lozenge every 2–4 hours in weeks 7–9 and finally, 1 lozenge every 4–8 hours in weeks 10–12. Recommended duration of therapy is 12 weeks. (Patients who smoke within 30 minutes of waking require 4 mg and those who have first cigarette later in the day require 2 mg lozenge.)</td>
<td>• Some patients prefer this delivery method</td>
<td>• Some patients find taste unpleasant</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Unclear</td>
<td>Increases cessation rates about 2 times control at 1 year</td>
<td>Begin 1–2 weeks before quit date 150 mg every day for 3 days then 150 mg twice daily through end of therapy (max 7–12 weeks)</td>
<td>• Some antidepressant activity, may be a good option for patients with history of depression</td>
<td>• Some patients find taste unpleasant</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Reduces cravings via nicotine receptor agonist</td>
<td>Increases cessation rates over 3.5 times control and almost 2 times bupropion at 12 weeks.</td>
<td>Begin 0.5 mg once daily on days 1–3, then 0.5 mg twice daily on days 4–7, then 1 mg twice daily through end of therapy (12 weeks, consider additional 12 weeks to prevent relapse)</td>
<td>• No hepatic clearance</td>
<td>• Some patients find taste unpleasant</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• No clinically significant drug interactions have been reported</td>
<td>• Requires prescription</td>
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<td></td>
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<td></td>
<td></td>
<td>• Side effects include drowsiness, fatigue, nausea, sleep disturbance, constipation, flatulence</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Safety in pregnancy unclear</td>
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<td></td>
<td></td>
<td></td>
<td>• Avoid in renal disease (adjust dose if creatine clearance ≤50 mL/min)</td>
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</tbody>
</table>

* Avoid nicotine replacement in patients with recent myocardial infarction, arrhythmia, and unstable angina. Safety of nicotine replacement in pregnancy unclear.

† Several formulations of patches are available. Dosing guidelines are for patches designed to stay in place for 24 hours and that come in doses of 21 mg, 14 mg, and 7 mg. Clinicians should check prescribing information on nicotine patches that come in other doses or that are designed for application for fewer than 24 hours/day.
instance, the patch can cause skin irritation while the gum and nasal spray can cause throat irritation.

Studies have found no significant difference between nicotine replacement therapy lasting 8 weeks or longer, or between abrupt withdrawal or gradual tapering. While no clear evidence has been found for high-dose nicotine replacement therapy (>22 mg/24 hours), it may be useful for selective smokers. Conversely, low-dependence smokers may be comfortable taking a lower-than-average starting dose.

Combination nicotine replacement therapy may be superior to monotherapy; however, research results are not clear on this issue. One trial that investigated the effects of combination therapy with the nicotine patch and nasal spray showed that this treatment regimen was more that twice as effective than the nicotine patch alone for smoking cessation at 1 year (27% vs. 11%; \( P = 0.001 \)), and the trend persisted at 6 years (16% vs. 8%; \( P = 0.08 \)) (26).

**Bupropion**

Bupropion, the first nonnicotine medication to be approved for smoking cessation, is known to inhibit serotonin, norepinephrine, and dopamine, but its mechanism of reducing cravings and enhancing smoking abstinence is unknown. Definitive head-to-head comparisons of bupropion to nicotine replacement are unavailable, but one study showed that bupropion use resulted in a 30% 1-year quit rate, about double that of nicotine replacement therapy (27).

Bupropion therapy, using the sustained-release formulation, usually begins 1 to 2 weeks before the quit date and continues for 8 to 12 weeks. Dosage for the first 3 days is 150 mg once daily followed by 150 mg twice daily for the duration of therapy. The optimal duration of bupropion therapy has not been fully assessed. The medication has been safely used for long periods in the treatment of depression. Side effects of use include insomnia and dry mouth. Bupropion can be used in combination with nicotine replacement for patients who do not quit with monotherapy, but definitive evidence about combination therapy is lacking.

**Varenicline**

Varenicline is a nonnicotine drug designed specifically for smoking cessation. It binds to a nicotine receptor associated with the relaxing effects felt with smoking, providing a less relaxing effect. It reduces the cravings felt by smokers who quit.

A recent randomized trial compared 12 weeks of treatment with varenicline, sustained-release bupropion, or placebo in 1025 smokers. During weeks 9 to 52, continuous abstinence rates were 21.9% for varenicline, 16.1% for bupropion, and 8.4% for placebo. Nausea was reported by 28.1% of patients on varenicline (28).

Another recent trial randomized 1236 smokers who achieved abstinence for at least 7 days after 12 weeks of open-label varenicline to either an additional 12 weeks of varenicline or placebo. The varenicline group had higher continuous abstinence rates than the placebo group at 13 to 24 weeks (70.5% vs. 49.6%) and 13 to 52 weeks (43.6% vs. 36.9%) (29).

**Other Pharmacologic Therapies**

Other therapies that have not been approved by the FDA for smoking cessation are sometimes used. Methods for which there is limited evidence for effectiveness include clonidine or nortriptyline or naltrexone to block nicotine withdrawal symptoms, alprazolam to treat withdrawal-related anxiety, silver acetate to give cigarettes a bad taste, mecamylamine to antagonize nicotine effects, and lobeline (an alkaloid derived from the leaves of an Indian tobacco plant). Clonidine and nortriptyline are recommended second-line therapies for treating nicotine-withdrawal symptoms, and naltrexone is under consideration. These alternate therapies may be used when first-line medications are contraindicated or ineffective. The antihyptertensive drug clonidine has the strongest evidence of benefit, but it has undesirable side effects like dry mouth, drowsiness, and dizziness.

When should clinicians consider pharmacologic interventions for smoking cessation and how should they select from among the available therapies?

For patients ready to quit, support, behavioral therapy, and pharmacotherapy should be offered, since these interventions together provide the most benefit. Because of a lack of evidence to rank nicotine replacement, bupropion, and varenicline, the choice of a specific first-line pharmacotherapy should be guided by factors like clinician familiarity with the medications; contraindications for selected patients; previous patient experience with a specific pharmacotherapy; and patient characteristics, including concerns about weight gain or a history of depression (Table 3).

Are there conditions that contraindicate or caution against pharmacologic therapy for smoking cessation?

Nicotine Replacement

People using nicotine replacement therapy should not continue to smoke. Nicotine use is contraindicated in patients with a history of recent myocardial infarction, severe angina, and life-threatening arrhythmias. In these patients, the use of nicotine replacement therapy requires consideration of the potential adverse effects of the drug versus the risks associated with continued smoking. Nicotine replacement appears to be safe in persons with stable coronary disease, despite some theoretical concerns. Two randomized trials of nicotine replacement therapy in patients with stable ischemic heart disease found no increase in adverse cardiac events (30). A meta-analysis examining the incidence of adverse effects in individuals using the nicotine patch found no excess of cardiovascular outcomes in participants treated with the patch (31). At this time, the balance of risk and benefit from nicotine replacement therapy in pregnancy is unclear. Nicotine may be safer than smoking for pregnant women, but pregnant patients should use it only after failure of behavioral programs.

Bupropion

Bupropion is contraindicated in persons with a recent history of seizures, eating disorders, or other conditions that lower the seizure threshold. The seizure rate with bupropion is about 1 per 1000 persons treated. Drug interactions with antipsychotics and monoamine oxidase (MAO) inhibitors have been reported. Patients who are currently using or have used an MAO inhibitor or a drug with MAO inhibitor-like activity (e.g., furazolidone, linezolid, procarbazine, or selegiline) within the past 14 days should not receive bupropion. Similarly, other drugs that can lower the seizure threshold should be used with great caution or avoided in patients taking bupropion. Drugs that may lower the seizure threshold include some antidepressants, antipsychotics, cocaine, psychostimulants, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, theophylline, tramadol, and systemic corticosteroids. Blood pressure should be monitored in patients using bupropion as it has been associated with hypertension requiring treatment. Two forms of bupropion should not be administered together. Bupropion is a category B drug for pregnancy and should be considered only if behavioral interventions are unsuccessful.

Varenicline

Clinicians should use varenicline cautiously in patients with renal impairment. Dosage adjustments are necessary in patients with creatinine clearance ≤50 mL/min. The most common (>5%, and twice the rate seen in placebo) adverse reactions to varenicline were nausea/vomiting, sleep disturbance (insomnia, abnormal dreams, sleep disorder, nightmares), constipation, and flatulence. There are no adequate, well-controlled studies of varenicline in pregnant women (FDA pregnancy category C). Therefore, pregnant women should use varenicline only if the potential benefits outweigh the potential risk to the fetus. It is not known whether
Varenicline is excreted in human milk, but it is excreted in animal milk.

How long should patients receive pharmacologic therapy for smoking cessation before declaring it ineffective?
Nicotine replacement therapy is typically prescribed for 12 to 16 weeks, but repeat courses may be necessary after failed quit attempts. The safety and effectiveness of long-term use is not known, although some people who quit smoking continue to use nicotine replacement for long periods to prevent relapse. Many clinicians encourage patients to use nicotine replacement for as long as needed to prevent relapse.

The optimal duration of bupropion or varenicline therapy has not been fully assessed. Bupropion is typically prescribed for 8 to 12 weeks. It is safely used for long periods in treatment of depression, and the FDA has approved its use for long-term maintenance. Current dosing recommendations for varenicline state to use it for 12 weeks with consideration of an additional 12 weeks to prevent relapse.

What strategies are effective for preventing relapse after quitting smoking?
Relapse is common, even among patients who succeed in quitting for extended periods. For instance, a follow-up study examined rates of smoking 8 years after enrollment in an RCT of the nicotine patch. The study found that 46% (CI, 38% to 54%) of those who had quit had relapsed, and relapse rates were similar in both treatment and control groups (32). Evidence about specific relapse prevention interventions to help smokers maintain abstinence as part of a smoking cessation program is lacking (33). The evidence to date, however, does not support skills training or other specific interventions to help individuals who have successfully quit smoking to avoid relapse. Clinicians and patients should not give up after failed quit attempts or relapse, as many patients require several attempts before achieving durable abstinence.

Should clinicians recommend that smokers switch to smokeless tobacco products if they are unable to cease tobacco use?
Chewing tobacco is the form of smokeless tobacco most widely available in the United States, but tobacco companies are developing new products, such as sachets and lozenges, that may appeal to groups, such as women, that currently have low rates of smokeless tobacco use. Smokeless tobacco products deliver the nicotine that smokers crave, but without exposing the lungs to the other harmful ingredients in cigarettes. As a result, some people perceive them as safer than cigarettes. However, smokeless tobacco products vary widely in the amount of nicotine, carcinogens, and other toxins that they contain and have clear associations with cancer of the oral cavity and pharynx, dental and periodontal disease, pregnancy-related health problems, and nicotine addiction. A recent National Health Institute State of the Science Conference concluded that high-quality studies comparing smokeless tobacco with proven pharmacologic and behavioral smoking cessation interventions are needed to help inform public health strategy about smokeless tobacco (2).

Are there adverse effects of smoking cessation, such as weight gain, that clinicians should prepare patients for?
Patients who stop smoking may gain weight and have depressive symptoms. However, the potential for these events should not discourage the initiation of smoking cessation interventions, but physicians should monitor for both.

Weight Gain
Weight gain is common among smokers who quit. Although the amount of weight gained is not usually more than a few pounds and it poses less of a health risk than continued smoking, it can trigger resumption.
of smoking and many smokers use weight gain as an excuse not to quit.

One large study (34) found that adults who quit smoking were significantly heavier than patients who smoked. Men who were former smokers were on average 4.4 kg heavier than men who continued smoking. Women who were former smokers were on average 5.0 kg heavier than women who continued smoking.

Nicotine gum and bupropion have been shown to delay, but not prevent, the weight gain associated with smoking cessation. Recent research suggests that the antiopioid drug naltrexone may be an effective alternative therapy for smoking cessation, particularly for patients concerned about gaining weight. However, further evidence is needed to identify naltrexone’s place among other therapies for smoking cessation.

Smokers who took 25-mg naltrexone daily with nicotine replacement therapy for 6 weeks gained 1.5 pounds compared with 4.2 pounds for the group that did not take the drug. While the 25-mg dose did not increase quit rates over nicotine replacement alone, a higher dosage—100 mg daily—raised 6-week abstinence rates to 71.6% compared with 48% for nicotine replacement alone. Nausea was a common side effect (35).

Depression

People who stop smoking may develop depressive symptoms. These symptoms may be severe enough to warrant treatment, particularly in persons with a history of major depression. For adherent patients who do not respond to nicotine replacement, it is important to consider a psychiatric problem, such as depression.

One study involving 100 smokers who were enrolled in a 2-month smoking cessation program and who had a history of major depression not currently requiring treatment found that the OR for an episode of major depression was 7.17 in patients who successfully quit compared with patients who did not (CI, 1.5 to 34.5) (36).

Bupropion and nortriptyline are recommended for smokers with depression who are trying to quit smoking. Both drugs provide efficacy for smoking cessation related to their antidepressant effects; more evidence supports the use of bupropion. Other antidepressants, particularly selective serotonin inhibitors, do not aid long-term smoking cessation.

The United States’ Healthy People 2010 initiative aims to reduce smoking prevalence to less than 12% in adults and less than 16% in youth. Currently, an estimated 21% of American adults and 22% of American high school students smoke. A concerted effort by health professionals will be critical in achievement of the Healthy People 2010 objectives.

Do U.S. stakeholders consider smoking cessation when evaluating the quality of care a physician delivers?

In April 2005, The Ambulatory Care Quality Alliance (AQA) released a set of 26 health care quality indicators for clinicians, consumers, and health care purchasers to use in quality improvement efforts, public reporting, and pay-for-performance programs (www.ahrq.gov/qual/aqastart.htm). In May 2005, the Centers for Medicare and Medicaid Services endorsed the development of these indicators. Of the 26 indicators, 7 focus on preventive care and 1 of these measures relates to smoking cessation. It is important that clinicians be aware of these measures for both clinical and administrative reasons. First, AQA selected these measures because they have been linked to better clinical outcomes for patients. Second, over coming years Medicare and other payers will increasingly link reimbursement to physician performance with respect to these quality indicators. AQA recommends that the
percentage of patients queried about tobacco use one or more times during a 2-year assessment period be a standard criterion to assess physician performance.

What do professional organizations recommend with regard to smoking cessation?

In 2003, the United States Preventive Services Task Force issued recommendations about counseling to prevent tobacco use (Table 4). Other professional organizations, particularly those that focus on cardiovascular or pulmonary diseases, or cancer, similarly advocate screening for tobacco use and promoting cessation.

Studies examining smoking cessation training programs found that these programs increased the likelihood that physicians would perform smoking cessation tasks. However, there was no strong evidence that training led to increased smoking cessation rates (37). Special training does not seem to be necessary if physicians wish to improve their effectiveness in helping their smoking patients to quit.

Practice Improvement... The Ambulatory Care Quality Alliance recommends that the percentage of patients queried about tobacco use one or more times during a 2-year assessment period be a standard criterion to assess physician performance. Special training does not appear to be necessary if physicians wish to improve their effectiveness in helping their patients to quit smoking. However, physicians must integrate routine assessment of smoking status, willingness to quit, and recommendation of cessation interventions into daily practice.

Table 4. U.S. Preventive Services Task Force (USPSTF) 2003 Recommendations: Counseling to Prevent Tobacco Use

The USPSTF strongly recommends that clinicians screen all adults for tobacco use and provide tobacco cessation interventions for those who use tobacco products.

- Good evidence supports brief smoking cessation interventions, including screening, brief behavioral counseling (less than 3 minutes), and pharmacotherapy delivered in primary care settings, are effective in increasing the proportion of smokers who successfully quit smoking and remain abstinent after 1 year.
- Good evidence documents that smoking cessation lowers the risk for heart disease, stroke, and lung disease.
- Good indirect evidence shows that even small increases in the quit rates from tobacco cessation counseling would produce important health benefits.

The USPSTF strongly recommends that clinicians screen all pregnant women for tobacco use and provide augmented pregnancy-tailored counseling to those who smoke.

- Good evidence supports that extended or augmented smoking cessation counseling (5–15 minutes) using messages and self-help materials tailored for pregnant smokers, compared with brief generic counseling interventions alone, substantially increases abstinence rates during pregnancy and leads to increased birth weights.
- Reducing smoking during pregnancy is likely to have substantial health benefits for both the baby and the expectant mother.

The USPSTF concludes that the evidence is insufficient to recommend for or against routine screening for tobacco use or interventions to prevent and treat tobacco use and dependence among children or adolescents.

- There is limited evidence that screening and counseling children and adolescents in the primary care setting are effective in either preventing initiation or promoting cessation of tobacco use.

see: www.ahrq.gov/clinic/uspstf/uspstbac.htm

The United States’ Healthy People 2010 initiative aims to reduce smoking prevalence to less than 12% in adults and less than 16% in youth.
in the clinic

Smoking Cessation Tool Kit

Web Resources

Centers for Disease Control
http://www.cdc.gov/tobacco/

The CDC TIPS Web site contains a wealth of information for clinicians, smokers, and the public including the Surgeon General Reports and other publications, educational materials, research reports, and how-to-quit guides. Many of the materials are available in Spanish.

MedlinePlus

Public-oriented information related to smoking cessation including information from the educational information from the National Institutes of Health, information about ongoing clinical trials, recent studies, and news. Includes material targeted to specific demographic groups.

Smoking Cessation Leadership Center
http://smokingcessationleadership.ucsf.edu/

The Smoking Cessation Leadership Center is a national program office of the Robert Wood Johnson Foundation that aims to increase smoking cessation rates by assisting health professionals in their efforts to help their patients quit smoking. The site includes information for health professionals and smokers.

Other Media

Information for Patients
www.annals/intheclinic/clinicaltools

Download a copy of the patient information sheet that appears on the next page for duplication and use in your practice.

http://foundation.acponline.org/hl/ht_smo_en.htm

Order pads of brief Health Tips on smoking cessation to distribute to patients.

Office Posters
www.cdc.gov/tobacco/sgr/sgr_2004/sgrposters.htm

The CDC offers single, free copies of several posters promoting smoking cessation suitable for office display.

Cards to Refer Patients to National Telephone Quit Line
http://smokingcessationleadership.ucsf.edu/1800QuitNow.html

The Smoking Cessation Leadership Center offers a small, plastic card to help promote the quit line for 18 cents/card.

Counseling for Behavior Change Videotape
www.acponline.org/atpro/timssnet/catalog/electronic/behvchng.html

Order a videotape that demonstrates through office visit scenarios how to move patient through behavior change.

Tutorial on Counseling for Behavior Change
www.acponline.org/private/abimpim/diabetes/cardio_counsel.ppt

View a slide presentation that describes the stages of behavior change, diagnostic clues to each stage of change, and counseling strategies to help move a patient through the stages of change.

Pharmacologic Therapies to Help Smokers Quit
www.acponline.org/private/abimpim/diabetes/quitsmoking.html

View a printable discussion of pharmacologic aids to smoking cessation.

Personalized Patient Educational Prescription
www.acponline.org/private/abimpim/diabetes/smoking.html

Follow this link to print out a personalized educational prescription to refer patients to the MedlinePlus materials on smoking cessation.
Whatever your age, the amount you smoke, or when you started... quitting will improve your health.

**HEALTH TIPS**

**WHAT YOU CAN DO**

- Smoking can make you sick and shorten your life.
- If you quit now, you will be healthier.
- Quitting is hard work, but there are ways to help you.
- Medicines to help stop the urge to smoke

After starting your program, set up times to see your doctor.

To help you fight the urge to smoke:

- Set a date in the next 2 weeks to stop smoking and stick to it.
- Throw away all your cigarettes and ashtrays
- Stay away from other smokers.
- Tell your family and friends you are quitting and ask for their help.
- See your doctor to keep track of your progress.
- Talk to your doctor if you are having trouble, especially if quitting makes you gain weight or feel depressed.
- Stick with your plan.
- If you fail, don’t give up. Try again. Some people need to start over 3 or 4 times before they beat the habit.

For free advice about quitting call: 1-800 QUIT-NOW

*HEALTH TIPS are developed by the American College of Physicians Foundation and PIER
1. A 55-year-old man is evaluated for cough, scant clear-to-yellow sputum, and malaise of 3 days' duration. He has not had fever, chills, wheezing, or pleuritic chest pain, or recent contact with anyone who has been ill. He has a 40-pack-year smoking history and has had similar symptoms three times in the past 6 months, feeling well in the intervals between episodes.

On physical examination, temperature is 37.2 °C (99.0 °F), and pulse rate, respiration rate, and blood pressure are normal. The cardiopulmonary examination is normal, including clear lungs on auscultation with no signs of consolidation.

Which of the following is the most appropriate initial smoking-cessation management step during this visit?
A. Recommend nicotine gum
B. Provide a clear, personalized message to the patient
C. Refer the patient to a behavioral modification program
D. Prescribe bupropion

2. A 66-year-old woman is evaluated for pain and cramping of her right leg while vacuuming and shopping. She has no nocturnal pain. She is a long-time smoker (40–pack-year history) and has made multiple efforts during which she used nicotine replacement therapy. She states that she is ready to quit smoking. She has failed 3 previous attempts during which she used nicotine patch starting with one 21 mg patch/24-hour period for 6 weeks, and schedule a follow-up visit in 4 weeks.

Which of the following is the most appropriate next step before providing this patient with a prescription for varenicline?
A. Provide encouragement and schedule a follow-up visit in 3 months
B. Prescribe clonidine and schedule a follow-up visit in 3 months
C. Prescribe bupropion and schedule a follow-up visit in 3 months
D. Provide encouragement, prescribe nicotine patch starting with one 21 mg patch/24-hour period for 6 weeks, and schedule a follow-up visit in 4 weeks
E. Refer patient to a hypnotherapist

3. A 66-year-old woman with chronic obstructive pulmonary disease is evaluated because of chronic cough and dyspnea. She currently uses a long-acting bronchodilator twice per day, an inhaled corticosteroid twice per day, ipratropium 4 times per day, and albuterol 4 to 6 times per day. She smokes 1 pack of cigarettes per day.

On physical examination, her vital signs are normal. Her oxygen saturation at rest and with exertion is 94%. She has diminished breath sounds, a prolonged expiratory phase, and no wheezes. Her heart rate and rhythm are regular, with a normal S1, a physiologically split S2, and no murmurs or rubs. Chest radiograph reveals hyperinflation, increased retrosternal airspace, and flattened hemidiaphragms bilaterally.

Which of the following should be initiated at this time to address this patient's cough and dyspnea?
A. Increase her use of the long-acting bronchodilator
B. Prescribe supplemental oxygen
C. Provide emergency treatment for tension pneumothorax
D. Discuss techniques to help her quit smoking
E. Increase her dosage of inhaled corticosteroid

4. Smokers are at higher risk than non-smokers for all except which of the following health problems?
A. Macular degeneration
B. Cervical cancer
C. Cataract
D. Peripheral vascular disease
E. Bladder cancer

5. A 45-year-old woman has a history of well-controlled type 2 diabetes (hemoglobin A1c 6.9%) and hypertension (blood pressure 135/85 mm Hg on hydrochlorothiazide 25 mg/day). She weighs 179 pounds. She has smoked since age 18 and currently smokes 2 packs per day. She usually has her first cigarette within 10 to 29 minutes of waking in the morning. She has made multiple unsuccessful attempts to quit smoking over the previous 5 years. She did not use pharmacologic therapy for smoking cessation during these previous attempts. During a routine follow-up visit for diabetes care, you inform her that quitting smoking would be an important way to reduce her risk for cardiovascular disease. She states that she is ready to quit.

Which of the following is the most appropriate next step in assisting this patient to stop smoking?
A. Provide encouragement and schedule a follow-up visit in 3 months
B. Check liver function tests
C. Estimate the patient's creatinine clearance
D. Maximize the antihypertensive regimen
E. Refer patient to a hypnotherapist

6. During a routine visit with her internist, a 51-year-old woman with hypertension (blood pressure 138/88 mm Hg on hydrochlorothiazide 25 mg daily), hepatitis C infection, and chronic renal insufficiency brings in a newspaper clipping about the drug varenicline, and says she is ready to quit smoking. She has failed 3 previous attempts during which she used nicotine replacement therapy.

Which of the following would be the most appropriate next step before providing this patient with a prescription for varenicline?
A. Ask the patient whether she has ever had a seizure
B. Check liver function tests
C. Estimate the patient's creatinine clearance
D. Maximize the antihypertensive regimen

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 free CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.