Although improvements in smoking-cessation rates have occurred in the past decades, it appears that the Healthy People 2010 goal of reducing the number of adult smokers to 12% of the population will be not be achieved without additional intervention. Healthcare professionals must increasingly identify individuals who smoke and provide them with nonpharmacologic and pharmacologic support for smoking-cessation efforts. The US Department of Health and Human Services’ 2000 Clinical Practice Guideline for smoking cessation suggests that if patients are willing to quit, they should be provided with a first-line pharmacologic agent. First-line therapies listed in the 2000 guidelines include nicotine-replacement therapies (eg, patch, gum, lozenge, inhaler, and nasal spray) and bupropion sustained release. Varenicline, approved in 2006, is also considered a first-line treatment for smoking cessation. Second-line therapies, including nortriptyline and clonidine, may be beneficial in selected patients. Also, alternative dosing regimens of first-line agents or combinations of pharmacotherapy may benefit some patients who have struggled with cessation in the past. Research is ongoing to improve the quit rates achieved with pharmacotherapy for smoking cessation. Vaccines that use antibodies to target nicotine are under investigation. Rimonabant, a cannabinoid-1 receptor antagonist, is also in clinical trials. Pharmacists can use their knowledge and positioning within the healthcare system to assist patients with choices about the use of pharmacotherapy for smoking cessation. Individual choices should balance efficacy, adverse effects, patients’ previous experiences with these agents, costs, and contraindications. (Adv Stud Pharm. 2007;4(8):216-220)

In 2002, for the first time, more than 50% of all individuals who had ever smoked quit smoking. However, in 2005, approximately 21% of adults smoked cigarettes, a number considerably higher than the projected goal of 12%, as proposed by the 2010 Healthy People initiative. Today, smoking remains the leading cause of preventable death in the United States. The US Department of Health and Human Services’ (HHS) Treating Tobacco Use and Dependence: Clinical Practice Guideline in 2000 was one of the first evidenced-based documents to recognize that smoking is a chronic condition that often requires repeated interventions to be successful at achieving and maintaining abstinence. To this end, healthcare practitioners must be as vigilant in the recognition and management of tobacco use as they are in the care of other chronic diseases. This includes equipping individuals who indicate a desire to quit smoking with available resources, including counseling and pharmacologic agents, to improve the success of a cessation attempt.
IDENTIFICATION AND TREATMENT OF PATIENTS WHO SMOKE

Smoking status should be assessed during every interaction an individual has with the healthcare system. An algorithm targeting pharmacist-specific steps for the identification and treatment of patients who smoke is provided in the Figure. For a current smoker, the patient should be advised to quit smoking and his willingness to quit should be assessed. Unless there are contraindications, the HHS guidelines encourage practitioners to provide smokers who are willing to quit with one of the effective pharmacologic agents for smoking cessation. Pharmacologic choices should be made based on an individual’s previous experience with these agents, patient preference, economic considerations, and contraindications. Pharmacists who are knowledgeable about these agents, including their differences, benefits, and adverse effects, are better able to support smoking-cessation efforts. Awareness of available community resources and counseling strategies are also important.

FIRST-LINE THERAPIES APPROVED BY US FOOD AND DRUG ADMINISTRATION

NICOTINE-REPLACEMENT THERAPIES

By providing a lower dose of nicotine through an alternate route of administration, nicotine-replacement therapies (NRT) reduce tobacco withdrawal symptoms. Although NRTs have proven efficacy and approximately double the success rate of quitting, men tend to exhibit a better response rate than women. Multiple NRT formulations are available (e.g., patch, lozenge, gum, inhaler, and nasal spray). These different formulations allow flexibility for the smoker and healthcare practitioner to select an option that best fits an individual’s needs.

Cardiovascular disease was once considered a contraindication to NRTs; however, analyses have not demonstrated an increased risk of cardiovascular disease with their use. Manufacturers of these products continue to emphasize caution, especially in individuals with serious or worsening angina, serious arrhythmias, and those in the immediate (2-week) postmyocardial infarction period.

The adverse effects of smoking on pregnancy outcome are related to all of the components of cigarette smoke, not just exposure to nicotine. Although in most cases it is best to avoid taking medication during pregnancy, the benefits of smoking cessation may outweigh the potential risks of taking an NRT. Use of an

Figure. Pharmacist-Directed Smoking-Cessation Algorithm

- **Patient-Pharmacist Interaction**
  - Ask about smoking every time

- **Nonsmoker**
  - Emphasize positive life choice

- **Current Smoker**
  - Advise to quit
  - Assess willingness to make an attempt to quit

- **Former Smoker**
  - Congratulate on success
  - Reinforce positive life choice

- **Unwilling at this time**
  - Provide motivation to consider future attempt

- **Special population**
  - Provide additional information specific to the smoker’s unique circumstance(s). May consult with primary care provider

- **Willing to make a quit attempt**
  - Assist patient with attempt
  - Discuss pharmacotherapy options with patient (shaded box)
    - Include discussion about previous use, current smoking level, economic concerns, and patient preference
  - Provide counseling or refer patient to additional counseling resource

- **First-line Therapies**
  - NRTs
  - Bupropion
  - Varenicline

- **Second-line Therapies**
  - Clonidine
  - Nortriptyline

NRT = nicotine-replacement therapies.
NRT will result in continued exposure to nicotine, but will remove exposure from other harmful components of smoking if the mother successfully abstains from smoking. The pharmacist is advised to work with the pregnant patient’s obstetrician to determine the most appropriate quitting strategy for the patient. Pregnancy is not considered a contraindication to the use of NRTs, but use should be accompanied by a discussion of the known dangers associated with continued smoking during pregnancy, in addition to the risks of NRT use during pregnancy. General adverse effects associated with the use of NRTs include headache, insomnia, nausea, vertigo, vivid dreams, and tachycardia. Product-specific adverse effects of the various NRT formulations are summarized in the Table.4,7,8

**Bupropion**

Originally marketed as an antidepressant, bupropion was the first non-nicotine–based smoking-cessation aid to be licensed in the United States. Bupropion’s mechanism of action in the management of nicotine addiction is not yet completely defined; however, it is believed to act as a weak dopaminergic antagonist, modifying the pleasure reinforcement that is produced through the action of nicotine. Bupropion is as effective in individuals who are not or have never experienced depression as in those who are depressed.4

Administered as a 150-mg sustained-release tablet twice daily beginning approximately 1 week before the quit date, bupropion doubles the success rate of quit attempts.4 The use of bupropion sustained-release tablets is contraindicated in patients with a history of an eating or seizure disorder, individuals with a head injury, those who use alcohol heavily, those who are using bupropion in another form, and those who have used a monoamine oxidase inhibitor in the past 2 weeks.4,9 Use in pregnancy should be considered only when nonpharmacologic options alone have failed, and the risks of bupropion and the possible benefits of therapy outweigh the known risks of continued smoking. Common adverse effects of bupropion therapy are mostly mild and transient; these effects include insomnia and dry mouth.10 If adverse effects persist, a dose reduction may avoid the need for discontinuation.

**Varenicline**

Varenicline, a new molecular entity, received priority US Food and Drug Administration (FDA) review in 2006 because of the potential for significant public health benefit.11 The first new smoking-cessation agent approved in more than a decade, it has a unique mechanism of action that involves partial agonist activity at the α4β2 nicotinic receptor. This receptor is believed to be responsible for the reinforcing properties of nicotine. As a highly-selective, partial agonist, varenicline is able to block the activity of nicotine at the receptor, thereby mitigating the nicotine-stimulated release of dopamine while maintaining a sustained level of dopamine through partial agonist activity.12 This

<table>
<thead>
<tr>
<th>Table. Product-Specific Adverse Effects of Nicotine Replacement Therapies</th>
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<tbody>
<tr>
<td><strong>Formulation</strong></td>
</tr>
<tr>
<td>Inhaler</td>
</tr>
<tr>
<td>Coughing (32%)</td>
</tr>
<tr>
<td>Rhinitis (23%)</td>
</tr>
<tr>
<td>Nasal spray</td>
</tr>
<tr>
<td>Transient changes in smell and taste</td>
</tr>
<tr>
<td>Patch</td>
</tr>
<tr>
<td>Gum</td>
</tr>
<tr>
<td>Nausea, dyspepsia, flatulence, and hiccups</td>
</tr>
<tr>
<td>May stick to dental work</td>
</tr>
<tr>
<td>Lozenge</td>
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<tr>
<td>Sore throat</td>
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</tbody>
</table>

Data from Fiore et al; Wall and McClellan; and Henningfield et al.4
dopamine modulation is believed to minimize the development of withdrawal symptoms and craving.

Administered orally, the recommended dose of varenicline is 1 mg twice daily for 12 weeks, beginning 1 week before the quit date. In clinical trials that included more than 2000 smokers, the 4-week continuous abstinence rate (for weeks 9–12) for varenicline was 44%, compared with 30% for individuals receiving bupropion sustained-release tablets and 18% for those receiving placebo. Patients who received open-label treatment with varenicline for 12 weeks and had quit for at least 7 days were randomized to receive an additional 12 weeks of varenicline or placebo. Continuous abstinence rates for weeks 13 to 24 and weeks 13 to 52 were higher in those treated with varenicline than placebo (70% vs 50%, P < .001 and 44% vs 37%, P = .02, respectively).

Adverse effects associated with the administration of varenicline in clinical trials were generally mild and associated with a low discontinuation rate (12% compared with 10% for placebo). Commonly reported adverse effects include nausea (30%), sleep disturbance (18%), and constipation (8%).

SECOND-LINE THERAPIES

Second-line therapies are considered efficacious for assisting smoking-cessation efforts, with successful quit rates that are similar to first-line agents. These therapies are relegated to second-line status because they do not have US FDA approval for smoking cessation, and there is more concern about their adverse effects than the first-line agents.

CLONIDINE

The use of clonidine for smoking cessation in doses ranging from 0.1 to 0.75 mg per day has been shown to approximately double the success rate of quit attempts compared with placebo. Common adverse effects include dry mouth (40%), drowsiness (33%), dizziness (16%), sedation (10%), and constipation (10%). Rapid discontinuation of clonidine is associated with a rapid increase in blood pressure, headache, tremor, nervousness, and agitation.

NORTRIPTYLINE

A limited number of studies with small numbers of patients demonstrated the effectiveness of nortriptyline for smoking cessation. Compared with placebo, use of nortriptyline is associated with almost a tripling of the abstinence rate. There is a risk of arrhythmias with nortriptyline use; therefore, caution must be exercised before using it in patients with cardiovascular disease. Nortriptyline must be initiated 10 to 28 days before the target quit date. Adverse effects include sedation, dry mouth, blurred vision, urinary retention, lightheadedness, and shaky hands.

COMBINATION OR HIGH-DOSE THERAPY

Combining the nicotine patch with another form of self-administered NRT is associated with an increase in the quit rate. Individuals who have had difficulty with cessation despite the use of a single NRT may have improved success with the use of combination therapy. The patch in combination with the gum or nasal spray has shown improved efficacy over monotherapy. Combinations of bupropion and nortriptyline with NRTs have also shown improvements in the abstinence rates. In heavy smokers, higher doses of NRT have been evaluated with mixed results. No information is available regarding the combination of varenicline with other cessation therapies. Combination therapies should only be used after consultation with the patient's primary care provider.

EMERGING TREATMENTS FOR TOBACCO DEPENDENCE

VACCINES

Under investigation are vaccines that target nicotine by inducing antibodies against the nicotine molecule, preventing it from reaching the site of action. Early results indicate that a vaccine could be useful for smoking cessation; however, there remains a concern about the incompleteness of the blockade leaving room for individuals to increase their tobacco intake to attain the same level of satisfaction. Additional data will need to be reviewed to determine the place of vaccines in the management of smoking cessation.

RIMONABANT

The cannabinoid receptor system also has been associated with the reward and satiety center in the brain, thus cannabinoid receptor antagonists may offer another option for smoking cessation. Rimonabant is a cannabinoid-1 receptor antagonist being investigated for weight loss and smoking cessation. In patients given rimonabant 20 mg per day, the cessation rate was improved compared with placebo at 1 year (36.2% vs 20.6%, respectively). Use of rimonabant also was associated with a slight decrease in weight.
CONCLUSIONS

The individual smoker desiring to make a cessation attempt has a variety of treatment options from which to choose. Pharmacists can offer these individuals guidance with respect to choice of therapy, possible contraindications, and adverse effects. All individuals making a smoking-cessation attempt should be offered assistance with a pharmacologic agent, unless contraindicated, to improve the chances of success.

REFERENCES