Medications to Aid Smoking Cessation
Megan E. Wren, MD, FACP

ABSTRACT

Smoking cessation is a difficult process; physicians can help patients by providing brief counseling and by recommending the use of pharmacotherapies. Nicotine replacement therapy is available in 5 forms: gum, patch, inhaler, nasal spray, and lozenge. Nicotine replacement therapy is safe to use in most patients—including those with coronary artery disease—and, if used correctly, can approximately double the proportion of patients who achieve abstinence. The antidepressants nortriptyline and sustained-release bupropion will also nearly double the quit rate. Some patients may benefit from combination therapy. (Adv Stud Med. 2003;3(9):507-516)

“Giving up smoking is easy. I’ve done it hundreds of times.” — popularly attributed to Mark Twain

Helping patients stop smoking can be discouraging. In 2000, almost a quarter of adult Americans were current smokers: 23.3% or 46.5 million people. On the optimistic side, smoking cessation is indeed possible; of all Americans who have been smokers, almost half have quit (48.8%). In 2000, an estimated 70% of smokers said they wanted to quit, and 41% had tried to quit during the previous year.

Cigarette smoking is a powerful addiction. It is estimated that only about 7% of patients who attempt smoking cessation will be abstinent 1 year later. Most smokers require several quit attempts before achieving long-term abstinence. The physician should recognize tobacco dependence as a chronic disease, subject to periods of remission and relapse, and requiring ongoing counseling. Fortunately, effective interventions are now available that may be able to increase long-term quit rates to 15% to 30%.

Smoking increases the risk of a multitude of illnesses, including cancer; coronary, carotid, and peripheral arterial disease; chronic obstructive lung disease; respiratory infections; gastric ulcers; and osteoporosis. After smoking cessation there is a gradual decline in the excess risk of disease and for some conditions the ex-smoker can eventually reach the same risk level as someone who never smoked. Regarding all-cause mortality, smokers who quit before the age of 50 have half the risk of dying in the next 15 years compared to those who continue to smoke. Risk of lung cancer, in turn, is halved after 10 years of abstinence, but may never approach the level in never-smokers. The excess risk of coronary heart disease is halved after just 1 to 2 years of abstinence, and after 15 years of abstinence reaches the level of nonsmokers. The goal remains absolute abstinence from smoking; evidence suggests that reducing smoking by 50% does not lead to any decrease in all-cause mortality or mortality from cardiovascular disease (CVD) or smoking-related cancers.

A consortium of 7 governmental and nongovernmental nonprofit organizations...
met to produce a clinical practice guideline based on experimentally validated tobacco dependence treatments and practices. Participants included representatives from the Agency for Healthcare Research and Quality (AHRQ, an agency of the US Public Health Service), the Centers for Disease Control and Prevention, and the National Cancer Institute. The resulting guideline was published by the Public Health Service (PHS) and may also be found in its entirety at www.surgeongeneral.gov/tobacco. A brief summary also was published in JAMA in June 2000. The consensus guideline emphasizes the importance of providing a brief intervention ("The 5 As") to all tobacco users at every clinical encounter, which is designed to take less than 3 minutes of time from the office visit (Table 1). (Those unfamiliar with this intervention are encouraged to learn more at www.surgeongeneral.gov/tobacco.) If the physician assesses the patient's readiness for change and feels that the patient is ready to make a serious quit attempt, medications should be prescribed. However, medications will have little effect in patients who are not psychologically ready for the daunting task of smoking cessation. The Surgeon General stresses that "all patients attempting to quit should be encouraged to use effective pharmacotherapies for smoking cessation except in the presence of special circumstances." “Special circumstances” include pregnancy, breast-feeding, adolescence, and cardiac disease; these are all only relative contraindications. The safety of nicotine replacement therapies will be discussed later. Medications approved by the Food and Drug Administration (FDA) to aid smoking cessation include nicotine polacrilex gum, nicotine patch, nicotine inhaler, nicotine nasal spray, nicotine lozenge, and sustained-release bupropion.

Assessment of Nicotine Dependence

It is more difficult to treat smokers who are highly dependent on nicotine. A research tool often used to estimate dependence is the Fagerstrom Tolerance Questionnaire. Smokers who score at least 7 out of 11 points are considered highly dependent. The 2 questions most strongly correlated with dependence are: the time to first cigarette in the morning (<30 vs >30 minutes) and the number of cigarettes per day. Individuals who smoke up to 15 cigarettes each day are considered light smokers; 16 to 25 cigarettes/day, moderate smokers; and 26 or more cigarettes/day, heavy smokers. There is some evidence that heavier smokers are more likely to continue smoking long-term. In the Normative Aging Study, heavy smokers were twice as likely to continue smoking over the 25-year follow-up period.

The amount of nicotine absorbed from a cigarette varies according to the intensity of smoking, but there is little correlation between the measured absorption (as assessed by salivary cotinine, a nicotine metabolite) and the nicotine yield as stated on the package. In one study, people who smoked cigarettes labeled as containing <2 mg nicotine/cigarette actually absorbed slightly more nicotine per day than those who smoked cigarettes with a labeled content of 6 to 12 mg nicotine/cigarette. Overall, smoking 1.5 packs per day resulted in a 24-hour absorption of about 20 to 28 mg of nicotine.

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) provides an alternative source of nicotine to ease withdrawal symptoms (ie, dysphoria, insomnia, irritability, frustration, anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, and increased appetite) while the patient learns new nonsmoking behaviors. Many well-designed randomized controlled trials (RCTs) have documented that the use of NRT can significantly increase the abstinence rate compared to a placebo group, almost doubling the long-term success rate. NRT is most effective when combined with counseling. The effectiveness of counseling increases with the intensity of treatment, but even brief interventions are of benefit.

### Table 1. Brief Office Intervention (The 5 As)

<table>
<thead>
<tr>
<th>Task</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask about smoking</td>
<td>Every patient, every visit; make it one of the vital signs</td>
</tr>
<tr>
<td>Advise smokers to quit</td>
<td>Clear, strong, personalized message; example: “Qutting smoking is the most important thing you can do to protect your health now and in the future. I can help you.”</td>
</tr>
<tr>
<td>Assess willingness to make a quit attempt</td>
<td>Is the patient willing to make a serious quit attempt in the next 30 days?</td>
</tr>
<tr>
<td>Assist in quit attempt</td>
<td>If the patient is ready to make a serious attempt to quit, then invest time to help:</td>
</tr>
<tr>
<td></td>
<td>- Help the patient set a quit date in the next couple of weeks</td>
</tr>
<tr>
<td></td>
<td>- Discuss anticipated triggers and challenges and strategies to cope with them</td>
</tr>
<tr>
<td></td>
<td>- Provide educational materials</td>
</tr>
<tr>
<td></td>
<td>- Provide support and encouragement</td>
</tr>
<tr>
<td></td>
<td>- Recommend pharmacotherapy, except in special circumstances</td>
</tr>
<tr>
<td>Arrange follow-up</td>
<td>Follow up in person or by phone within the first week and again within the first month</td>
</tr>
</tbody>
</table>

---

508 Vol. 3, No. 9 October 2003
Five forms of NRT are currently available in the United States: nicotine polacrilex gum, patch, inhaler, nasal spray, and a new nicotine lozenge. Other formulations under development include a sublingual tablet and a buccal adhesive tablet. The various methods of drug delivery differ in their rapidity of onset and duration of effect, but used chronically each will produce blood levels of nicotine equal to about half the level produced by cigarette smoking. Price also varies among the medications, based on delivery method and availability over-the-counter.

Table 2 shows the relative prices of different forms of NRT and other medications to aid smoking cessation, and which medications are available without a prescription. Most cost more than $100/month, which can be problematic for patients.

### Nicotine Polacrilex Gum

Nicotine polacrilex is a resin that contains nicotine in an alkaline formulation designed to be absorbed through the buccal mucosa. Extensive first-pass metabolism in the liver limits the amount of nicotine that reaches the bloodstream following gastrointestinal absorption of swallowed nicotine. The oral absorption is much slower than the respiratory absorption of nicotine from a cigarette, so users will not experience the immediate rush of “satisfaction” that a cigarette delivers. Plasma levels rise slowly over 30 minutes, then slowly decline. Patients usually absorb about half of the nicotine in each piece of gum.

The PHS consensus panel conducted a systematic review of the available literature. Their meta-analysis of 13 studies showed that nicotine gum increases long-term abstinence rates by 30% to 80% relative to placebo; the overall odds ratio (OR) was 1.5 (95% confidence interval [CI], 1.3-1.8). The estimates of absolute abstinence rates were 17% for placebo and 24% for nicotine gum. A meta-analysis conducted by the Cochrane Collaboration showed a similar OR of 1.66 for nicotine gum relative to placebo, with 18% of patients allocated to nicotine gum achieving abstinence at 1 year.

Nicotine gum can be difficult for patients to use correctly (see Patient Tips for Success With NRTs). In the first 1 to 2 months, the gum should be used on a fixed schedule: 1 piece every 1 to 2 hours, aiming for daily use of 10 to 15 pieces. There is some evidence that the use of at least 8 to 9 pieces per day in the first month after quitting results in better long-term abstinence rates. Additional pieces may be used as needed for relief of withdrawal symptoms. After at least 6 weeks of abstinence the daily dosage can be gradually tapered (reduction of 1 piece/day every 4 to 7 days).

The nicotine polacrilex gum is available over-the-counter in 2-mg and 4-mg strengths; there is some evidence that the 4-mg gum is more efficacious in highly dependent smokers and therefore is recommended for those who smoke more than 24 cigarettes (2 packs) per day. Some authors recommend 4 mg for those who smoke more than 15 cigarettes per day and for those who have previously failed with the 2-mg gum.

The most common adverse effects are mouth and jaw soreness, dyspepsia, heartburn, and hiccups. Denture wearers may have difficulty chewing the gum. The used gum still contains a significant amount of nicotine and should be disposed of out of the reach of children and pets.

### Table 2. Relative Costs of Medications to Aid Smoking Cessation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Rx/OTC</th>
<th>Approximate cost per month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine polacrilex gum — Nicorette</td>
<td>OTC</td>
<td>$115-135 for 9 pieces/day</td>
</tr>
<tr>
<td>(GlaxoSmithKline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine patch — NicodermCQ</td>
<td>OTC</td>
<td>$100</td>
</tr>
<tr>
<td>(GlaxoSmithKline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine patch — generic</td>
<td>OTC</td>
<td>$100</td>
</tr>
<tr>
<td>(W algrens/PAR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine patch — Nicotrol</td>
<td>OTC</td>
<td>$100</td>
</tr>
<tr>
<td>(Pharmacia Consumer Healthcare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine patch — ProStep</td>
<td>Rx</td>
<td>$120</td>
</tr>
<tr>
<td>(Lederle Labs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine patch — Habitrol</td>
<td>Rx</td>
<td>$140-170</td>
</tr>
<tr>
<td>(Novartis Consumer Health, USA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine inhaler — Nicotrol</td>
<td>Rx</td>
<td>$250 for 8 cartridges/day</td>
</tr>
<tr>
<td>(Pharmacia Consumer Healthcare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine nasal spray — Nicotrol</td>
<td>Rx</td>
<td>$120 for 14 doses/day</td>
</tr>
<tr>
<td>(Pharmacia Consumer Healthcare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine lozenges — Commit</td>
<td>OTC</td>
<td>$180 for 10 lozenges/day</td>
</tr>
<tr>
<td>(GlaxoSmithKline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline (generic) 75 mg qhs</td>
<td>Rx</td>
<td>$13-18</td>
</tr>
<tr>
<td>(GlaxoSmithKline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR — Zyban 150 mg bid</td>
<td>Rx</td>
<td>$110-120</td>
</tr>
<tr>
<td>(GlaxoSmithKline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine 0.1 mg bid</td>
<td>Rx</td>
<td>$10</td>
</tr>
<tr>
<td>Clonidine patches — Catapres TTS 2</td>
<td>Rx</td>
<td>$80</td>
</tr>
</tbody>
</table>

Rx = by prescription; OTC = over-the-counter.  
Nicotine Patches

Nicotine transdermal patches are more convenient and much easier to use for many patients. Because transdermal absorption is slow, the time to maximal plasma concentration is 2 to 12 hours, depending on the brand. The 24-hour use of a patch results in a relatively stable plasma level after 2 to 3 days. Blood nicotine levels are usually less than the levels in pack-a-day smokers.\(^2\)

The PHS consensus panel conducted a systematic review of the available literature. Their meta-analysis of 27 studies showed that the use of transdermal nicotine almost doubles long-term abstinence rates (OR, 1.9; 95% CI, 1.7-2.2; estimated abstinence rate, 18%).\(^2\) The Cochrane Collaboration’s meta-analysis of the efficacy of nicotine patches found a similar overall OR of 1.74 for transdermal patches vs placebo, with 14% remaining abstinent at 1 year.\(^10\)

Nicotine patches are available over-the-counter and by prescription in 16- and 24-hour dosages. There is no evidence of a significant difference in effectiveness between them.\(^10\) Wearing the patch at night may contribute to insomnia and nightmares, but will ensure the presence of nicotine on awakening to help cope with early morning cravings.\(^17\)

Duration of use does not appear to be critical; study subjects typically wear the patch for 4 to 12 weeks. The European Collaborative European Anti-Smoking Evaluation (CEASE) trial included more than 3000 subjects and found no significant difference in abstinence between 8- vs 22-week treatment.\(^18\) It is customary to taper the dosage, but there is no evidence of benefit of this.\(^19\)

Nicotine Inhalers and Nicotine Nasal Spray

The nicotine inhaler is a cigarette-shaped plastic device with a nicotine cartridge inside; it is sold by prescription only. The patient “puffs” to extract the nicotine in a vapor form that can be absorbed from the nasopharynx. The 10-mg inhaler yields up to 4 mg nicotine, of which 2 mg is systemically available; the venous nicotine levels are similar to those with other forms of NRT.\(^19\) Compared to cigarette smoking, absorption is slower and plasma nicotine levels are much lower, decreasing the likelihood for abuse.\(^20,21\) Adverse effects include throat irritation and coughing. It has been speculated that the nicotine inhaler may serve as a substitute for some of the hand-to-mouth behaviors and oral satisfaction of cigarettes. However, some people find the inhaler embarrassing to use in public.\(^22\)

Nicotine nasal spray is available by prescription only, and is packaged in a pump spray bottle that delivers approximately 0.5 mg of nicotine per spray; 1 dose is 2 sprays (1 in each nostril). Patients should use 1 to 2 doses per hour, with a maximum of 40 doses per day; each bottle delivers about 200 sprays, or 100 doses. Although the plasma levels are similar to other forms of NRT, the rate of absorption is more rapid.\(^23,24\) Like other forms of NRT, the inhaler and spray approximately double the long-term abstinence rates compared with placebo.\(^19,23,25-28\) The most common side effects are nasal irritation, runny nose, throat irritation, watering eyes, sneezing, and cough.

Nicotine Lozenges

In 2002 the FDA approved a nicotine polacrilex lozenge for over-the-counter sales. Analogous to nicotine gum, the lozenge provides transmucosal absorption and is available in 2- and 4-mg strengths. Because the lozenge dissolves completely, it delivers its full dose of nicotine. It may prove easier to use, and more socially acceptable, than the gum.

A recently published RCT involving more
than 1800 smokers found good efficacy for the lozenge when used for up to 24 weeks.\textsuperscript{29} Compared to those randomized to placebo, low-dependence smokers randomized to the 2-mg strength had an OR of 2.10 for abstinence at 28 days (95% CI, 1.59-2.79). Highly dependent smokers assigned to the 4-mg strength had an OR of 3.69 (95% CI, 2.74-4.96). At 1 year, the ORs were 2.14 and 2.69 (still statistically significant) for low- and high-dependence smokers, respectively. The manufacturer suggests that the 2-mg strength be used by low-dependence smokers who typically smoke their first cigarette more than 30 minutes after waking, and the 4-mg strength by those who smoke within 30 minutes of waking.

### Safety of NRT

Excessive use of NRT, with or without superimposed smoking, can result in nicotine toxicity. Typical symptoms include nausea, vomiting, cold sweats, headache, dizziness, weakness, and confusion. Massive overdosage, such as in accidental ingestion by a child, could lead to hypotension, prostration, respiratory failure, and seizures. The most common adverse effects experienced during regular use result from contact with the irritative nicotine: nasal stinging, sore throat, skin rash, etc. The nicotine patch may be problematic in individuals with sensitive skin and the inhaler or nasal spray may not be good choices in patients with asthma.\textsuperscript{30}

In clinical practice the most common question about the safety of NRT concerns its use in patients with coronary artery disease (CAD) and other vascular disease. Nicotine causes sympathetic neural stimulation and systemic catecholamine release, but NRT provides lower nicotine doses and slower delivery compared to cigarette smoking. The flat dose-response relation for nicotine ensures that the effects of smoking along with NRT are similar to that of smoking alone. Importantly, NRT is free of the carcinogenic “tar” compounds and carbon monoxide of cigarettes. Numerous studies have documented the safety of NRT, especially compared to continued smoking, and the American Heart Association supports the use of NRT to aid in smoking cessation.\textsuperscript{31}

The use of nicotine gum has not been statistically associated with rates of cardiovascular deaths or hospitalization for cardiovascular conditions, even in patients who smoked while using NRT.\textsuperscript{32} Similarly, in a multicenter Veterans Affairs (VA) study of smokers with known CAD there was no increase in cardiovascular morbidity or mortality in the NRT group compared with the placebo group.\textsuperscript{33}

A number of studies have examined nicotine effects on various cardiovascular risk factors and markers. A study of transdermal nicotine in doses up to 63 mg/24 hrs (triple the maximum marketed dose) found that, compared with smoking, there were no differences in 24-hour recordings of heart rate, blood pressure (BP), or their circadian patterns.\textsuperscript{34} A similar study in smokers with known CAD showed no significant differences in heart rate, BP, or duration or frequency of ischemic episodes on ambulatory electrocardiogram monitoring.\textsuperscript{35} Benowitz and colleagues found no differences in systolic BP in subjects who were smoking, using transdermal nicotine, or using a nicotine nasal spray, but diastolic BP was slightly higher when smoking. Smoking produced higher levels of plasma epinephrine, beta-thromboglobulin, and fibrinogen than transdermal nicotine; nicotine nasal spray produced intermediate levels.\textsuperscript{36} An investigation of cardiovascular risk factors showed that when smokers abstained with the help of the nicotine patch plus nicotine gum, plasma fibrinogen and exhaled carbon monoxide decreased, and transcutaneous partial oxygen tension increased.\textsuperscript{37} The use of transdermal nicotine in nonsmokers can mimic the endothelial dysfunction seen in smokers. However transdermal nicotine use in smokers did not worsen endothelial dysfunction, due to the development of tolerance in chronic smokers.\textsuperscript{38}

Questions have often been raised about the danger of smoking cigarettes while using NRT. Mahmarian and colleagues studied 36 smokers with known CAD using treadmill exercise testing with thallium single photon emission computerized tomography imaging to assess perfusion defect size. Testing was done before and after the
Another area of clinical concern is the use of NRT in pregnant women. Although it would be ideal for pregnant women to abstain from smoking without the use of pharmacologic agents, not all women can do so. In individual women the risks of NRT must be weighed against the risks of continued smoking with its attendant increases in carbon monoxide. Ogburn and colleagues studied smokers in the third trimester of pregnancy in an inpatient setting. Fetal well-being was assessed by measuring fetal heart rate and reactivity, systolic/diastolic ratio of blood flow in the umbilical artery, and fetal activity on ultrasound biophysical profiles while mothers smoked, abstained, and used nicotine patches. There were no indications of fetal compromise with nicotine patches.40 The American College of Obstetrics and Gynecology supports the use of NRT in pregnant women who have failed prior attempts to quit smoking without medications.41

Non-nicotine Therapies

The only non-nicotine medication approved by the FDA for use in smoking cessation is sustained-release bupropion (bupropion SR). It is thought to work by enhancing dopaminergic activity in the central nervous system.42 A recently updated Cochrane Review examined the use of antidepressants for smoking cessation.43 Selective serotonin reuptake inhibitors have not been shown to be efficacious for smoking cessation, but there is an approximate doubling of the quit rate with nortriptyline (OR, 2.8; 95% CI, 1.81-4.32) or bupropion SR (OR, 1.97; 95% CI, 1.67-2.34).44 Subjects treated with bupropion SR for only 7 weeks had abstinence rates about twice that of the placebo group at 1-year follow-up: 23.1% vs 12.4% in 1 study of 615 smokers,44 and 28% vs 14% in another study of 629 smokers with CVD.45 Bupropion SR has also been studied in smokers who failed a previous quit attempt with bupropion; 12 weeks of bupropion SR resulted in a 6-month abstinence rate of 12% vs 2% in the placebo group.46 In direct comparison studies, bupropion SR was more effective than nicotine patches and the combination of bupropion plus nicotine patch was slightly more effective than either one alone.47,48 There is some evidence that bupropion SR, with or without NRT, may attenuate the weight gain associated with smoking cessation.49,50

Bupropion SR should be started 1 week before the patient's quit date, at 150 mg once daily for 3 days, then 150 mg twice daily for 7 to 12 weeks. Bupropion SR should be taken in the morning and early evening (at least 8 hours later); late evening dosing may lead to insomnia. The most common side effects are insomnia (30% to 40%), dry mouth (10%), and nausea.49 The most serious adverse effect related to bupropion is increased risk of seizures— affecting approximately 1 in 1000 patients (excluding those with known risk factors for seizure) when dose is limited to 300 mg.50,51 Bupropion SR should not be used in patients with a history of seizure, head trauma, brain tumor, or in those with anorexia/bulimia, hepatic failure, or those using drugs that may increase the risk of seizures (ie, theophylline, systemic steroids, antipsychotics, antidepressants, hypoglycemics' insulin; or abusive levels of alcohol or stimulants).

The tricyclic antidepressant nortriptyline is not FDA approved for smoking cessation, but there have been several published reports that demonstrate its efficacy in smoking cessation. Hall et al52 randomized smokers to nortriptyline or placebo, stratified by whether they had a history of major depression. The nortriptyline group achieved higher abstinence rates than the placebo group (24% vs 12% with continuous abstinence at week 64 [OR, 2.42]), regardless of whether they had a history of depression. Nortriptyline treat-
ment also attenuated the negative mood after smoking cessation. A short-term study in veteran and Army smokers showed that nortriptyline 75 mg daily resulted in better rates of biochemically verified abstinence at 6 months (14% vs 3% in the placebo group). The nortriptyline group also had a significant decrease in several withdrawal symptoms, including irritability, tension, and difficulty concentrating. Another study included a bupropion arm vs nortriptyline titrated to therapeutic serum levels. Both the nortriptyline and bupropion groups had higher point-prevalence abstinence rates compared with placebo, but neither drug attained statistical significance at 1 year for continuous abstinence (bupropion 20.7%, nortriptyline 13.2%, placebo 11.8%). A study of Brazilian smokers showed that nortriptyline 75 mg/day for 6 weeks produced a cessation rate of 20% at 6 months' follow-up vs 5% in the placebo group.

As with other tricyclic antidepressants, nortriptyline caused frequent adverse effects in most studies, but not all. The most common symptoms were dry mouth, dysgeusia, and constipation. It should be dosed at bedtime to minimize daytime sedation. Nortriptyline also has potential for serious adverse effects in individuals with CAD, including sinus tachycardia, increased ischemic episodes, and increased ventricular ectopy. An advantage of nortriptyline is its affordability.

The Surgeon General's report and a Cochrane Review ranks clonidine as a second-line agent. Clonidine can be inexpensive, but is commonly associated with troublesome side effects including dry mouth, sedation, and orthostatic hypotension. Abrupt cessation of high-dose clonidine can cause rebound hypertension. Of 5 studies reviewed, clonidine (doses ranging from 0.1 mg to 0.75 mg/day) approximately doubled the quit rate. Recommended dosage is 0.1 mg twice daily, starting 2 to 3 days before the quit date, with titration up to a maximum of 0.2 mg twice daily.

A Cochrane Review did not find adequate evidence to support the use of anxiolytics, including buspirone, benzodiazepines, or beta-blocking agents.

**Choice of Medication**

All forms of NRT have similar efficacy in studies. In subjects randomized to 4 forms of NRT (gum, patch, inhaler, nasal spray), all groups had similar abstinence rates of about 20% to 24% at 12 weeks, despite low compliance with all except the patch. Choice of NRT can be guided by patient preference and individual characteristics. For example, the patch is not a good choice for a person with very sensitive skin, nor is nicotine nasal spray a good choice for a person with chronic rhinitis. A patient who does not wish to advertise his quit attempt may prefer discrete use of the patch. A smoker who wants hand-and-mouth activity may prefer the gum or inhaler. If a patient has had previous success with a technique, it is reasonable to try it again, with increased emphasis on relapse prevention.

Each of the approved therapies has modest long-term effectiveness, leading to the hope that combining therapies might produce additive or synergistic effects. A number of studies have examined the use of nicotine patches plus a short-acting form of NRT. The theory is that the patch will produce a steady basal level of nicotine replacement while the gum, inhaler, or spray will provide additional nicotine on an as-needed basis (entirely analogous to using combinations of long- and short-acting narcotics for chronic pain). In one study, use of patch or gum alone produced similar abstinence rates and combining the 2 was significantly better at 12 and 24 weeks, but not at 52 weeks (18.1 vs 12.7%, P=0.191). Similarly, a trial compared the patch alone, the nasal spray alone, and both used together, and found better abstinence rates with the combination therapy at 6 weeks but not at 6 months. Some studies have shown a sustained benefit to combination therapy: inhaler vs inhaler plus patch, and patch vs patch plus nasal spray. Combination therapy should be considered in those who failed quit attempts with one medication alone and in those concerned about strong cravings.

There is some evidence that heavier smokers may do better with higher doses of NRT. Some studies show this to be only a short-term effect, whereas others found a sustained benefit to higher doses. Heavy smokers who failed to quit with standard doses of NRT may receive higher doses by using 2 of the 21-mg/day patches simultaneously.

In direct-comparison studies, bupropion SR was more effective than nicotine patches and the combination of bupropion plus nicotine patch was slightly more effective than either alone. In practice, the choice of NRT or bupropion can be individualized. It is reasonable to start with the product that inspires the most confidence in the patient, or that has been successful in the past. Some patients may have a preference for pill form vs nonpill, or for nicotine vs non-nicotine-containing products. The patient's medical history may be a guide: for example, those at increased risk of seizures should not use bupropion and those with asthma should not use the nicotine inhaler. Patients concerned about weight gain may
want to consider bupropion SR.\textsuperscript{64,66} The successful use of bupropion does not depend on a history of current or past depression, but it could be a particularly appropriate choice for smoking cessation in patients with a history of depression. Nortriptyline and clonidine may have a role in treating patients who have contraindications to, or have failed to respond to, first-line agents.

Although the over-the-counter status of some NRTs makes them more accessible to patients, they may be less efficacious when self-administered without a physician's support.\textsuperscript{67} Additional work is needed to define which counseling techniques, medications, and delivery methods work best for different subgroups of patients, based on clinical variables such as age, sex, ethnicity, smoking habits, level of dependence, history of depression, and coexisting medical conditions. Concerns have been raised that the persons most likely to quit have already done so due to societal pressures and the remaining population of smokers are more recalcitrant.\textsuperscript{68} Ultimately, the most important goal is to find effective ways to prevent young people from starting smoking at all.

**CONCLUSION**

Smoking cessation is a daunting prospect; too often physicians get discouraged and stop giving their patients more than perfunctory advice. It is important to remember that quitting smoking is a long-term process: it can take years to make a serious quit attempt and most patients who achieve long-term abstinence do so only after multiple attempts.\textsuperscript{69} Although we lack a "magic bullet" that would guarantee a high success rate, we do have medications that help. And, the importance of counseling in conjunction with pharmacologic therapy should not be overlooked; providing intensive counseling in addition to medication can further boost quit rates.\textsuperscript{70} With patience and persistence, many smokers can eventually achieve long-term abstinence.

**REFERENCES**


34. Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA. A prospective safety surveillance study for bupropion sustained-release in the treat-


