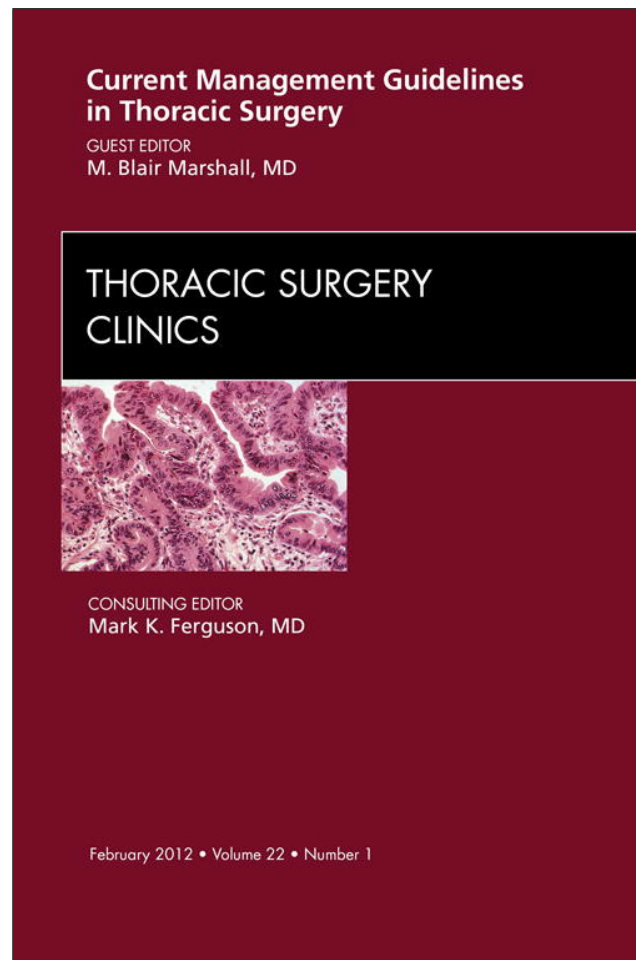


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# Perioperative Smoking Cessation

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## KEYWORDS

- Smoking cessation • Pharmacotherapy • Counseling
- Preoperative

It is impossible to overstate the impact of tobacco use on national and global health, because tobacco consumption remains the largest single preventable cause of death in the world. Worldwide, tobacco causes approximately 1 in 10 deaths, and by 2030 this figure is expected to rise to 1 in 6, or 10 million deaths each year.<sup>1,2</sup> Globally, smoking is still a very common practice, with 48% of the world's men and 10% of women classified as habitual smokers.<sup>3</sup> The prevalence of smoking in the United States has declined among men from 57% to 23% and among women from 34% to 18% during the period between 1955 and 2005.<sup>4</sup> Although cigarette consumption has declined in recent years, an estimated 21% of United States adults smoked in 2004.<sup>5</sup> The highest rate of decline in smoking occurred between 1965 and 1990 and seemed to be related to public health measures, such as bans on smoking in public places, increased cigarette taxes, mass media antismoking campaigns, and restrictions on marketing of cigarettes. Since 1990, however, there seems to be minimal progress, indicating a need for new strategies as the number of smokers in the United States remains greater than 43 million.

The economic and healthcare costs of tobacco use in the United States exceed \$400 billion annually.<sup>6</sup> Smoking cessation is one of the most effective ways to promote public health and reduce healthcare costs.<sup>7</sup> The 2008 report from the surgeon general concluded that tobacco-dependence treatments are effective across

a broad range of populations and recommended that pharmacotherapy be offered to all cigarette smokers. Despite substantiation that evidence-based effective interventions exist and that most adult smokers want to quit, only a small proportion of tobacco users are offered assistance or receive treatment. This disconnect epitomizes a significant quality of healthcare predicament.

Of the approximately 6 billion people alive today, half a billion people will be killed by tobacco products. By 2020, tobacco is expected to kill more people than any single disease.<sup>8,9</sup> Half of these deaths will occur in people in their middle age, depriving societies of their most productive workers and burdening healthcare systems. The World Health Organization Framework Convention on Tobacco Control aims to reduce the health consequences of tobacco use through the worldwide implementation of evidence-based tobacco control actions.<sup>10</sup> The Framework Convention on Tobacco Control treaty is the first global plan attempting to regulate the tobacco industry, and it has now been signed by 168 countries, making it the most widely accepted treaty in United Nations history.

Smoking causes more than 435,000 premature deaths in the United States alone.<sup>11</sup> It is estimated that smoking eventually kills one in two smokers and that the sequelae of tobacco dependence kill approximately 10% of adults worldwide. No other product exists that causes the premature death of 50% of those who use it as intended.<sup>12</sup> Current smokers have nearly three times the risk

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of premature death compared with nonsmokers. Smokers also have up to a 20-fold increase in the risk of developing lung cancer compared with lifetime nonsmokers.<sup>13</sup> In addition, smoking accounts for at least 23.9% of all cancer deaths (33.4% men and 9.6% women) including carcinoma of the lung, lip, oral cavity, pharynx, larynx, esophagus, pancreas, uterine cervix, kidney, bladder, and stomach.<sup>14,15</sup> On average, male smokers lose 13.2 years of life expectancy, and female smokers lose 14.5 years.

## SMOKING CESSATION

### *Benefits of Quitting*

The positive effects of smoking cessation are measurable almost immediately. As soon as 20 minutes after the last cigarette, blood pressure decreases and peripheral vasoconstriction is reduced. After 8 hours, carbon monoxide levels drop to normal. After 24 hours the chance of a coronary artery occlusive event is reduced. After 1 to 9 months, respiratory ciliary function returns to normal allowing for appropriate clearance of mucus and particulate matter. In addition, patients with lung cancer who quit also experience decreased fatigue and shortness of breath and improved performance status, appetite, sleep, and mood.<sup>16</sup> The risk of coronary heart disease drops to half of that of a smoker after 1 year of abstinence and to the level of a nonsmoker after 15 years. The risk of stroke is reduced to the level of a nonsmoker after 5 to 15 years of abstinence.<sup>17</sup> Perhaps most significant is a sharp reduction in mortality because on average, smokers die 13 to 14 years earlier than nonsmokers. Other benefits of quitting include reduction in all-cause mortality,<sup>18</sup> improved response to chemotherapy and radiation,<sup>19,20</sup> improved quality of life,<sup>21</sup> reduction in second primary lung cancer,<sup>22</sup> and decreased postoperative complications.<sup>23–26</sup>

### *Smoking Cessation and the Diagnosis of Lung Cancer*

At diagnosis of lung cancer, up to 18% of patients are never smokers, 58% are former smokers, and 24% to 40% are current smokers. It is estimated that 20% of patients smoke at the time of lung cancer surgery and about half of these continue to smoke afterward.<sup>27</sup> Despite encouragement to quit smoking and strong intentions to quit, continued tobacco use after diagnosis of lung cancer remains a problem in this population, with an estimated 10% to 20% of patients smoking at some point after diagnosis.<sup>28</sup> Lung cancer surgery may be viewed as a “teachable moment” and cessation programs at the time of surgery have

been shown to be more effective than cohorts attempting to quit for general health benefits.<sup>29</sup>

### *Quitting Before Surgery*

Preoperative smoking cessation seems to offer important benefits in reducing complications. Patients with resected stage I to III non-small cell lung carcinoma who quit smoking after the diagnosis and before the operation have a lower risk of dying compared with smokers who continue to smoke at the time of the operation, suggesting that smoking cessation is beneficial for patients with lung cancer at any time before surgery.<sup>30</sup> A prospective study in general surgery patients demonstrated a predictive role of tobacco smoking on operative mortality, total postoperative complications, admission to the intensive care unit, and lower respiratory tract infections.<sup>23</sup> It is generally believed that 4 to 8 weeks of abstinence from smoking are required to reverse the smoking-induced abnormalities in respiratory cell function. Data from a few observational studies seem to support this concept, noting that 4 to 8 weeks of smoking abstinence before surgery were required to significantly reduce the risk of postoperative pulmonary complications. Indeed, two small studies noted a paradoxical increase in the rate of pulmonary complications among patients who quit or reduced their smoking within 4 to 8 weeks before surgery.<sup>31,32</sup> Recent quitters had a numerically higher but not statistically significant rate of pulmonary morbidity than current smokers, with a relative risk up to 6.7 for smokers who quit smoking within 4 to 8 weeks of surgery. Patients who quit smoking closest to the date of the surgery had the highest rate of pulmonary complications.<sup>33</sup> These data have made it difficult for physicians when counseling patients preoperatively about smoking cessation, when surgery cannot be delayed for an optimal time to allow prolonged smoking cessation.

More recent studies, however, have failed to reproduce the paradoxical increase in pulmonary complications suggesting that it is safe to encourage smoking cessation, regardless of the time, before surgery.<sup>34</sup> In addition, longer periods of smoking cessation seem to be more effective in reducing the incidence or risk of postoperative complications without an increased risk in perioperative complications from short-term cessation.<sup>35</sup> A recent randomized trial demonstrated that on an intention-to-treat analysis the overall complication rate in the control group (smokers) was 41% and in the intervention group (quitters) was 21%, a statistically significant difference favoring the cessation group.<sup>36</sup> A systematic

review of randomized clinical trials containing 1194 patients undergoing a variety of surgical procedures demonstrated that intensive preoperative smoking cessation interventions reduced the occurrence of postoperative complications.<sup>24</sup> Despite the conflicting data on the timing of smoking cessation and perioperative pulmonary complications, there is no evidence of increased mortality for recent quitters. A prospective study of 300 patients showed an increased postoperative complication rate in smokers compared with nonsmokers but failed to show any evidence of an increased complication rate in those patient who quit smoking less than 2 months before surgery.<sup>37</sup> There has been a recent emerging body of evidence showing the benefit of preoperative and long-term postoperative smoking cessation.<sup>24,38</sup>

Clinical trials have evaluated smoking cessation interventions at varying times before surgery and found clinically meaningful reductions in complications. A meta-analysis of 6 randomized trials and 15 observational studies demonstrated a relative risk reduction of 41% of postoperative complications. In addition, it was demonstrated that each week of cessation increases the magnitude of effect by 19%.<sup>25</sup> Another recent meta-analysis involving 9 studies and 448 patients also demonstrated that the notion that recent smoking cessation increases the risk of postoperative complications is unfounded and emphasized that physicians should advise their patients to quit at any time before surgery.<sup>26</sup> Risk of hospital death and pulmonary complications after lung cancer resection were increased by smoking and mitigated slowly by perioperative cessation. No optimal interval of smoking cessation was identifiable.<sup>39</sup> The consistent decrease noted in postoperative pulmonary complications as interval of smoking cessation increased suggests that clinicians can safely counsel patients about the benefits of smoking cessation preoperatively, regardless of the interval. Although the relative risk for active smokers or recent quitters is substantial, unduly delaying the operation does not seem justified because of the low overall risk of pulmonary complications and the long-term period during which risk remains elevated. A recent Cochrane review on interventions for preoperative smoking cessation concluded that all smokers should be advised to quit and offered effective interventions, including behavioral support and pharmacotherapy.<sup>40</sup> Contrary to the notion that a short period of smoking cessation results in reduced surgical risk, data demonstrate that even after a year of smoking cessation, risk-adjusted mortality remains elevated compared with lifetime nonsmokers,

suggesting that adverse effects never completely disappear.

## CESSATION INTERVENTIONS

### *Counseling*

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Techniques for assisting smokers to quit include behavioral counseling to enhance motivation, cognitive therapy to impart adjustment skills, and pharmacologic interventions to reduce nicotine reinforcement or chemically mediated effects of nicotine withdrawal. Although the goal of any intervention is permanent tobacco abstinence, it is rarely achieved with a single treatment. Indeed, relapse is the most likely outcome from any single quit attempt. Most patients do not reach 6 months of abstinence without relapsing and half of those abstinent at 6 months relapse during the subsequent 8 years.<sup>41</sup> Healthcare providers need to be aware that most patients require six or more quit attempts before achieving permanent abstinence and should not view prior attempts as total failures.

Smoking cessation treatment should be conceptualized using a chronic illness model.<sup>42,43</sup> Smoking can be effectively addressed within a busy clinical practice using strategies similar to those used to manage other chronic medical conditions, such as hypertension and diabetes. Medication adjustments and behavioral support should be provided until acceptable therapeutic targets are met and, just as a healthcare provider would not consider discontinuing antidiabetic agents for a patient whose hemoglobin A<sub>1c</sub> was not at goal, the healthcare professional should not discontinue treatment for tobacco users until permanent quitting is achieved.

The most universally accepted paradigm for treatment of tobacco use and dependence is the Five A's model of the United States Public Health Services (USPHS) Clinical Practice Guideline for Treating Tobacco Use and Dependence (ask, advise, assess, assist, and arrange) (**Table 1**).<sup>44,45</sup> The first step is to identify and document tobacco use status for every patient at every visit. This entails systematically screening all patients for tobacco use (ask). The second step is to stalwartly recommend in a strong and personalized manner to every tobacco user to quit smoking (advise). The third step is to determine willingness to make a quit effort (assess). The fourth step addresses smokers willing to make a quit attempt. These patients should be offered medication and counseling or referral for additional treatment (assist). Finally, the fifth step refers to the necessity for follow-up assistance, either in person or by telephone, beginning the first week after the quit date (arrange).

**Table 1**  
The five As model for treating tobacco use and dependence

Ask about tobacco use	Identify and document tobacco use status for every patient at every visit
Advise to quit	In a clear, strong, and personalized manner urge every tobacco user to quit at every visit
Assess willingness to quit	Determine willingness to make a quit attempt
Assist in quit attempt	Offer medication and provide or refer for counseling or additional treatment to help the patient quit
Arrange follow-up	Arrange for follow-up contacts, beginning the first week after the quit date

*Adapted from* The Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A US Public Health Service report. *Am J Prev Med* 2008;35(2):158–76; with permission.

The updated USPHS Clinical Practice Guideline for Treating Tobacco Use and Dependence<sup>44</sup> endorses a condensed user-friendly model for the healthcare provider who does not have the time, inclination, or expertise to provide the more comprehensive tobacco cessation counseling as recommended by the Five A's guideline. Ask-advise-refer is designed to promote cessation intervention by even the busiest of providers (Table 2).<sup>46</sup> The ask-advise-refer approach integrates the Five A's into an abbreviated intervention that remains consistent with recommended

guidelines and is designed such that any health-care provider can easily integrate meaningful cessation intervention into practice on a routine basis.

Telephone quitlines are a primary resource to further assist patients with the quitting process. These services provide one-on-one counseling, self-help kits, and individualized cessation information at no charge to the patient. Studies have shown that patients who receive quitline counseling are twice as likely to quit compared with patients who quit on their own.<sup>47</sup>

**Table 2**  
The AAR (ask-advise-refer) abbreviated method for tobacco dependence treatment

Tobacco Cessation Counseling	Comment
Ask: Ask if the patient smokes or uses smokeless tobacco products	<ul style="list-style-type: none"> <li>• Many smokers want to quit and appreciate the encouragement of health professionals</li> </ul>
Advise: Advise the patient to quit The benefits of quitting include <ul style="list-style-type: none"> <li>• Decreased risk of a heart attack, stroke, coronary heart disease; lung, oral, and pharyngeal cancer</li> <li>• Improved sense of taste and smell</li> <li>• Improved circulation and lung function</li> <li>• Improved health of family members</li> </ul>	<ul style="list-style-type: none"> <li>• Smokers are more likely to quit if advised to do so by health professionals</li> <li>• The perioperative examination provides the perfect opportunity to discuss smoking cessation with the patient</li> <li>• Tobacco use is a risk factor for coronary heart disease, heart attack, and lung cancer; second-hand smoke is unhealthy for family members</li> </ul>
Refer: Tell the patient that help is a free telephone call away; provide patient with quitline numbers	<ul style="list-style-type: none"> <li>• Evidence suggests quitline use can more than triple success in quitting</li> <li>• Quitlines provide an easy, fast, and effective way to help smokers quit</li> <li>• By simply identifying smokers, advising them to quit, and sending them to a free telephone service, clinicians can save thousands of lives</li> </ul>

*Adapted from* Zillich AJ, Corelli RL, Hudmon KS. Smoking cessation for the busy clinician. *The Rx Consultant* 2007;16(8): 1–8; with permission.

## **Pharmacotherapy**

Since 1988, when the US Surgeon General concluded that nicotine is the prime component instigating tobacco addiction, it has also been recognized as the most highly addictive of all chemical substances commonly abused. A chief impediment for most smokers who try to quit is the neurobiology of tobacco dependence, which is fed by the most efficient delivery device of nicotine that exists: the cigarette. Cigarette smoking delivers high concentrations of nicotine to the central nervous system within seconds of each puff. The primary target for nicotine in the central nervous system is the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor, which when activated by nicotine binding results in the release of dopamine and provides the positive reinforcement observed with cigarette smoking. Smoking one cigarette results in a high level of occupancy of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptors; three cigarettes completely saturates these receptors for as long as 3 hours. Craving results when the receptor occupancy declines over time, and reducing that craving requires achieving virtually complete receptor saturation.<sup>48–51</sup>

The USPHS 2008 update of the Treating Tobacco Use and Dependence clinical practice guidelines categorizes pharmacotherapy into first-line and second-line medications and also addresses combinations of medications. All first-line medications seem to be of similar effectiveness. First-line medications include nicotine replacement therapy (NRT), bupropion, and varenicline (**Table 3**).<sup>44,52</sup> All of these medications were found to be effective first-line medications in the guideline's meta-analyses. Second-line medications include clonidine and nortriptyline. There is significant evidence that the odds of a smoker quitting are increased by using a pharmacologic approach.<sup>44,52</sup>

Regardless of the level of physical addiction or the number of cigarettes smoked daily, the guideline recommends that all patients attempting to quit should be encouraged to at least try one or more of the effective pharmacotherapy agents. The goal of cessation pharmacotherapy is to alleviate or diminish the symptoms of nicotine withdrawal and diminish the urge to smoke.

## **Nicotine Replacement Therapy**

NRT was the first proven effective medication for the treatment of nicotine dependence and remains a first-line pharmacotherapy in the management of nicotine withdrawal symptoms.<sup>53</sup> NRT makes it easier to abstain from tobacco by replacing, at least partially, the nicotine obtained

from tobacco and to quash the nicotine withdrawal symptoms and cravings seen on discontinuation of tobacco use.

NRT is available in five modalities, including the long-acting nicotine patch and the short-acting gum, lozenge, inhaler, and nasal spray (see **Table 3**). All NRTs are nicotinic acetylcholine receptor agonists but compared with smoking a cigarette, the nicotine by NRT products is delivered much more slowly and at a lower dose and do not reproduce the rapid and high levels of nicotine achieved through inhalation of cigarette smoke. Therefore, amelioration of symptoms of nicotine withdrawal is not absolute and dose adjustment is required. The transdermal patch system offers a continuous release of nicotine over 15 or 24 hours depending on the brand, whereas the oral formulations are short-acting, so the dose can be self-titrated, thus time-adjusted to the patient's needs.

A Cochrane review of 132 trials with more than 40,000 patients found that all forms of NRT increase quit rates by 50% to 70%.<sup>54</sup> Combination NRT (eg, the patch plus the gum) may further improve quit rates. The efficacies of the various forms of NRT are generally similar but compliance with the various delivery forms may be the limiting factor. One study comparing four forms of NRT found comparable 12-week abstinence rates (20%–24%) but compliance varied: 11% with the inhaler, 15% with the nasal spray, 38% with the gum, and 82% with the patch.<sup>55</sup>

It seems possible to improve the efficacy of NRT by combining the transdermal patch with an oral formulation that permits ad libitum nicotine delivery.<sup>56</sup> NRT is typically started the day of the quit date, although precessation treatment is considered safe and it may be advantageous for smokers to try NRT before the stress of quitting to determine which agent or agents are preferable. The PHS prescribing guideline does not officially recommend using NRT while smoking; however, it is becoming more common for patients to be started on NRT before their quit date.

Physicians who prescribe NRT for tobacco dependence should individualize the dose and duration of treatment based on the patient's response including the subjective relief of withdrawal symptoms and cravings. If NRT is selected for treatment, a combination therapy of nicotine patches and short-acting NRT is usually preferred over monotherapy with a short-acting NRT product. Short-acting NRT is best used for the acute management of nicotine withdrawal symptoms and cravings in combination with longer-acting medications, such as nicotine patches, bupropion, or varenicline. Nicotine doses

**Table 3**  
Pharmacologic smoking cessation aids

	Patches	Gum	Lozenge	Nasal Spray	Inhaler	Zyban (Bupropion)	Chantix (Varenicline)
Duration of therapy	12 wk or more, then can use as needed	12 wk or more, then can use as needed	12 wk or more, then can use as needed	12 wk or more, then can use as needed	12 wk or more, then can use as needed	12 wk or more; start 1–2 wk before quitting	12 wk or more; start 1–2 wk before quitting
Dose	21 mg if smoke a pack a day, 14 mg if smoke half a pack a day; 7 mg if smoke 4–5 cigarettes a day (can double up on patches or use patch with another system if smoke more than a pack a day)	4 mg if smoke a pack a day, 2 mg if smoke less than a pack a day – chew at least 1 piece for every 2 cigarettes smoked	4 mg if smoke a pack or more a day, 2 mg if smoke less than a pack a day – can use 1 lozenge every 1–2 h	Dose once or twice an hour (not more than 48 sprays in 24 h)	6–12 cartridges a day	Bupropion SR: One 150-mg tablet every morning for 3 d, then one 150-mg tablet twice a day at least 8 h apart on Day 4 and thereafter Bupropion extended release: one 150-mg tablet every morning for 1 wk, then one 300-mg tablet every morning thereafter	One 0.5-mg tablet for 3 d, then one 0.5-mg tablet twice a day for 4 d, then one 1-mg tablet twice a day thereafter; take each tablet after a meal and with a full glass of water
Pros	Very easy to use; automatically gives the right dose in 24-h period; helps with early morning cravings	Easy to regulate dose; can help prevent overeating; can provide extra help at difficult moments	Easy to regulate dose; can help prevent overeating; can provide extra help at difficult moments	Gives fast relief and easy to adjust dose	Helps keep hands and mouth busy, easy to regulate, could help prevent overeating	Good short-term research results; easy to use; noticeable reduction in number and severity of urges to smoke	Better than Zyban short- and long-term research results; easy to use; noticeable reduction in number and severity of urges to smoke; no cigarette “reward”
Cons	Can cause vivid dreams at night; not orally gratifying; small possibility of skin reaction	Difficult to use correctly (nothing to drink 20 min prior; chew and park)	Difficult to use correctly (nothing to drink 20 min prior; let dissolve slowly)	May cause nasal irritation	Feels and looks like a cigarette; very conspicuous method	Possible sleep disruption and can cause dry mouth	Possible nausea, vivid dreams; Possible association with increased depression or suicidal ideation

should be increased for patients experiencing pronounced withdrawal symptoms, such as irritability, anxiety, loss of concentration, or cravings.

Nicotine gum is available as an over-the-counter product, in 2- and 4-mg doses. Patients should be instructed in its proper use to “chew and park” and to avoid acidic beverages that lower the intraoral pH and thereby reduce nicotine absorption. Nicotine gum can be used as monotherapy or in combination with other NRT or bupropion.

The nicotine lozenge is available as an over-the-counter product. The nicotine lozenge is available in 2- and 4-mg doses, with the latter indicated for use in high-dependence smokers (ie, time to first cigarette of the day of <30 minutes after arising). The method of delivery (transbuccal) is similar to that of nicotine gum, and it can be used alone or in combination with other NRT or bupropion.

Nicotine nasal spray delivers nicotine directly to the nasal mucosa and has been observed to be effective for achieving smoking abstinence as monotherapy. This device delivers nicotine more rapidly than other therapeutic nicotine replacement delivery systems and reduces withdrawal symptoms more quickly than nicotine gum.<sup>52</sup> The reduction in withdrawal symptoms may be partially attributable to the rapidity with which nicotine is absorbed from the nasal mucosa.

The nicotine vapor inhaler has also been shown to be effective as monotherapy for increasing smoking abstinence.<sup>57</sup> The device delivers nicotine in vapor form that is absorbed across the oral mucosa. Although the device is called an inhaler, this is a misnomer because little of the nicotine vapor reaches the pulmonary alveoli, even with deep inhalations.

Nicotine patch therapy delivers a steady dose of nicotine for 24 hours after a single application. The once-daily dosing requires little effort on the part of the patient, which enhances compliance. Nicotine patches are available without a prescription in doses of 7, 14, and 21 mg. In nearly every randomized clinical trial performed to date, the nicotine patch has been shown to be effective compared with placebo, usually with a doubling of the smoking abstinence rate.<sup>54</sup>

Most patients use NRT for 4 to 8 weeks but it is safe for longer use if needed to maintain smoking abstinence. The optimal length of treatment has not been determined but longer-term treatment (>14 weeks) seems to provide benefit over standard lengths of treatment when combining nicotine patches and nicotine gum.<sup>43</sup> Furthermore, long-term treatment of up to 6 months with triple combination therapy (nicotine patches, bupropion, and nicotine vapor inhaler) seems superior to standard-dose nicotine patch therapy given over

a 10-week period.<sup>43</sup> For the best chance at success with these therapies, they may be used in combination and should be dose-appropriate based on the patient's need.

### ***Label Warning and Contraindications for NRT Products***

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The labeling on NRT products still instructs tobacco users to consult their physician if there is a history of heart disease, ulcers, hypertension, pregnancy, or breast-feeding. This is despite the fact there is a documented lack of an association between NRT and acute cardiovascular events even in patients who continue to smoke while on the patch. Because trials specifically excluded patients with unstable angina, serious arrhythmias, and recent myocardial infarction, the Clinical Practice Guideline recommends that NRT be used with caution among patients in the immediate (within 2 weeks) post-myocardial infarction period, those with serious arrhythmias, and those with serious or worsening angina because of a lack of safety data. Despite this caution, it is widely believed that the risks of NRT in patients with cardiovascular disease are minimal relative to the risks of continued tobacco use. The guideline recommends use of NRT in pregnancy if other therapies have failed. Clearly, the fetus is exposed to significantly less nicotine with NRT than with smoking and most importantly is not exposed to carbon monoxide, carcinogens, and toxins from cigarettes.

### ***Nonnicotine Medications***

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There are two nonnicotine medications specifically developed to help adults quit smoking that have been proved to be the most effective pharmacotherapy treatment: bupropion and varenicline (see **Table 3**). Varenicline is considered more effective based on randomized trials.<sup>58,59</sup> The US Food and Drug Administration (FDA) has issued boxed warnings for both drugs because of reports of increased risks of psychiatric symptoms and suicide. Given the well-established link between smoking and psychiatric disease, there is no easy way to determine whether or not these adverse events are directly related to the medications. Unfortunately, these warnings may deter clinicians from discussing or prescribing bupropion and varenicline.

### ***Bupropion (Wellbutrin/Zyban)***

Bupropion sustained release (SR) was the first nonnicotinic medication approved by the FDA for smoking cessation. It has been on the market as an antidepressant since the 1980s. Bupropion is

known to inhibit the reuptake of norepinephrine and dopamine, and it is a nicotinic acetylcholine receptor antagonist. The exact mechanism for its efficacy in smoking cessation is unknown and likely multifactorial.

Bupropion has been shown to increase smoking cessation rates from 12% in patients using placebo to 23% in those using bupropion.<sup>60</sup> In addition, studies have suggested that a combined approach with bupropion plus a nicotine patch may be even more effective. The dose of bupropion is 150 mg of the SR form starting with one tablet per day, preferably on waking, for 3 days, then increasing to one table twice daily. The doses should be separated by at least 8 hours with the second dose as far away from bedtime as possible. The 2008 USPHS Guideline recommends the combined use of bupropion SR and NRT for at least 3 months.<sup>45</sup>

Unlike other antidepressants, bupropion typically does not cause weight gain (and may suppress it) or sexual dysfunction so it may be especially of interest to those patients concerned about weight gain when quitting smoking. Bupropion extended release is also available for once-a-day dosing. Treatment with bupropion with either dosing is typically initiated 1 to 2 weeks before quit date.

### **Varenicline**

The most recent nonnicotine medication is varenicline (Chantix), a partial agonist selective for a specific nicotine receptor subtype. Varenicline was approved in by the FDA in 2006 and introduced in the updated 2008 guideline. It is a partial agonist at the  $\alpha 4\beta 2$  neuronal nicotinic acetylcholine receptor causing a sustained moderate level of dopamine release, which is thought to reduce withdrawal symptoms. It also acts as an antagonist at the  $\alpha 4\beta 2$  neuronal nicotinic acetylcholine receptor, which may inhibit the rewarding effects of nicotine and reduce or eliminate satisfaction relating to smoking. There are currently no known contraindications to varenicline therapy. It should be used in caution in patients with chronic kidney disease and the dose should be lowered by half in patients with creatinine clearance less than 30 mL/min.

Evidence suggests that using varenicline can appreciably increase quit rates compared with bupropion and placebo.<sup>58,59,61</sup> Varenicline has demonstrated superior efficacy compared with placebo in multiple clinical trials, several of which were conducted before regulatory approval in 2006 in the United States and Europe. Meta-analyses have confirmed the increased efficacy of varenicline at the dosage of 2 mg/day during

a 12-week treatment on smoking quit rates compared with placebo and also with bupropion. Varenicline has also been shown to perform better than treatment with the transdermal NRT patch. The combination of varenicline with NRT or bupropion seems safe and the latter may result in better quit rates than monotherapy.<sup>62,63</sup>

Pivotal trials in healthy smokers comparing varenicline at a dose of 1 mg twice daily with placebo or bupropion SR have demonstrated that varenicline is more effective, with end of treatment (12 weeks) continuous smoking abstinence rates of 44% versus 30% for bupropion SR and 18% for placebo.<sup>64,65</sup> An additional 12 weeks of varenicline has been shown to be effective in maintaining smoking abstinence in smokers who had stopped smoking after 12 weeks of open-label varenicline treatment.

Varenicline is supplied in a "Starting Month Pack" and a "Continuing Month Pack." The Starting Pack begins with 0.5 mg daily for 3 days, followed by 0.5 mg twice daily for 4 days. The target quit date is Day 8 when the maintenance dose of 1 mg twice daily begins. The initial treatment period should be at least 12 weeks (one starting pack plus two continuing packs). The decision to continue past 12 weeks should be individualized, keeping in mind that higher quit rates are seen with longer duration of treatment.

### **Combination Therapy**

For the first time, the 2008 clinical practice guideline update assessed the relative effectiveness of cessation medications and multiple combinations of medications were shown to be effective. These comparisons showed that two forms of pharmacotherapy, varenicline (Chantix) used alone and the combination of a long-term nicotine patch plus as-needed nicotine nasal spray or gum, produced significantly higher long-term quit rates than did the patch by itself. Combining two kinds of NRT with different types of delivery (the more rapid oral products with the slower absorbed patch) has been shown to improve quit rates.<sup>54</sup> More recent data suggest that aggressive regimens in the form of triple-combination therapy (inhaler, patch, and nasal spray) in combination with bupropion are a safe and effective treatment.<sup>66</sup> Combination therapy with medications from different classes, including the patch with bupropion, has shown improved efficacy over monotherapy. Preliminary data also suggest varenicline in combination with NRT or bupropion may be efficacious and well tolerated.<sup>62</sup> However, future controlled trials are required to confirm these

findings. Combination therapy is “off label” use but now it is definitively medically sanctioned.

### **Relapse**

Relapse should be seen as a probable event, especially within the first 3 months of the quit attempt. Even among patients who succeed in quitting for extended periods, relapse occurs in 75% of first-time quitters.<sup>42</sup> Relapse is usually preceded by slips, defined as taking one puff or smoking an entire cigarette. If slips occur for more than 7 days, the patient is considered to be a regular smoker again. Smokers who have been abstinent for 24 to 48 hours have made a serious attempt at quitting and are the most vulnerable to relapse.<sup>67</sup> Smokers who experience a lapse in the first few weeks of cessation are also at high risk for returning to smoking. Most relapse (75%) happens in conjunction with alcohol consumption, whereas 50% of relapse occurs if living, socializing, or working with other smokers.<sup>41</sup> The most common thought preceding a slip is, “I can have just one.”

Smokers who are unable to quit on their target quit date but eventually quit using pharmacotherapy seem to benefit from additional 12 weeks of therapy. Smokers taking varenicline have the most success quitting compared with those taking other first-line pharmacotherapy for treating tobacco dependence.

### **RECOMMENDATIONS AND BEST PRACTICES FOR SMOKING CESSATION**

The updated Clinical Practice guideline<sup>45</sup> analyses suggest that a wide variety of clinicians can effectively implement cessation strategies. Cessation interventions as brief as 3 minutes can significantly increase cessation quit rates. Successful tobacco abstinence not only reduces general medical costs in the short-term but also reduces the number of future hospitalizations. Smoking cessation intervention is extremely cost-effective relative to other common disease prevention interventions and medical treatments,<sup>44</sup> such as the treatment of hypertension and hypercholesterolemia, and preventive screening interventions, such as periodic mammography and Papanicolaou tests.

A practical way to ensure assessment of tobacco consumption is to consider tobacco use as “the new vital sign” obtained and recorded by the office staff who records other routine vital signs. Once identified, all smokers should receive clear, concise, and simple advice to quit (see **Tables 1** and **2**). Smokers need assistance in developing a plan for quitting that includes a quit

date, practical counseling help, and effective medications.

A brief (3 minute) counseling session should focus on two key questions. First the clinician should ask if the patient has knowledge about how to quit. If the patient responds to this question affirmatively, the clinician should set a quit date and recommend a cessation pharmacotherapy. Few health interventions have such overwhelming evidence of effectiveness as smoking cessation medications. The seven first-line FDA-approved therapies reliably increase long-term smoking abstinence rates (see **Table 3**). All approximately double the rate of cessation compared with placebo.

### **SUMMARY**

Although providing evidence-based treatment for tobacco-dependent patients can be a challenge for the busy surgeon, it is a realistic clinical endeavor. In contrast to two decades ago, tobacco users are now able to select from many treatment options. It is well established that the use of approved medications for cessation at least doubles the odds of quitting and medications should be coupled with approaches that promote behavioral changes, such as advice from a health-care provider.

The 2008 clinical practice guideline presents more compelling evidence for the efficacy and cost effectiveness of treatment for tobacco use and dependence. For clinicians, the guideline offers four key conclusions: (1) tobacco dependence is a chronic remitting and relapsing condition and repeated attempts to quit should be encouraged for all smokers at every opportunity; (2) counseling as brief as 3 minutes is an effective treatment for tobacco dependence; (3) a larger number of effective medications and medication combinations are currently available and should be used for all smokers who are motivated to quit; and (4) of all the first-line medications provided as monotherapy, varenicline seems to have the greatest efficacy after 3 to 6 months. Clinicians should take every opportunity to encourage smoking cessation and provide effective treatment.

The most important message professionals can communicate to tobacco users is that it is never too late to quit. Even for long-term smokers, quitting smoking carries major and immediate health benefits for men and women of all ages. Benefits apply to healthy people and to those already suffering from smoking-related disease. For United States surgeons, the potential benefits far outweigh the investment. If all of the estimated

10 million smokers undergoing elective surgery this year were offered a smoking cessation intervention that succeeded in only 25% of cases, 2 million complications would be avoided.<sup>25</sup> Global fiscal implications are even more staggering because up to 70 million adult smokers undergo major surgery annually. As third-party payers and hospitals know, complications escalate healthcare costs. It is time for physicians, surgeons, hospitals, and payers to embrace routine preoperative smoking-cessation practices.

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