

Treating Tobacco Dependence: Review of the Best and Latest Treatment Options

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Globally, an estimated 85% of lung cancer in men and 47% of lung cancer in women is attributable to tobacco smoking. Tobacco dependence treatment remains the most cost-effective way to prevent morbidity and mortality from lung cancer. Several effective pharmacotherapies are available to treat tobacco dependence. However, the long-term effectiveness of these treatments has been limited because the majority of smokers who attempt to stop smoking eventually relapse. Approaching the treatment of tobacco use and dependence as a chronic disease and the development of innovative drug therapies offer new hope for the treatment of tobacco-dependent patients. The diagnosis of lung cancer provides a teachable moment to motivate patients to attempt tobacco abstinence on which clinicians should capitalize. We review the currently available pharmacologic approaches to the treatment of tobacco dependence.

Key Words: Tobacco use cessation, Smoking cessation, Nicotine, Bupropion, Varenicline, Drug therapy.

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Lung cancer has been the most common cancer in the world since 1985.¹ By 2002, lung cancer represented 12.4% of all new cancer cases globally and 17.6% of global cancer deaths, approximately one half of which occurred in developing countries.² Tobacco smoking accounts for an estimated 85% of lung cancer in men and 47% of lung cancer in women, a diagnosis that carries a 15% 5-year survival rate.² Treating tobacco dependence is the most cost-effective way to prevent deaths from lung cancer.

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For busy clinicians, the assessment of tobacco use status for all patients is encouraged and the provision of a brief clinical intervention for all tobacco users is crucial. The most effective treatment for dependence involves both pharmacologic and behavioral interventions. For tobacco users willing to make a quit attempt, pharmacotherapy should be offered unless there is a contraindication.³

The purpose of this article is to review the currently available pharmacologic approaches to the treatment of tobacco dependence. A summary of each medication discussed is provided (Tables 1 and 2).

GENERAL APPROACH

Patient-specific variables (preferences, contraindications, insurance coverage, drug cost, previous experience, smoking intensity) and clinician familiarity with the medications should be incorporated into the decision when choosing a specific medication or combination of medications.³ Relapse to smoking should not be considered a treatment failure but reframed as an opportunity to try different medications, higher doses, or treatment combinations. Such an approach is similar to the treatment of patients with hypertension, diabetes, and heart failure who may require medication adjustments to control the underlying disease.

The U.S. Public Health Service (USPHS) guideline *Treating Tobacco Use and Dependence* categorized available pharmacotherapies according to the strength of evidence for their efficacy and safety.³ First-line medications have been found to be safe and effective for the treatment of tobacco dependence and are approved by the U.S. Food and Drug Administration (FDA) for this use (Table 1). Since the publication of the USPHS guideline, the nicotine lozenge (Commit; GlaxoSmithKline; Philadelphia, PA) and varenicline (Chantix; Pfizer; New York, NY) have been approved for the treatment of tobacco dependence (Table 1). Second-line medications are treatments for which evidence of efficacy exists but which play a limited role due to lack of FDA approval for this indication and their potential for side effects and drug interactions (Table 2). Second-line medications should be considered after first-line medications have been tried. In general, the use of pharmacotherapy doubles the odds of smoking abstinence compared with placebo at 6 months.

TABLE 1. First-line and New Pharmacotherapies for the Treatment of Tobacco Dependence

Medication	Pros/Cons	Comments	Dosing Recommendations
First-Line Pharmacotherapies			
Nicotine Gum (OTC) 2mg, 4mg Flavors: Orange, Mint, Regular	<p>Pros</p> <ul style="list-style-type: none"> Convenient/flexible dosing Faster delivery of nicotine than patches <p>Cons</p> <ul style="list-style-type: none"> May be inappropriate for people with dental problems and those with temporomandibular joint (TMJ) syndrome Should not eat or drink 15 minutes before or during use Frequent use during the day required to obtain adequate nicotine levels 	<p>Many people use this medication incorrectly. Instruct patients to read the packaging instructions for proper use. The nicotine is absorbed through the oral mucosa.</p>	<p>Dosing as Monotherapy*</p> <p>Based on cigarettes/day (cpd)</p> <ul style="list-style-type: none"> >20 cpd: 4 mg gum <20 cpd: 2 mg gum <p>Based on time to first cigarette of the day:</p> <ul style="list-style-type: none"> <30 minutes = 4 mg >30 minutes = 2 mg <p>Initial dosing is 1–2 pieces every 1–2 hrs (10–12 pieces/day)</p> <p>Taper as tolerated.</p>
Nicotine Patch (OTC) 24 hour delivery systems 21, 14, 7 mg/24 hr 16 hour delivery systems 15 mh/16 hr	<p>Pros</p> <ul style="list-style-type: none"> Achieve high levels of nicotine replacement Easy to use Only needs to be applied once/day Few side effects <p>Cons</p> <ul style="list-style-type: none"> Less flexible dosing Slow onset of delivery Mild skin rashes and irritation 	<p>Patches vary in strengths and the length of time over which nicotine is delivered. Depending on the brand of patch used, may be left on for anywhere from 16 to 24 hours. Patches may be placed anywhere on the upper body-including arms and back. Rotate the patch site each time a new patch is applied.</p>	<p>Dosing* (24 hour patch)</p> <ul style="list-style-type: none"> >40 cpd = 42 mg/day 21–39 cpd = 28–35 mg/day 10–20 cpd = 14–21 mg/day <10 cpd = 14 mg/day <p>Adjust based on withdrawal symptoms, urges, and comfort. After 4–6 weeks of abstinence, taper every 2–4 weeks in 7–14 mg steps as tolerated</p>
Nicotine Nasal Spray (Rx only)	<p>Pros</p> <ul style="list-style-type: none"> Flexible dosing Can be used in response to stress or urges to smoke Fastest delivery of nicotine of currently available products but not as fast as cigarettes <p>Cons</p> <ul style="list-style-type: none"> Nose and eye irritation is common but usually disappears within one week Frequent use during the day required to obtain adequate nicotine levels 	<p>Unlike nasal sprays used to relieve allergy symptoms, the nicotine spray is not meant to be sniffed. Rather, it is sprayed against the lining of each nostril. Delivers nicotine through the lining of the nose.</p>	<p>Dosing as Monotherapy</p> <ul style="list-style-type: none"> 1 spray in each nostril 1–2 times/hr (up to 5 times/hr or 40 times/day) <p>Most average 14–15 doses/day initially</p> <p>Taper as tolerated.</p>
Nicotine Inhaler (Rx only)	<p>Pros</p> <ul style="list-style-type: none"> Flexible dosing Mimics the hand-to-mouth behavior of smoking Few side effects 	<p>Puffing must be done frequently, far more often than with a cigarette. Each cartridge designed for 80 puffs over 20 minutes of use. Patient does not need to inhale deeply to achieve an effect.</p>	<p>Dosing as Monotherapy</p> <ul style="list-style-type: none"> Minimum of 6 cartridges/day, up to 16/day <p>Taper as tolerated.</p>

(Continued)

TABLE 1. (Continued)

Medication	Pros/Cons	Comments	Dosing Recommendations
Bupropion SR	<p>Cons</p> <ul style="list-style-type: none"> ● Frequent use during the day required to obtain adequate nicotine levels ● May cause mouth or throat irritation <p>Pros</p> <ul style="list-style-type: none"> ● Easy to use ● Pill form ● Few side effects ● May be used in combination with NRT (nicotine patches, spray, gum and inhaler)* <p>Cons</p> <ul style="list-style-type: none"> ● Contraindicated with certain medical conditions and medications 	<p>The inhaler delivers nicotine to the oral mucosa, not the lung, and enters the body much more slowly than the nicotine in cigarettes.</p> <p>A slight risk of seizure (1:1000) is associated with use of this medication. Seizure risk should be assessed. Risk of seizure is increased if:</p> <ul style="list-style-type: none"> ● Personal history of seizures ● Significant head trauma/brain injury ● Anorexia nervosa or bulimia ● Concurrent use of medications that lower the seizure threshold 	<p>Start medication one week prior to the Target Quit Date (TQD):</p> <p>150 mg once daily for 3 days, then 150 mg twice daily for 4 days, then On TQD STOP SMOKING</p> <p>Continue at 150 mg BID 12 weeks, or longer if necessary. May stop abruptly; no need to taper. Take doses at least 8 hours apart.</p>
New Pharmacotherapies			
Nicotine Lozenge (OTC) 2 mg, 4 mg Flavors: Mint, Cherry	<p>Pros</p> <ul style="list-style-type: none"> ● Easy to use ● Delivers doses of nicotine approximately 25% higher than nicotine gum <p>Cons</p> <ul style="list-style-type: none"> ● Should not eat or drink 15 minutes before use or during use ● Should not be chewed or swallowed ● Nausea frequent (12-15%) 	<p>Efficacy and frequency of side-effects related to amount used</p> <p>Delivers nicotine through the lining of the mouth while the lozenge dissolves.</p>	<p>Dosing as Monotherapy</p> <p>Based on time to first cigarette of the day:</p> <ul style="list-style-type: none"> <30 minutes = 4 mg >30 minutes = 2 mg <p>Based on cigarettes/day (cpd)</p> <ul style="list-style-type: none"> >20 cpd: 4 mg <20 cpd: 2 mg <p>Initial dosing is 1-2 lozenges every 1-2 hours (minimum of 9/day)</p> <p>Taper as tolerated</p> <p>Take with food</p> <p>Start medication one week prior to the Target Quit Date (TQD)</p> <p>0.5 mg once daily × 3 days, then 0.5 mg twice daily × 4 days, then ON TQD STOP SMOKING AND</p> <p>Take 1.0 mg twice daily × 11 weeks</p> <p>If not smoking at the end of twelve weeks, may continue at 1.0 mg twice daily for an additional 12 weeks</p> <p>May stop abruptly. No need to taper.</p>
Varenicline (Rx only)	<p>Pros</p> <ul style="list-style-type: none"> ● Easy to use ● Pill form ● Generally well-tolerated ● No known drug interactions <p>Cons</p> <ul style="list-style-type: none"> ● Nausea is common 	<ul style="list-style-type: none"> ● Taking the medication with food and titrating the dose as directed will help decrease risk of nausea. ● Use with NRT may increase the risk for nausea. ● Dose must be adjusted if kidney function is impaired with CrCl < 30 mL/min. 	

OTC, over the counter; NRT, nicotine replacement therapy; Rx, prescription; CrCl, creatinine clearance.

*Some of the dosing recommendations are not contained in current product labeling information. Adapted from other sources.^{3,17,27}

TABLE 2. Second-line pharmacotherapies for the treatment of tobacco dependence

Medication	Pros/Cons	Comments	Dosing Recommendations
Nortriptyline (Rx only)	<p>Pros</p> <ul style="list-style-type: none"> ● Inexpensive ● Pill form ● May be used in combination with NRT (nicotine patches, nasal spray, gum, lozenge or inhaler)* <p>Cons</p> <ul style="list-style-type: none"> ● Second-line medication because of many potential side-effects 	<ul style="list-style-type: none"> ● Can cause: sedation; weight gain; dry mouth; constipation; difficulty urinating. ● Requires monitoring of electrocardiogram 	<p>Typical dosing is 25 mg/day increasing gradually to a target of 75–100 mg/day</p> <p>Treat for 12 weeks</p> <p>Start 10–28 days before target quit date (TQD)</p>
Clonidine (Rx only)	<p>Pros</p> <ul style="list-style-type: none"> ● Inexpensive ● Pill/patch form ● May be used in combination with NRT (nicotine patches, nasal spray, gum, lozenge or inhaler)* <p>Cons</p> <ul style="list-style-type: none"> ● Second-line medication because of many potential side-effects 	<ul style="list-style-type: none"> ● Can cause: dry mouth; drowsiness; dizziness; sedation; and constipation. ● Requires monitoring of blood pressure 	<p>Initial dosing is typically 0.10 mg by mouth twice per day or 0.10 mg/day transdermal. This can be increased by 0.10 mg/day per week if needed. Treat for 3 to 10 weeks.</p> <p>Start up to 3 days before quit date.</p>
Combination Nicotine Replacement Therapy (Rx only)	<p>Pros</p> <ul style="list-style-type: none"> ● Permits sustained levels of nicotine with rapid adjustment for acute needs ● More efficacious than monotherapy <p>Cons</p> <ul style="list-style-type: none"> ● May increase risk of nicotine toxicity ● Cost 	<p>Providing two types of delivery system, one passive and one active, appears to be more efficacious. Should be considered for those who have failed single therapy in the past and those considered highly tobacco dependent.</p> <p>Not an FDA-approved strategy.</p>	<p>Dose the patch as described. Prescribe 2 mg gum, 2 mg lozenge, nicotine inhaler or nicotine nasal spray on an as needed basis when acute withdrawal symptoms and urges to use tobacco occur. Adjust dose of patch if frequent use of other NRT. Goal is to minimize need for short-acting NRT dosing.</p>

NRT, nicotine replacement therapy; Rx, prescription; FDA, U.S. Food and Drug Administration.
 *Some of the dosing recommendations are not contained in current product labeling information.
 Adapted from other sources.^{3,17,27}

FIRST-LINE PHARMACOTHERAPIES

Nicotine Gum

Nicotine gum is a nicotine replacement therapy (NRT) that has been available for almost two decades. Nicotine gum is available over the counter (OTC) in both 2- and 4-mg doses and in a variety of flavors. The 4-mg gum has been shown to be more efficacious than the 2-mg gum in heavier smokers (≥ 20 cigarettes per day [cpd]).

Patients should be instructed to chew the gum until a tingling or peppery taste is detected and then “park it” in the cheek before chewing again. This process should be repeated for about 30 minutes per piece of gum. Patients should be instructed to avoid acidic beverages (e.g., colas, coffee) while using the gum because ionization of nicotine in an acidic environment decreases nicotine absorption.

The most common side effects of the nicotine gum are nausea, indigestion, sore gums, and mouth ulcers. Proper use can minimize symptoms.

Nicotine Patch

Nicotine patch therapy is the cornerstone of NRT. Nicotine patches are readily available OTC in doses of 7, 14, and 21 mg.⁴ Significant underreplacement of serum cotinine (i.e., nicotine metabolite) concentrations has been observed in moderate and heavy smokers receiving 22 mg/day (62% and 41% for 20 cpd smokers and 40 cpd smokers, respectively).⁵ Evidence suggests that higher dose nicotine patch therapy (i.e., >22 mg/day) may increase smoking abstinence rates compared with standard doses, and nicotine patches doses up to 63 mg/day have been shown to be safe in cigarette smokers.^{4,6}

As a rough guide, we recommend initial nicotine patch dosing based on the number of cigarettes smoked per day. For example, a patient who smokes 30 cpd could be started on a nicotine patch dose of 35 mg/day (21 mg/day + 14 mg/day). Clinical monitoring for nicotine withdrawal symptoms such as irritability, anxiety, frustration, loss of concentration, or cravings should dictate an increase in the patch dosing. Although the optimal length of nicotine patch treatment has not been established, most patients should use the nicotine patch for approximately 8 weeks, but it is safe to use longer if needed to maintain abstinence. Research trials have suggested that treatment of 8 weeks or less have been shown to be as efficacious as longer treatment periods. If the patient has not completely stopped smoking after 2 weeks, nicotine patch therapy may need to be discontinued, a new stop date selected, and a different dose (i.e., usually higher) of nicotine patch or combination therapy should be considered.

The most common side effect of the nicotine patch is local skin irritation (50%) but this is usually mild, does not require patch discontinuation and can be treated with topical OTC steroids. Patch site rotation to another site should be encouraged. Few patients have reactions that require discontinuation of patch therapy. Some patients will have vivid dreams, and if this is disturbing, the patch can be removed at night.

According to the USPHS guideline, the patch should be used with caution in patients with recent cardiovascular events (past 2 weeks), cardiac dysrhythmias, or accelerating angina. Data are available suggesting that the nicotine patch is not

associated with an increase in cardiovascular events in high-risk outpatients with cardiac disease.^{7,8} Our clinical experience suggests that NRT is safe even in this population of patients.

Nicotine Nasal Spray

The nasal spray delivers nicotine more rapidly than any of the other NRTs, but not as rapidly as cigarette smoking, and rapidly reduces withdrawal symptoms. Abuse liability has been a concern; however, only 15% to 20% patients report using it longer than recommended (i.e., 6–12 months) and only 5% in higher-than-recommended doses.³

Proper instruction on the use of this medication is important and patients should be instructed to spray against the lower nasal mucosa and not to sniff, swallow, or inhale. Most patients experience nasal airway and throat irritation and coughing that is moderate to severe in the first few days of medication use.⁹ Continued use of the product results in attenuation of these adverse effects as well as in a transient altered taste and smell that can also occur.

Nicotine Inhaler

The nicotine inhaler was designed to supplement nicotine while replacing the “oral, handling, and sensory reinforcements” of cigarette smoking, which may be important for some smokers.^{10,11} The inhaler has the appearance of a cigarette rod into which cartridges containing nicotine are placed. Once the cartridge is placed in the device, the membrane is punctured and a porous plug in the capsule delivers nicotine vapor through active puffing. The nicotine from the inhaler is absorbed through the mucosal membranes of the mouth and pharynx. Approximately 80 puffs over 20 minutes are needed to obtain 2 mg of nicotine. The nicotine from the inhaler is absorbed through the oral mucosa, so it is important to remind patients to refrain from the use of acidic beverages that would decrease nicotine absorption.

The most common side effects are local irritation in the mouth and throat, coughing, and rhinitis. These symptoms are mild and decrease with continued use.

Bupropion Sustained Release (SR)

Bupropion SR was the first non-nicotine medication approved by the FDA for the treatment of tobacco dependence. Bupropion SR is an antidepressant that inhibits the reuptake of dopamine and norepinephrine. Long-term treatment with bupropion SR may reduce or delay smoking relapse.¹² Bupropion SR has been consistently shown to be effective for the treatment of the broad population of smokers including those who have relapsed, smokers with comorbid psychiatric conditions, African Americans, women, and smokers with medical comorbidities.¹³ Bupropion SR can be used in combination with NRTs. Bupropion SR may attenuate weight gain among continuously abstinent smokers and may, therefore, be of particular use for smokers concerned about postcessation weight gain. Importantly, with short-term use, weight gain occurs after the medication is discontinued.¹⁴ All smokers attempting to stop should be encouraged to make appropriate modifications to their diet and to increase exercise.

Bupropion SR can be continued for 6 to 12 months if the risk of tobacco relapse is high. Bupropion SR is contra-

indicated in patients with a history of an eating disorder and seizures and among those who have recently used (past 2 weeks) a monoamine oxidase inhibitor (MAO-I). Among patients with a history of closed head trauma (CHT), CHT associated with loss of consciousness (LOC) in the past 5 years, LOC or amnesia 30 minutes or longer at any time, CHT resulting in skull fracture, or CHT with brain contusion and/or intracranial bleeding have a somewhat increased risk of seizures and thus have a relative contraindication for the use of bupropion SR.¹³

The most common side effects with the use of bupropion SR are dry mouth (10%) and insomnia. If insomnia is a problem, patients should be instructed to take the second dose in the late afternoon but always 8 hours after the first dose.

NEW PHARMACOTHERAPIES

Nicotine Lozenges

The nicotine lozenge (trade name Commit; GlaxoSmith-Kline, Philadelphia, PA) was developed based on the long history of safe oral mucosal delivery of nicotine and the desire among tobacco users for alternative NRT products for better esthetics, ease of use, and fewer limitations because of oral health (i.e., dental work, temporomandibular joint syndrome).¹⁵ Like the nicotine gum, the nicotine lozenge provides active self-dosing in response to cravings.^{16,17} The lozenge dissolves as a result of saliva bathing, physical abrasion, and manipulation in the oral cavity. The nicotine lozenge has low abuse liability.¹⁸

The nicotine lozenge is available in the 2- and 4-mg doses. The recommended dose for cigarette smokers is based on the time to first cigarette in the morning. The 4-mg strength is indicated for individuals whose first cigarette is within 30 minutes of waking, and the 2-mg strength is suggested for smokers whose first cigarette is more than 30 minutes after waking.

The efficacy of the 2- and 4-mg nicotine lozenges for smoking cessation has been demonstrated in a large clinical trial.¹⁷ The nicotine lozenge significantly reduces cravings and withdrawal. The most common side effects with the nicotine lozenge are headache, diarrhea, flatulence, heartburn, hiccups, and nausea.

Varenicline

Varenicline (trade name Chantix; Pfizer, New York, NY) is a partial nicotine agonist at the $\alpha 4\beta 2$ subtype of the nicotinic acetylcholine receptor. The partial agonist activity theoretically relieves nicotine withdrawal and craving while blocking the reinforcing effects of continued cigarette smoking.¹⁹

Two double-blind, randomized, placebo-controlled trials have been published assessing the efficacy of varenicline compared with placebo and bupropion SR for smoking cessation.^{19,20} The primary outcome was the continuous abstinence for the final 4 weeks (weeks 9–12) of 3 months of treatment. Continuous smoking abstinence rates from weeks 9 to 12 were 44% in the varenicline group compared with 30% in the bupropion SR group and 18% in the placebo group. This translates into a nearly fourfold increase in the odds of smoking abstinence with varenicline compared with

placebo and a nearly doubling of the odds of quitting with varenicline compared with bupropion SR at end of treatment. The continuous smoking abstinence rate from weeks 9 to 52 was 22% with varenicline and 8% with placebo. Bupropion SR had a 52-week continuous smoking abstinence rate of 16%, which was not significantly different from varenicline. Both studies demonstrated a gradually increasing 7-day point-prevalence abstinence rate from the target quit date through approximately weeks 6 to 8. A possible interpretation of this result is that quitting activity increased through a cumulative effect of varenicline over the course of several weeks after the target quit date. The results also demonstrated that craving, withdrawal symptoms, and smoking satisfaction were diminished in subjects receiving varenicline. Varenicline taken for 24 weeks has also been shown to increase smoking abstinence rates at 1 year compared to varenicline taken for 12 weeks followed by placebo for 12 weeks.²¹

The most common side effect of varenicline is nausea (29%), but it is mostly mild to moderate, and only 2.5% of the patients discontinued participation in the clinical trials due to this side effect.

SECOND-LINE PHARMACOTHERAPIES

Nortriptyline

Nortriptyline is a tricyclic antidepressant that has not been approved by the FDA for the treatment of tobacco dependence. Nortriptyline is associated with anticholinergic side effects at therapeutic doses, which limits its clinical utility. However, the efficacy of nortriptyline for smoking cessation has been established in several randomized clinical trials.²² Nortriptyline should be prescribed only after considering all the other first-line medications and newer pharmacotherapies.

Clonidine

Clonidine is used primarily as an antihypertensive medication and has been shown to be effective for increasing smoking-cessation rates.²³ It is associated with dose-dependent side effects such as dry mouth and sedation. Like nortriptyline, clonidine has not been approved by the FDA as a smoking-cessation medication and should be prescribed only after considering first-line medications and newer pharmacotherapies.

Combination Therapy

Although combination therapy with multiple nicotine replacement therapies (i.e., gum and patch) is not an FDA-approved strategy for treating tobacco dependence, it has been shown to be more effective than single-agent therapy. Combination NRT increases long-term smoking abstinence rates compared with single-agent therapy for the combination of nicotine patch and the 2-mg nicotine gum and nicotine patch and the nicotine nasal spray.^{24,25}

Combination NRT use provides patients with continuous, passive nicotine dosing with the nicotine patch and ad libitum dosing with gum, lozenge, inhaler, and/or nasal spray nicotine, allowing the user to control craving and withdrawal symptoms.²⁶ Combination therapy should be considered for

patients if their previous attempts to stop smoking with a single medication have been unsuccessful or if a patient experiences significant tobacco withdrawal symptoms with a single agent at standard doses.²⁷ Therapy dose and duration should be based on the patient's need for withdrawal symptom relief and for support of abstinence. The selection of NRT doses that can be taken ad libitum (nasal spray, inhaler, gum, and lozenge), if used in combination therapy, is generally lower compared with their use as monotherapy.

Treatment with bupropion SR alone or in combination with a nicotine patch results in significantly higher long-term smoking-cessation rates than use of either nicotine patch alone or placebo. Abstinence rates have been observed to be higher with combination therapy than with bupropion SR alone, although the difference was not statistically significant.²⁸

PREGNANCY

In pregnancy, the nicotine patch, nasal spray, gum, inhaler, and nortriptyline are FDA Class D medications. The nicotine patch, clonidine, and varenicline are Class C medications, and bupropion SR is a class B medication. According to a position statement by the American College of Obstetricians and Gynecologists: "the use of nicotine replacement products or other pharmaceuticals for smoking cessation aids during pregnancy have not been sufficiently evaluated to determine their efficacy or safety."²⁹ American College of Obstetricians and Gynecologists further recommends that medications should be considered if behavioral therapies have failed. If used, medications should be short acting, and if a nicotine patch is used, it should be removed at night. We recommend that these agents be used during pregnancy after discussion with the woman about the potential risks and benefits of use and the assistance of and supervision by the woman's physician.

SMOKING CESSATION AND LUNG CANCER

Smoking cessation remains an important clinical consideration for patients diagnosed with lung cancer because continued smoking has a negative impact on survival and quality of life. Cigarette smoking has been associated with decreased overall survival among patients receiving treatment for non-small cell lung cancer,^{30–35} small cell lung cancer (SCLC),³⁶ and all cell types.^{37,38} In SCLC patients receiving chemotherapy, continued smoking has been associated with poor prognosis.³⁹ Smoking cessation has been associated with a decreased risk of the development of a second primary tumor after therapy for SCLC.^{40–42} We have also observed that continued smoking is associated with a decreased quality of life among patients with a new lung cancer diagnosis.⁴³ For lung cancer patients needing surgery, smoking cessation preoperatively may reduce their risk of postoperative morbidity.⁴⁴

The diagnosis of lung cancer can serve as a "teachable moment" to promote a health behavior change in patients and motivate an attempt at tobacco abstinence.⁴⁵ Unfortunately, cancer is underused as a teachable moment.⁴⁶ Clinicians should inform their lung cancer patients of the negative impact of continued smoking on survival and quality of life and provide them with appropriate pharmacotherapy and counseling.

CLINICAL DECISION-MAKING

Limitations exist to standard or fixed-dose treatment regimens with most drugs in clinical practice, necessitating the use of clinical knowledge of pharmacotherapy to individualize drug doses. The nicotine patch and bupropion SR should be the "floor" upon which to build a pharmacotherapeutic approach. The use of either as a stand-alone in treating patients with mild tobacco dependence or those who relapse is recommended. Depending on the individual patient, we use the nicotine patch in combination with bupropion SR with shorter acting NRTs for symptom control. For patients with more severe tobacco dependence, we use combination therapy with three or more products simultaneously. No pharmacologic rationale supports the concomitant use of varenicline and NRT, so varenicline can be used as a monotherapy or in combination with bupropion SR.⁴⁷

CONCLUSIONS

Globally, tobacco dependence is one of the most preventable causes of death and disability and is the most important causal factor for lung cancer in men and women. Tobacco dependence is a chronic disease characterized by relapse and remission. A variety of safe and effective pharmacotherapies for the treatment of tobacco dependence exists. All smokers who are motivated to quit should be treated with appropriate behavioral and pharmacologic therapy. The diagnosis of lung cancer should be used as a teachable moment to promote an attempt at tobacco abstinence. Treating smokers who have failed to achieve permanent abstinence with a variety of agents and in different combinations will increase the likelihood of success.

REFERENCES

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993;54:594–606.
2. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
3. Fiore MC, Bailey WC, Cohen SJ. Treating Tobacco Use and Dependence. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, 2000.
4. Silagy C, Lancaster T, Stead L, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2004;CD000146.
5. Dale LC, Hurt RD, Offord KP, et al. High-dose nicotine patch therapy. Percentage of replacement and smoking cessation. *JAMA* 1995;274:1353–1358.
6. Benowitz NL, Zevin S, Jacob P. 3rd. Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. *J Pharmacol Exp Ther* 1998;287:958–962.
7. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996;335:1792–1798.
8. Rigotti NA, Arnsten JH, McKool KM, et al. The use of nicotine-replacement therapy by hospitalized smokers. *Am J Prev Med* 1999 Nov.;17:255–259.
9. Hurt RD, Dale LC, Croghan GA, et al. Nicotine nasal spray for smoking cessation: pattern of use, side effects, relief of withdrawal symptoms, and cotinine levels. *Mayo Clin Proc* 1998;73:118–125.
10. Tonnesen P, Norregaard J, Mikkelsen K, et al. A double-blind trial of a nicotine inhaler for smoking cessation. *JAMA* 1993;269:1268–1271.
11. Rose JE. The role of upper airway stimulation in smoking. *Prog Clin Biol Res* 1988;261:95–106.
12. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. a randomized, controlled trial. *Ann Intern Med* 2001;135:423–433.

13. Hays JT, Ebbert JO. Bupropion for the treatment of tobacco dependence: guidelines for balancing risks and benefits. *CNS Drugs* 2003;17:71–83.
14. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195–1202.
15. Choi JH, Dresler CM, Norton MR, et al. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tob Res* 2003;5:635–644.
16. West R, Shiffman S. Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. *Psychopharmacology (Berl)* 2001;155:115–122.
17. Shiffman S, Dresler CM, Hajek P, et al. Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 2002;162:1267–1276.
18. Houtsmuller EJ, Henningfield JE, Stitzer ML. Subjective effects of the nicotine lozenge: assessment of abuse liability. *Psychopharmacology (Berl)* 2003;167:20–27.
19. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:56–63.
20. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47–55.
21. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006;296:64–71.
22. Wagena EJ, Knipschild P, Zeegers MP. Should nortriptyline be used as a first-line aid to help smokers quit? Results from a systematic review and meta-analysis. *Addiction* 2005;100:317–326.
23. Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. *Cochrane Database Syst Rev* 2004;3:CD000058.
24. Kornitzer M, Boutsen M, Dramaix M, et al. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med* 1995;24:41–47.
25. Blondal T, Gudmundsson LJ, Olafsdottir I, et al. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ* 1999;318:285–288.
26. Stapleton J. Commentary: Progress on nicotine replacement therapy for smokers. *BMJ* 1999;318:289.
27. Dale LC, Ebbert JO, Hays JT, et al. Treatment of nicotine dependence. *Mayo Clin Proc* 2000;75:1311–1316.
28. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685–691.
29. ACOG committee opinion. Number 316, October 2005. Smoking cessation during pregnancy. *Obstet Gynecol* 2005;106:883–888.
30. [Factors influencing long term survival after resection of bronchogenic carcinoma; an analysis of 1,118 cases]. *Zhonghua Yi Xue Za Zhi* 1974;191:682–686.
31. Fujisawa T, Iizasa T, Saitoh Y, et al. Smoking before surgery predicts poor long-term survival in patients with stage I non-small-cell lung carcinomas. *J Clin Oncol* 1999;17:2086–2091.
32. Martins SJ, Pereira JR. Clinical factors and prognosis in non-small cell lung cancer. *Am J Clin Oncol* 1999;22:453–457.
33. Sioris T, Husgafvel-Pursiainen K, Karjalainen A, et al. Survival in operable non-small-cell lung cancer: role of p53 mutations, tobacco smoking and asbestos exposure. *Int J Cancer* 2000;86:590–594.
34. Sobue T, Suzuki T, Fujimoto I, et al. Prognostic factors for surgically treated lung adenocarcinoma patients, with special reference to smoking habit. *Jpn J Cancer Res* 1991;82:33–39.
35. Tammemagi MC, McLaughlin JR, Mullen JB, et al. A study of smoking, p53 tumor suppressor gene alterations and non-small cell lung cancer. *Ann Epidemiol* 2000;10:176–185.
36. Wolf M, Holle R, Hans K, et al. Analysis of prognostic factors in 766 patients with small cell lung cancer (SCLC): the role of sex as a predictor for survival. *Br J Cancer*. 1991;63:986–992.
37. Hinds MW, Yang HY, Stemmermann G, et al. Smoking history and lung cancer survival in women. *J Natl Cancer Inst* 1982;68:395–399.
38. Xavier F, Henn L, Oliveira M, et al. Smoking and its relation to the histological type, survival, and prognosis among patients with primary lung cancer. *Rev Paul Med* 1996;114:1298–1302.
39. Johnston-Early A, Cohen MH, Minna JD, et al. Smoking abstinence and small cell lung cancer survival. *JAMA* 1980;244:2175–2179.
40. Richardson GE, Tucker MA, Venzon DJ, et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. *Ann Intern Med* 1993;119:383–390.
41. Kawahara M, Ushijima S, Kamimori T, et al. Second primary tumours in more than 2-year disease-free survivors of small-cell lung cancer in Japan: the role of smoking cessation. *Br J Cancer* 1998;78:409–412.
42. Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. Lung Cancer Working Cadre. *J Natl Cancer Inst* 1997;89:1782–1788.
43. Garces YI, Yang P, Parkinson J, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. *Chest* 2004;126:1733–1741.
44. Moller AM, Villebro N, Pedersen T, et al. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet* 2002;359:114–117.
45. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. *Health Educ Res* 2003;18:156–170.
46. Gritz ER, Fingeret MC, Vidrine DJ, et al. Successes and failures of the teachable moment: smoking cessation in cancer patients. *Cancer* 2006;106:17–27.
47. Hurt RD. Treating tobacco dependence in the medical setting: best practices. Presented at VA in the Vanguard: Building on Success in Smoking Cessation, San Francisco, CA, 2004.