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Smoking Cessation for the Busy Clinician

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OVERVIEW

Smoking remains the leading cause of preventable death in the United States, negatively impacting individuals at all stages of life - unborn babies, infants, children, adolescents, adults, and seniors.¹ Although smoking harms nearly every organ of the body, causing many diseases and reducing the health of smokers in general (Inset, page 2), more than one in five adult Americans smoke either every day or some days.² The reductions in the prevalence of adult smoking that we observed throughout much of the 1980s and 1990s have leveled off in recent years, and teen smoking continues to be pervasive - in 2006, 21.6% of 12th graders (22.4% of males and 20.1% of females) had smoked one or more cigarettes in the past 30 days.³ In addition to the well-established health consequences of active smoking, involuntary exposure to secondhand smoke contributes to the death of an estimated 50,000 Americans annually.⁴ Tobacco dependence is a chronic disease that leads to chronic illness and contributes to the death of at least half of those who use tobacco.⁵

The good news is that 70% of patients who smoke want to quit.⁶ Yet for most, the process of quitting is characterized by a series of quit attempts and subsequent relapses - on average, former smokers report 11 quit attempts over a period of almost 19 years before quitting for good.⁷ Effective treatments are available, but few smokers use them, and more than 95% of quit attempts end in relapse. In general, patients who get help with quitting - behavioral, pharmacologic, or both - can experience quit rates of around 20% (at least 6 months after quitting).⁸

The Bottom Line

- Cigarette smoking is the single most preventable cause of premature death in the U.S. Each year, more than 440,000 Americans die from smoking-related illnesses. One in every five deaths in the U.S. is smoking related.¹
- Effective medications are available to help patients quit smoking. Unless medically contraindicated, all patients who are trying to quit should be encouraged to use one or more approved medications. Drug therapy should be combined with behavioral counseling to further increase patients' chances for success.
- FDA-approved first-line medications for smoking cessation include the nicotine patch, nicotine gum, nicotine lozenge, nicotine nasal spray, nicotine oral inhaler, sustained-release bupropion, and varenicline.

What You Can Do

- For the busy clinician, apply the *Ask, Advise, Refer* method. *Ask* about tobacco use, *Advise* tobacco users to quit, and *Refer* tobacco users to other resources for further assistance.

Continuing Education Objectives

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After reading this article, the clinician should be able to:

- Apply the *Ask, Advise, Refer* method promoting tobacco cessation with patients.
- Assist patients with smoking cessation product selection and dosing. Discuss adverse effects for the seven FDA-approved medications for tobacco cessation.
- Provide instruction on the use of approved medications for tobacco cessation.

Approaches to Treatment

In contrast to two decades ago, tobacco users are now able to select from many treatment options for quitting. It is well established that (a) the use of approved medications for cessation at least doubles the odds of quitting, and (b) medications should be coupled with approaches that promote behavioral change, such as advice from a healthcare provider.⁸⁻¹² A meta-analysis of 29 studies determined that patients who receive a

Health Consequences of Smoking¹

Cardiovascular disease: coronary heart disease, cerebrovascular disease, peripheral vascular disease, abdominal aortic aneurysm, sudden death, myocardial infarction

Cancer: lung, oral cavity, pharynx, larynx, esophagus, bladder, stomach, cervix, kidney, pancreas, leukemia (acute myeloid leukemia)

Respiratory diseases: asthma (poor control), chronic obstructive pulmonary disease (COPD), pneumonia, cough, dyspnea, excessive phlegm, wheezing

Reproductive effects: infertility, low-birth weight, pregnancy complications (premature rupture of membranes, placenta previa, placental abruption, preterm delivery, fetal death), sudden infant death syndrome

Other effects: osteoporosis, cataracts, peptic ulcer disease, periodontitis, postoperative complications (delayed wound healing, wound infections, respiratory complications), otitis media, increased risk of cognitive decline in the elderly

tobacco cessation intervention from a non-physician clinician or a physician are about twice as likely to quit (for ≥ 5 months) compared with patients who do not receive an intervention from a clinician.⁸ Although more intensive interventions yield higher quit rates, even brief advice - as few as three minutes - has been shown to have an important impact on patients' likelihood of quitting.⁸ Even the busiest of clinicians can have an important role in initiating the quitting process for patients who smoke.

Tobacco Cessation

Tobacco Dependence and Withdrawal

Tobacco products are carefully-engineered formulations, designed to optimize the delivery of nicotine, a chemical that meets the criteria for an addictive substance:

(1) nicotine induces psychoactive effects, (2) nicotine is used in a highly controlled or compulsive manner, and (3) behavioral patterns of tobacco use are reinforced by the pharmacological effects of nicotine.¹³ The behavioral and pharmacologic processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine.¹³

Nicotine is readily absorbed across the respiratory tract epithelium, buccal mucosa (cheek), and skin. While most U.S. cigarettes contain between 7-13 mg of nicotine¹⁴, a smoker, on average, absorbs about 1 mg of nicotine per cigarette.¹⁵ After inhalation, nicotine reaches the brain in about 10-19 seconds,¹⁶ resulting in the rapid onset of behaviorally-reinforcing effects on the nervous system, including pleasure, relief of anxiety, improved repetitive task performance, improved memory, mood modulation, and skeletal muscle relaxation.¹⁶ These positive effects give way to negative withdrawal effects in the absence of nicotine among dependent tobacco users. Withdrawal symptoms include anger, irritability, anxiety, difficulty concentrating, drowsiness, fatigue, hunger/weight gain, impatience, and restlessness. These symptoms tend to peak 24-48 hours after cessation and gradually diminish over 2-4 weeks, although cravings for tobacco can persist for years. Weight gain is common but typically does not exceed 10 pounds and may be delayed by the use of bupropion and some forms of nicotine replacement therapy (e.g., gum and lozenge).^{8,17}

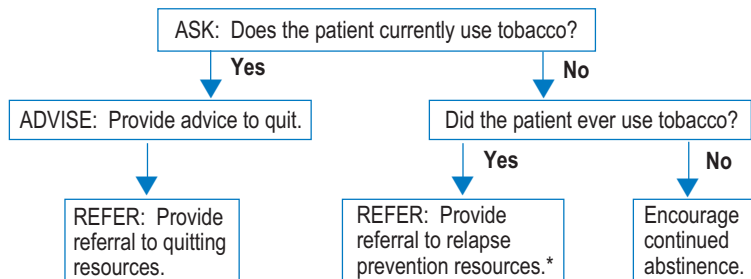
Helping Patients to Quit

The Clinical Practice Guideline for Treating Tobacco Use and Dependence⁸ recommends five key components of comprehensive tobacco cessation coun-

seling. Known as the 5 A's, these are: (1) **Ask** all patients whether they use tobacco, (2) **Advise** all tobacco users to quit, (3) **Assess** tobacco users' readiness to quit, (4) **Assist** patients with the quitting process, and (5) **Arrange** follow-up care. When time, logistics, or lack of expertise are not conducive to providing more comprehensive tobacco cessation counseling, clinicians are encouraged to take 30 seconds to apply an abbreviated protocol: **Ask** about tobacco use, **Advise** tobacco users to quit, and **Refer** patients to other resources (Figure 1). Even the busiest of clinicians can have an important role in initiating the quitting process for patients who smoke.

Ask: Because smoking interacts with many drugs¹⁹ (Table 3, page 9) and contributes to a wide variety of medical conditions, an important element of any drug history is to identify tobacco users. Tobacco use status

Figure 1. Ask, Advise, Refer Method for Tobacco Cessation Counseling¹⁸



*Relapse prevention interventions are not necessary for patients who have not smoked for many years and are not at risk for re-initiation.

(current, former, never) and level of use (e.g., number of cigarettes smoked per day) should be documented in the medical record and/or patient profile. Suggested phrases include: “Do you smoke or use any type of tobacco? I take the time to talk to all of my patients about tobacco use, because it helps me provide you with the best care that I can,” or “Smoking interacts with many drugs. It’s important to know whether you smoke, so we can adjust your medicines if necessary.” Failure to ask patients about tobacco use might imply that tobacco use is acceptable or that quitting smoking is not important.

Advise: Providers should advise all tobacco users to quit. The advice should be clear, strong, personalized, and delivered in a tone conveying concern for the patient’s health and a commitment to help with quitting. Messages can be personalized by linking the importance of quitting to the individual’s current health status, medication use, motivation to quit, tobacco’s social and economic costs, and/or the effects of their tobacco use on others. One suggested phrase to provide advice is “Quitting is the single most important thing you can do to improve your health now and in the future. I strongly recommend that you quit as soon as possible, and I can help.”

Refer: Quitting tobacco often requires a multi-component treatment plan involving both drug therapy and behavioral therapy. Table 1 provide tips for clinicians to use when counseling patients about tobacco cessation. While busy clinicians can prescribe medications with minimal time commitment, behavioral therapy can require significant time. In the absence of time or expertise for providing comprehensive behavioral counseling, patients can be referred to other resources. Several resources are listed in the inset on the *Patient Connection* insert. The following phrases can be used by clinicians to provide referrals to patients: “Consider calling the national quitline number, 1-800-QUIT-NOW. Smoking cessation specialists will give you personalized help, by telephone, at no cost”, or “The medications for quitting include access to a free behavior change program. To maximize your chances of quitting for good, I strongly recommend that you enroll in the program,” or “Here’s a list of resources to consider. Let’s review the list and determine what would be best for you.”



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. Quitlines are capable of serving a broad, diverse population, reaching patients who might otherwise have limited access to medical care because of geographic lo-

Table 1. Counseling Tips

- **What type and amount of tobacco used?**
Necessary for determining NRT dosing and for understanding the patient’s level of nicotine addiction.
- **Review previous quit attempts—What worked, what didn’t? Why or why not?**
Assess adequacy of dose and adherence with previous treatment regimens. Understand patient’s beliefs about the various medications for quitting before recommending therapy. Help patient identify reasons for the last relapse and techniques to avoid it.
- **How much confidence do you have in your ability to quit?**
Patients must believe that they are able to quit. If not, failure is likely. Patients should be encouraged to quit at a later date when they are ready.
- **Discuss medication options and consider potential contraindications to drug therapy.**
Consider patient’s desire to use a medication for quitting. Encourage use of medication, particularly for patients who have been unsuccessful in prior quit attempts. Present pros and cons of different options, ruling out medications that are medically contraindicated or otherwise not acceptable to a patient.
- **Counsel on appropriate use of medication(s).**
For patients who are ready to quit and have selected a medication, provide instruction for proper use, emphasizing the importance of adherence with the treatment regimen. Instruct patients taking bupropion SR or varenicline to start treatment before the quit date.
- **Strongly advise patient to seek additional professional advice, and provide a referral (tobacco quitline, local group program, web-based program, etc.) to address the behavioral aspects of quitting:**
Reasons and motivations for quitting, routines and triggers associated with tobacco use, selecting a quit date, coping strategies, social support, withdrawal symptoms and cravings, weight gain concerns, ongoing support for quitting (relapse prevention).
- **Commend patients for deciding to quit.** Educate them about the importance of receiving follow-up care.

cation or lack of insurance or financial resources. Studies have shown that patients who receive quitline counseling are twice as likely to quit compared with patients who quit on their own.²⁰

Drug Therapy

FDA-approved first-line agents for smoking cessation include five dosage forms of nicotine replacement therapy (NRT), sustained-release bupropion and

Table 2. FDA-Approved Medications for Smoking Cessation

	Nicotine Gum ^{OTC}	Nicotine Lozenge ^{OTC}	Nicotine Oral Inhaler ^{Rx}	Nicotrol NS ^{Rx}
Products	<i>Nicorette</i> [®] , generic • 2 mg, 4 mg (regular, mint, orange, FreshMint, Fruit Chill)	<i>Commit</i> [™] , generic • 2 mg, 4 mg (mint, cherry)	<i>Nicotrol</i> [®] Inhaler • 10 mg cartridge delivers 4 mg inhaled nicotine vapor	<i>Nicotrol NS</i> [®] • Metered spray • 0.5 mg nicotine aqueous nicotine
Dosing #	< 25 cigarettes/day: 2mg ≥ 25 cigarettes/day: 4mg Wk 1-6: 1 piece q 1-2 h Wk 7-9: 1 piece q 2-4 h Wk 10-12: 1 piece q 4-8 h	1st cigarette >30 minutes after waking: 2 mg 1st cigarette ≤30 minutes after waking: 4 mg Wk 1-6: 1 piece q 1-2 h Wk 7-9: 1 piece q 2-4 h Wk 10-12: 1 piece q 4-8 h	6-16 cartridges/day; about 1 cartridge every 1-2 hrs Duration: up to 6 months; begin using at least 6 cartridges daily (max 16 daily) for 3-12 weeks. Then taper the daily number of cartridges used over an additional 6-12 weeks. There is no single best method for dose tapering.	1 to 2 doses/hour 1 dose = 2 sprays Duration: 3-6 months at least 8 doses daily for 3-12 weeks. Then taper doses used over an additional 6-12 weeks. There is no single best method for tapering the dose.
Adverse Effects	<ul style="list-style-type: none"> • mouth/jaw soreness • hypersalivation • linked with incorrect chewing technique: <ul style="list-style-type: none"> - lightheadedness - nausea/vomiting - throat & mouth irritation 	<ul style="list-style-type: none"> • nausea • cough • headache • insomnia 	<ul style="list-style-type: none"> • mouth/throat irritation • rhinitis • unpleasant taste • headache 	<ul style="list-style-type: none"> • cough • dyspepsia • hiccups
Advantages	<ul style="list-style-type: none"> • might satisfy oral craving • might delay weight gain • patients can titrate therapy to manage withdrawal symptoms 	<ul style="list-style-type: none"> • might satisfy oral craving • might delay weight gain • patients can titrate therapy to manage withdrawal symptoms 	<ul style="list-style-type: none"> • patients can titrate therapy to manage withdrawal symptoms 	<ul style="list-style-type: none"> • patients can titrate therapy to manage withdrawal symptoms
Cost per day*	2 mg: \$3.28 - \$6.57 (9 pieces) 4 mg: \$4.31 - \$6.57 (9 pieces)	2 mg: \$3.66 - \$5.26 (9 pieces) 4 mg: \$3.66 - \$5.26 (9 pieces)	\$5.29 (6 cartridges)	\$3.28 (8 doses)

OTC = over-the-counter Rx = prescription product ** Transdermal patch formulations previously marketed, but no longer available: *Nicotrol*/5 mg, 10 mg, 15 mg delivered over 24 hours. Duration of therapy for smoking cessation is 3-6 months; however, some people may benefit from a prolonged (> 6 months) course of therapy. The decision to extend treatment to prevent relapse should be individualized. * Average Wholesale Price from 2007 Drug Topics Redbook. Montvale, NJ: Medical Economics Company, Inc.; 2007. **Reprinted with permission from reference 21, copyright 2007 by American Medical Association.**

varenicline. In general, the daily costs of these medications are comparable to the daily cost of smoking (Table 2).²¹ The available NRT products and bupropion exhibit comparable efficacy, approximately doubling the quit rate compared with placebo.^{8,22} Long-term quit rates (≥ 6 months) have been 8-12 percentage points greater with these products than with placebo. Limited evidence suggests that varenicline is somewhat more effective.

Selection of a specific drug for smoking cessation should be individualized. Factors to consider include patient preference, previous experience with medications, current medical conditions, medication compliance issues, and out-of-pocket cost of treatment.

Nicotine Replacement Therapy (NRT)

NRT formulations currently available in the U.S. are the nicotine gum, lozenge, transdermal patch, nasal spray, and oral inhaler. Table 2 presents the various products, dosing, adverse effects, advantages, and daily costs of treatment.²¹

The use of NRT helps patients with quitting by reducing nicotine withdrawal symptoms while they focus on the behavioral and psychological aspects of smoking. Additionally, because NRT formulations deliver nicotine more slowly and at lower levels, patients become less accustomed to the nearly immediate, reinforcing effects of inhaled tobacco. Before beginning NRT, patients should completely stop using all forms of tobacco.

Contrary to popular belief, NRT is not contraindicated in patients with a history of cardiovascular disease. While nicotine can increase the heart rate and blood pressure and is a coronary vasoconstrictor, randomized, controlled trials have found no significant increase in the incidence of cardiovascular events or death among patients with cardiovascular disease receiving NRT when compared to placebo.²³⁻²⁵ However, because these 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

ications for Smoking Cessation

Nasal Spray ^{Rx}	Nicotine Transdermal Patch ^{Rx/OTC **}	Bupropion SR ^{Rx}	Varenicline ^{Rx}
<p>100 doses/bottle in 50 µL (1 spray) in solution</p>	<p><i>Nicoderm CQ</i>[®], generic^{OTC}</p> <ul style="list-style-type: none"> • 21 mg, 14 mg, 7 mg • 24-hour release 	<p><i>Zyban</i>[®], generic 150 mg sustained-release tablet</p>	<p><i>Chantix</i>[®] 0.5 mg, 1 mg tablet</p>
<p>1 spray (one in each nostril) 2-4 months; begin using at 1 spray daily (max 40 daily) for 6-8 weeks; then reduce the daily number of sprays over the daily number of weeks by an additional 4-6 sprays; no single best method of dosing.</p>	<p>>10 cigarettes/day: 21 mg/day x 4-6 weeks[†] 14 mg/day x 2 weeks 7 mg/day x 2 weeks</p> <p>≤10 cigarettes/day: 14 mg/day x 6 weeks 7 mg/day x 2 weeks</p>	<p>150 mg po q am x 3 days then increase to 150 mg bid x 7-12 weeks</p>	<p>Days 1-3: 0.5 mg po q am then Days 4-7: 0.5 mg po bid then Weeks 2-12: 1 mg po bid</p>
<p>throat peppery (irritation) cough headache</p>	<ul style="list-style-type: none"> • local skin reactions (erythema, pruritus, burning) • headache • sleep disturbances (insomnia) or abnormal / vivid dreams (associated with nocturnal nicotine absorption) 	<ul style="list-style-type: none"> • insomnia • nervousness/ difficulty concentrating • dry mouth • rash • constipation • seizures (risk is 1/1000) 	<ul style="list-style-type: none"> • nausea • constipation • flatulence • sleep disturbances (insomnia, abnormal dreams) • vomiting
<p>substitute therapy withdrawal symptoms</p>	<ul style="list-style-type: none"> • provides consistent nicotine levels over 24 hrs • easy to use and conceal • once daily dosing linked with fewer compliance issues 	<ul style="list-style-type: none"> • easy to use; oral formulation may have fewer compliance problems • might be beneficial in patients with depression • might delay weight gain 	<ul style="list-style-type: none"> • easy to use; oral formulation may have fewer compliance problems • offers a new mechanism of action for patients who have failed other agents
<p>0.67 (100 doses)</p>	<p>\$1.90 - \$3.89 (1 patch)</p>	<p>\$3.62-\$6.04 (2 tablets)</p>	<p>\$4.00-\$4.22 (2 tablets)</p>

delivered over 16 hours and generic patch (formerly *Prostep*) 11 mg and 22 mg delivered over 24 hours. # In general, the recommended duration of treatment with medications for smoking cessation must be determined on a case by case basis. [†] Generic patches recommend 4 weeks at Step 1, while *NicoDerm CQ* recommends 6 weeks.
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(within 2 weeks) postmyocardial infarction period, those with serious arrhythmias, and those with serious or worsening angina, due to a lack of safety data.⁸ 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.²⁶⁻²⁹

Other conditions in which NRT should be used with caution include pregnancy and lactation. Animal studies suggest nicotine is harmful to the developing fetus and prescription formulations of nicotine are classified by the FDA as pregnancy category D agents. Despite these concerns, most experts believe the risks of NRT in pregnant or nursing women are small relative to the risks of continued smoking because the exposure to nicotine is significantly lower and the baby is not exposed to other toxins in tobacco smoke (e.g., carbon monoxide, heavy metals, carcinogens).³⁰

Nicotine Polacrilex Gum

Nicotine polacrilex gum (*Nicorette*[®], others) is a resin

complex of nicotine and polacrilin in a sugar free chewing gum base. The gum contains buffering agents (sodium carbonate, sodium bicarbonate) to increase salivary pH, thereby enhancing absorption of nicotine across the buccal mucosa. Nicotine plasma levels peak about 30 minutes after chewing a single piece of gum, then slowly decline over 2-3 hours. Use of nicotine gum is contraindicated in patients with active temporomandibular joint disease.

Nicotine Polacrilex Lozenge

The nicotine polacrilex lozenge (*Commit*[™], others) is a resin complex of nicotine and polacrilin in a sugar-free, light mint- or cherry flavored lozenge that is intended to be consumed like hard candy or a medicinal lozenge (e.g., sucked and moved from side to side in the mouth until fully dissolved). Because the nicotine lozenge dissolves completely, it delivers about 25% more nicotine than does an equivalent dose of nicotine gum.³¹ Like nicotine gum, the lozenge contains buffering agents (so-

dium carbonate and potassium bicarbonate) to increase salivary pH and enhance buccal absorption of nicotine. Peak nicotine concentrations with the lozenge are achieved after 30 to 60 minutes of use.

Unlike other forms of NRT, where dosing is determined by the number of cigarettes smoked per day, the recommended dosage of the nicotine lozenge is based on the time-to-first-cigarette of the day. Individuals who smoke their first cigarette within 30 minutes of waking are considered to be more highly dependent necessitating the use of the 4 mg lozenge; patients who smoke their first cigarette more than 30 minutes after waking are to receive the 2 mg lozenge.

Transdermal Nicotine Patch

Transdermal patch nicotine formulations (*Nicoderm*[®] CQ, others) consist of an impermeable surface layer, a nicotine reservoir, an adhesive layer, and a removable protective liner. While the transdermal delivery technology varies by manufacturer, nicotine in the patch is well absorbed across the skin. Plasma nicotine concentrations rise slowly over 1-4 hours and peak within 3-12 hours following application.³² The currently marketed transdermal formulations deliver nicotine continuously over 24 hours and nicotine blood levels fluctuate less than do those achieved with tobacco products or other NRT formulations. The nicotine patch should not be used in patients with underlying skin disorders (e.g., eczema, psoriasis, atopic dermatitis) as these individuals are more likely to experience skin irritation.

Nicotine Nasal Spray

The nicotine nasal spray (*Nicotrol*[®] NS) is an aqueous solution of nicotine for administration to the nasal mucosa. Plasma nicotine levels following administration rise rapidly and generally peak within 5-15 minutes. For best results, patients should be encouraged to use at least the recommended minimum of 8 doses per day.

During the first week of use, most patients will experience a hot, peppery feeling in the back of the throat or nose, sneezing, coughing, watery eyes, or runny nose. Because these side effects subside over time, patients should be advised not to stop using the medication. This product is not recommended for patients with known chronic nasal disorders (allergic rhinitis, polyps, sinusitis) or individuals with severe reactive airway disease, because bronchospasm has been reported in patients with asthma. Due to its faster onset of action, capacity for self titration, and rapid fluctuations in nicotine levels, the nasal spray has the highest likelihood for developing dependence among the NRT products.

Nicotine Oral Inhaler

The nicotine inhaler (*Nicotrol*[®] Inhaler) consists of a plastic mouthpiece and cartridge that delivers nicotine as an inhaled vapor from a porous plug containing nicotine. When puffed, the nicotine is vaporized and absorbed across the mouth and throat mucosa (not in the lungs). Peak plasma nicotine concentrations are achieved after 30 to 45 minutes of use and then slowly decline. The inhaler should be used with caution in patients with underlying severe reactive airway disease (asthma, chronic obstructive pulmonary disease) because the nicotine vapor may be irritating and provoke bronchospasm.

Bupropion Sustained-Release (SR)

Bupropion SR (*Zyban*[®]) is hypothesized to promote smoking cessation by blocking the reuptake of dopamine and norepinephrine in the central nervous system; and possibly by acting as a nicotine receptor blocker. These neurochemical effects are believed to modulate the dopamine reward pathway and reduce cravings for nicotine and symptoms of withdrawal.⁸

Seizures are a dose-related toxicity linked with bupropion therapy. Bupropion is contraindicated in patients with active seizure disorders (i.e., taking anti-seizure medication) and those who take other forms of bupropion (e.g., *Wellbutrin*[®]). Bupropion is also contraindicated in patients with anorexia or bulimia nervosa and in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines) due to the increased potential for seizures in these populations. The concurrent administration of bupropion and a monoamine oxidase (MAO) inhibitor is contraindicated and at least 14 days should elapse between stopping an MAO inhibitor and starting bupropion therapy.³³ Bupropion should be used with extreme caution in patients with a history of seizure, cranial trauma, patients taking medications known to lower the seizure threshold (e.g., antipsychotics, antidepressants) and those with severe hepatic cirrhosis. Bupropion is classified as a pregnancy category C drug, and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.³³ For patients experiencing side effects with 300mg/day some evidence suggests 150mg/day is better tolerated, with comparable long-term efficacy.³⁴

Varenicline

Varenicline (*Chantix*[®]), a partial agonist selective for a specific nicotine receptor subtype, was approved in 2006 for use as an aid to smoking cessation.³⁵ The drug's efficacy is believed to be the result of sustained, low-level agonist activity at the receptor site, combined with competitive blockade of nicotine binding. The partial agonist activity modestly stimulates receptors, leading to

increased dopamine levels that reduce nicotine withdrawal symptoms. By blocking the binding of nicotine to receptors in the central nervous system, varenicline inhibits the surge of dopamine release that occurs immediately following inhalation of tobacco smoke. This effect may help prevent relapse by reducing the pleasure linked with smoking.³⁶ Evidence suggests that individuals taking varenicline are about 3 times more likely to successfully quit smoking than persons taking a placebo. Limited evidence suggests persons treated with varenicline are 66% more likely to remain abstinent at 1 year compared with bupropion-treated individuals. Varenicline should be started 1 week before the patient stops smoking. During the first week of therapy, the dosage is gradually increased to minimize nausea and insomnia. Nausea is the most common adverse effect of this medication and lessens with continued use. The recommended treatment duration is 12 weeks. One clinical trial supports continuing use for an additional 12 weeks to prevent relapse; however, additional studies are needed to confirm the effectiveness of this strategy.

Varenicline is classified as a pregnancy category C drug, and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.³⁵

Combination Therapy

While the use of FDA-approved medications approximately double the likelihood of successfully quit smoking, data from clinical trials suggest that only 15–25% of patients remain abstinent for greater than six months.^{22,34,37} Given these low success rates, and because plasma levels of nicotine achieved with standard doses of NRT are generally much lower than those attained with regular smoking, investigators have explored the use of combination therapy.

One approach involves the use of a long-acting formulation of NRT (transdermal patch) in combination with a short-acting formulation (gum, lozenge, oral inhaler, or nasal spray). The long-acting formulation, which delivers relatively constant levels of nicotine, is used to prevent the onset of severe withdrawal symptoms while the short-acting formulation is titrated by the patient “as needed” to control withdrawal symptoms during potential relapse situations. This approach has been studied in 7 clinical trials with modest but encouraging preliminary results.²² An intensive regimen consisting of triple agent NRT (inhaler, transdermal patch, and nasal spray) in combination with bupropion SR appears safe and effective among highly dependent smokers.³⁸ Combination therapy with medications from different classes, including the transdermal nicotine patch with either bupropion or nortriptyline, has not been shown have improved efficacy over monotherapy.³⁴ The safety and effectiveness of

varenicline in combination with bupropion SR or NRT has not been established. However, one trial evaluating varenicline plus NRT reported a higher incidence of adverse effects, primarily nausea, with the combination (36%) compared with NRT alone (6%).³⁵

The use of combination therapy may slightly improve cessation rates. However, because long-term efficacy and safety data are lacking, these treatment strategies should be reserved for individuals who have been unable to quit using standard therapy. Clinicians should be aware that NRT products are not approved for combination use and the optimal combinations, dosages, and duration of therapy for this approach are unknown.

Summary

Healthcare providers are ideally positioned to identify tobacco users and assist them with quitting. By applying the “5 A’s” and combining drug therapy with counseling, clinicians can have a significant impact in reducing the public health burden of smoking. When time, logistics, or lack of expertise are not conducive to providing comprehensive counseling, the busy clinician can have an important impact on the health of patients by *asking* about tobacco use, *advising* tobacco users to quit, and *referring* them to other resources for quitting.

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Table 3. Drug Interactions with Smoking

Many interactions between tobacco smoke and medications have been identified. Note that in most cases it is the tobacco smoke—not the nicotine—that causes these drug interactions. Tobacco smoke may interact with medications through pharmacokinetic (PK) or pharmacodynamic (PD) mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. The majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking needed to have an effect has not been established and the assumption is that any smoker is susceptible to the same degree of interaction. The most clinically significant interactions are depicted in the shaded rows.

DRUG/CLASS	MECHANISM OF INTERACTION AND EFFECTS
Pharmacokinetic Interactions	
Alprazolam (Xanax)	<ul style="list-style-type: none"> • Possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Caffeine	<ul style="list-style-type: none"> • ↑ Metabolism. • Likely ↑ caffeine levels after cessation.
Chlorpromazine (Thorazine)	<ul style="list-style-type: none"> • ↓ Serum concentrations (24%). • ↓ Sedation and hypotension possible in smokers; smokers may need ↑ dosages.
Clozapine (Clozaril)	<ul style="list-style-type: none"> • ↑ Metabolism; ↓ plasma concentrations (18%).
Flecainide (Tambocor)	<ul style="list-style-type: none"> • ↑ Clearance (61%); ↓ trough serum concentrations (25%). • Smokers may need ↑ dosages.
Fluvoxamine (Luvox)	<ul style="list-style-type: none"> • ↑ Metabolism; ↓ plasma concentrations (32%). • Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Haloperidol (Haldol)	<ul style="list-style-type: none"> • ↑ Clearance (44%); ↓ serum concentrations (70%).
Heparin	<ul style="list-style-type: none"> • Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects. • Smokers may need ↑ dosages.
Insulin, subcutaneous	<ul style="list-style-type: none"> • Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance. • Interactions likely not clinically significant; smokers may need ↑ dosages.
Insulin, inhaled (Exubera)	<ul style="list-style-type: none"> • Systemic exposure is greatly increased in smokers; greater maximal insulin concentrations (3–5 fold) and faster (by 20–30 minutes). • Contraindicated in smokers and those who have discontinued smoking for less than 6 months.
Mexiletine (Mexitil)	<ul style="list-style-type: none"> • ↑ Clearance (25%); ↓ half-life (36%).
Olanzapine (Zyprexa)	<ul style="list-style-type: none"> • ↑ Metabolism; ↓ serum concentrations (12%). • Dosage modifications not routinely recommended but smokers may require ↑ dosages.
Propranolol (Inderal)	<ul style="list-style-type: none"> • ↑ Clearance (77%).
Tacrine (Cognex)	<ul style="list-style-type: none"> • ↑ Metabolism; serum concentrations three-fold lower. • Smokers may need ↑ dosages.
Theophylline (Theo Dur, etc.)	<ul style="list-style-type: none"> • ↑ Metabolism. • Levels should be monitored if smoking is initiated, discontinued, or changed. • ↑ Clearance with second-hand smoke exposure. • Maintenance doses are considerably higher in smokers.
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	<ul style="list-style-type: none"> • Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.
Pharmacodynamic Interactions	
Benzodiazepines (diazepam, chlordiazepoxide)	<ul style="list-style-type: none"> • ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.
Beta-blockers	<ul style="list-style-type: none"> • Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation. • Smokers may need ↑ dosages.
Corticosteroids, inhaled	<ul style="list-style-type: none"> • Asthmatic smokers may have less of a response to inhaled corticosteroids.
Hormonal contraceptives	<ul style="list-style-type: none"> • ↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives. • ↑ Risk with age and with heavy smoking (15 or more cigarettes per day) which is quite marked in women age 35 and older.
Opioids (propoxyphene, pentazocine)	<ul style="list-style-type: none"> • ↓ Analgesic effect; smoking may ↑ the metabolism of propoxyphene (15–20%) and pentazocine (40%). Mechanism unknown. • Smokers may need ↑ opioid dosages for pain relief.

Adapted from Zevin S, Benowitz NL. Drug interactions with tobacco smoking. *Clin Pharmacokinet* 1999;36:425–438.

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Questions are based on information provided in the text, tables and *Patient Connection* insert.

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- Which of the following is true regarding mortality related to smoking?
 - 1 in every 10 deaths in the U.S. is smoking related.
 - 1 in every 5 deaths in the U.S. is smoking related.
 - Sudden death and heart attacks are caused primarily by smoking.
 - Deaths from lung cancer related to smoking are rare.
- Why is it so important for healthcare providers to strongly recommend that patients stop smoking?
 - Patients who receive advice to quit from healthcare providers are more likely to quit compared with those who don't receive such advice.
 - Patients typically increase the number of cigarettes smoked per day if healthcare providers do not discuss quitting with them.
 - Healthcare providers have greater influence on patients than their spouses.
 - Patients generally do not try nicotine replacement products unless healthcare providers recommend them.
- Which of the following is a good recommendation when applying the "Refer" method to aid a patient's smoking cessation efforts?
 - suggest filtered cigarettes
 - suggest hiring a dietitian to help
 - suggest a telephone quitline
 - suggest spending more time alone
- Which of the following nicotine replacement products provides a consistent nicotine level to help alleviate withdrawal symptoms?
 - oral inhaler
 - lozenge
 - transdermal patch
 - nasal spray
- Which of the following is true regarding the use of nicotine gum?
 - The gum promotes weight gain compared to other NRT products.
 - Nicotine gum is less likely to adhere to dentures than regular gum.
 - Adults who smoke < 25 cigarettes/day should use the 4 mg strength.
 - Use is contraindicated in patients with temporomandibular joint disease.
- It is believed that the risks of NRT in patients with cardiovascular disease are minimal compared to the risks of continued tobacco use.
 - true
 - false
- Which of the following is a common side effect of nicotine nasal spray?
 - nightmares
 - tearing
 - skin erythema
 - hiccups
- Which of the following is important to tell a patient beginning use of a nicotine transdermal patch?
 - To manage sleep disturbances, apply one patch every other day.
 - Cut the patch into smaller pieces to adjust the dose if needed.
 - Water reduces patch effectiveness. Minimize exposure to water.
 - Rotate application sites each day; wait 1 week before using the same site.
- Which of the following NRT products require that patients avoid food and acidic beverages 15 minutes before and during use?
 - lozenge, patch, gum
 - lozenge, nasal spray, oral inhaler
 - gum, nasal spray, lozenge
 - lozenge, gum, oral inhaler
- Which of the following is the most concerning side effect of bupropion?
 - heart failure
 - severe skin reactions
 - seizures
 - hypertension
- Varenicline (*Chantix*[®]) may help prevent relapse by reducing the pleasure linked with smoking, thereby improving the odds of successfully quitting.
 - true
 - false
- When should varenicline (*Chantix*[®]) be started?
 - 1 month prior to the quit date
 - 3 days following the quit date
 - on the quit date
 - 1 week prior to the quit date

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