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Using Pharmacotherapy to Treat Tobacco Dependence in Primary Care Settings

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Smoking cessation interventions delivered by primary care physicians are essential in preventing the morbidity and mortality resulting from tobacco use. This article summarizes the major findings of the United States Public Health Service guideline: Treating Tobacco Use and Dependence *(USPHS guideline), a comprehensive, evidence-based strategy for treating tobacco dependence. It also provides recommendations for delivering effective clinical interventions to treat tobacco dependence in the primary care setting including behavioral therapies, first-line medications, and second-line medications. The article concludes with updated information about new medications under development. Primary care physicians can implement the strategies recommended by the USPHS guideline to treat their patients by identifying tobacco users, advising them to quit, assessing their willingness to quit, assisting them in quit attempts, and arranging follow-up care for those dependent on tobacco. After reading this article, primary care clinicians will:*

1) Understand the rationale for treating tobacco dependence;

2) Recognize why tobacco dependence is a chronic disease;

3) Be familiar with the 5 A's for providing brief clinical interventions for tobacco users willing to quit;

4) Be familiar with the 5 R's for motivating tobacco users not yet willing to make a quit attempt; and

5) Know the first-line medications proven to be effective for treating tobacco dependence. Note: This article contains information about an off-label use of nortriptyline and combined nicotine replacement therapies on pages 79 and 82, and information about new drugs in development on pages 83-84.

—The Editor

Definition of Problem

Tobacco use is the leading cause of preventable morbidity and mortality in the United States. Primary care physicians have an extraordinary opportunity to affect the health of their patients who use tobacco by providing evidence-based interventions to encourage smoking cessation. Approximately 84% of all lung cancer deaths in the United States are attributable to smoking and/or environmental tobacco smoke exposure.[1] Furthermore, about 30% of all cancer deaths are caused by smoking.[2] In total, cigarette smoking and exposure to environmental tobacco smoke accounts for more than 400,000 deaths annually in the United States.[3] Tobacco use is a primary cause of many of the diseases that lead patients to fill primary care offices each day, including angina, coronary artery disease, lung cancer, acute bronchitis, chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), stroke, and asthma. By providing brief counseling and pharmacotherapies effective in treating tobacco dependence, clinicians can increase smoking

cessation rates of patients seen in primary care practices.[4-6]

In 1996, the then Agency for Health Care Policy and Research (now the Agency for Health Care Research and Quality) published clinical practice guidelines for smoking cessation,[7] the first comprehensive, evidence-based guideline for the treatment of tobacco addiction in the clinical setting. In 2000, the U.S. Public Health Service published an updated version of the guideline, *Treating Tobacco Use and Dependence*, that is based on the screening and systematic review of 6,000 journal articles.[8] The guideline contains strategies and recommendations to help clinicians, tobacco-dependence treatment specialists, health administrators, and insurers deliver effective, evidence-based interventions to patients dependent on tobacco. This article will focus on USPHS guideline recommendations designed to help primary care clinicians treat their patients who are dependent on tobacco, giving particular attention to the brief clinical interventions and medications that are useful in the primary care setting.

Epidemiology of Tobacco Use

In 2001, the prevalence of smoking among adults 18 and older in the United States was 22.8%; 25.2% of men and 20.7% of women were current smokers.[9] While this represents enormous progress since the early 1960s when 44% of all adults smoked, almost 50 million Americans continue to use tobacco regularly.

Age. Most people try their first cigarette and become regular smokers during adolescence.[10] Smoking prevalence among adolescents rose dramatically during the 1990s. Though rates have leveled off, more than 20% of high school students continue to smoke.

Gender. Among adult males and females, the prevalence of smoking among men is slightly greater than among women, and men have been consistently heavier smokers than women. Among adolescents in the United States, the prevalence of smoking among males and females is similar.[1] Lung cancer now has surpassed breast cancer as the leading cause of cancer death among women.

Ethnicity/Race. In the U.S. adult population, the prevalence of tobacco use is highest among American Indians and Alaska Natives, followed by Caucasians and African-Americans, and lowest among Hispanic Americans and Asian/Pacific Islander Americans.[11] In the U.S. adolescent population, based on data from 12th-grade students, the prevalence of tobacco use is highest among American Indians, followed by whites, then Hispanics. African-American teenagers have the lowest prevalence of tobacco use.

Socioeconomic Status. Smoking prevalence is inversely related to level of education, such that those with 16 or more years of education have the lowest smoking rates. Currently, more than 30% of high school dropouts smoke, while only about 12% of college graduates smoke. Also, the prevalence of smoking among blue-collar and service workers is higher than among white-collar workers. Moreover, blue-collar workers are more likely to be heavy smokers. Persons who live below the poverty line are more likely to smoke than those who live at or above the poverty line.[1]

Basic Neurobiology of Tobacco Dependence

Nicotine is a potent substance with multiple physiological effects, including powerful psychoactive effects.[12,13] Nicotinic receptors are distributed throughout the central nervous system. These receptors facilitate the release of different neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, and β-endorphins. Nicotine activates the brain reward system by increasing dopamine release.[14] This brain reward system is the common pathway for pleasurable activities (e.g., sexual activity, eating) and for most drugs of addiction.[15] Arterial nicotine levels increase markedly—within 15 seconds—after inhaling smoke from a cigarette into the lungs.[16] Over time, this rapid delivery of nicotine to the central nervous system leads to tolerance to nicotine, which leads to an increase in cigarette consumption. Between cigarettes, the level of nicotine quickly declines and permits re-sensitization of receptors to the effects of the next cigarette. Individuals tend to smoke more frequently and heavily to obtain the desired effects of nicotine and avoid the unpleasant effects of withdrawal. Nicotine replacement therapy medications are designed to minimize withdrawal symptoms during the quitting process. In contrast to cigarettes and other tobacco products, nicotine replacement therapies have a much slower rate of absorption and delivery of nicotine and do not produce high plasma nicotine levels, which explains their minimal addictive potential.[17,18] Also, nicotine replacement therapies supply nicotine in a safe manner, without the other

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Table 1. Ask — Systematically Identify All Tobacco Users at Every Visit

ACTION	STRATEGIES FOR IMPLEMENTATION
Implement an office-wide system that ensures that, for *every* patient at *every* clinic visit, tobacco-use status is queried and documented.*	Expand the vital signs to include tobacco use or use an alternative universal identification system.†

VITAL SIGNS

Blood Pressure: _____

Pulse: _____ Weight: _____

Temperature: _____

Respiratory Rate: _____

Tobacco Use: (*circle one*) Current Former Never

* Repeated assessment is not necessary in the case of the adult who never used tobacco or has not used tobacco for many years, and for whom this information is documented clearly in the medical record.

† Alternatives to expanding the vital signs are to place tobacco-use status stickers on all patient charts or to indicate tobacco-use status using electronic medical records or computer reminder systems.

harmful, carcinogenic components contained in tobacco smoke.

Clinical Management

Primary care providers are in an ideal position to help individuals addicted to tobacco. Seventy percent (70%) of smokers visit a physician each year,[19] and most report that advice by a clinician is an important motivator in making a quit attempt.[20] In fact, a recent survey of smokers in the United States revealed that 52% tried to quit during the preceding year.[21] Despite the availability of assistance in the form of medications and behavioral therapy, an estimated 90% of smoking cessation attempts are unassisted (i.e., cold turkey), resulting in low, long-term success rates (3%-5%).[22] The first step in providing assistance in the primary care setting is to identify all tobacco users consistently so that clinicians are made aware of the need for intervention.

To achieve this first step, health care systems should be altered to promote the systematic identification of tobacco users during any and all health care visits.[8] Once tobacco users are identified, protocols that utilize the 5 A's (Ask, Advise, Assess, Assist, Arrange) outlined in the USPHS guideline should be used to address this disease properly and provide patients with evidence-based assistance known to improve quitting success rates. Given the chronic nature of tobacco dependence, providers must intervene by advising users to quit, assessing the willingness to quit, assisting users in quitting, and arranging follow-up care. Studies have shown that even brief smoking cessation treatment by health care providers can be effective.[5,23-25] Providers are well positioned to advise smokers to quit, provide appropriate interventions (counseling and medication), provide referrals to quitlines or community programs, and arrange follow-up visits to treat this chronic disease.

In addition to counseling, all smokers trying to quit should receive pharmacotherapy except in special circumstances, which include medical contraindications, pregnant/breastfeeding women, adolescent smokers, and those patients who smoke fewer than 10 cigarettes per day. In the presence of any of the above special circumstances, providers must weigh the risks and benefits of medications being considered. Research has shown that the use of nicotine replacement therapy or other pharmacological treatments significantly increase a smoker's chance of successfully quitting. It is equally important, however, to encourage these smokers to use some form of behavioral counseling (e.g., face-to-face, group, telephone, Internet) along with their pharmacological therapy. Effective strategies for smoking cessation include combined behavioral interventions and pharmacotherapy. With a combination of these interventions, a twofold or more increase in the rate of smoking cessation can be achieved.[8]

Tobacco addiction is a chronic disease requiring repeated interventions by clinicians who should see each encounter as an opportunity to reach smokers. Most tobacco users attempt cessation five or more times, typically cycling through multiple periods of relapse and remission, before experiencing long-term success.[8,26] This information should be used to guide treatment of tobacco dependence, which will involve ongoing chronic care, rather than one-time acute care. Treatment for tobacco dependence should be much like the type of care provided for other chronic diseases (e.g., diabetes and hypertension) and include repetitive, health education-type counseling and advice, as well as necessary adjustments in medication type and/or dose. Relapse should not be viewed as therapeutic failure, nor failure on the part of the patient, but as evidence of the addictiveness of tobacco and the chronic nature of tobacco dependence.

The 5 A's Model

To reach large numbers of smokers, systems must be in place for the identification and documentation of all smokers. The USPHS guideline recommends the 5 A's model —Ask, Advise, Assess, Assist, Arrange—for intervening in the primary care setting with patients to identify and treat those using tobacco. These intervention strategies are designed to be brief, requiring three to five minutes to administer.

Ask About Tobacco Use. Ask every patient, at every visit about smoking status and document the information in the medical record. The USPHS guideline recommends that smoking status be included as a vital sign, with chart stickers or with a computerized reminder system. (*See Table 1.*)

Advise to Quit. Once identified, all tobacco users should receive clear, strong, direct, personalized advice to quit using tobacco products. The advice should be clear that quitting—not just cutting down—is best. It should be strong and direct in reference to the burden of diseases caused by or exacerbated by smoking. It should be personalized to the health condition and life circumstances of the individual patient. (*See Table 2.*)

Table 2. Advise—Strongly Urge All Tobacco Users to Quit

ACTION

In a clear, strong, and personalized manner, urge every tobacco user to quit.

STRATEGIES FOR IMPLEMENTATION

Advice should be:

• *Clear*. "I think it is important for you to quit smoking now, and I can help you. Cutting down while you are ill is not enough."

• *Strong*. "As your clinician, I need you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. The clinic staff and I will help you."

• *Personalized*. Tie tobacco use to current health/illness, and/or its social and economic costs, motivation level/readiness to quit, and/or the impact of tobacco use on children and others in the household.

Encourage all clinical staff to reinforce the cessation message and support the patient's quit attempt.

Assess Willingness to Make a Quit Attempt. Determine the patient's willingness to make a quit attempt within the next 30-day period. Categorize responses into one of two categories: 1) patients willing to make a quit attempt at this time; and 2) those not willing to make a quit attempt. (*See Table 3.*) For patients in the first category, provide assistance at that time or refer patient to more intensive assistance if needed. For patients in the second category, provide a brief motivational intervention designed to make them think about the benefits of quitting. (*See Table 4.*)

Assist in the Quit Attempt. Patients who express an interest in quitting should be provided with assistance. (*See Table 5.*) Encourage patients to set a quit date and to prepare for it by getting rid of all smoking paraphernalia, telling family and friends of their decision, and changing their patterns of smoking leading up to the quit day. Discuss the type of withdrawal symptoms patients can expect once they have quit and the usual time course of those symptoms. Help patients plan how they will handle difficult situations and problems that arise by reviewing any past experiences with quitting and what situations led them to relapse. Provide some additional resources, such as supplemental materials to have at home, the number to a telephone quitline, and or helpful website addresses. Prescribe pharmacotherapy for patients except in special circumstances (i.e., contraindications). (*See section on medications.*)

Arrange Follow-up Care. Tobacco dependence is a chronic disease that requires ongoing management and follow-up care after the quit date similar to that required for treating other chronic diseases. Follow-up care can be in person or by telephone. Follow-up care should be timed optimally to help the patient during the first week after a quit attempt (when withdrawal symptoms will be present and risk of relapse is greatest), again within a month, and as needed thereafter. During follow-up sessions congratulate any success, have the patient recommit to abstinence, help them to problem solve, and assess medication effectiveness and or side effects. (*See Table 6.*)

Nonpharmacologic Behavioral Therapy (Individual, Group, or Proactive Telephone Counseling)

Ideal treatment for tobacco dependence includes behavioral therapy in addition to pharmacotherapy. Behavioral therapy in conjunction with medications has yielded quit rates of 30-40% at one-year follow-up, compared with medication-alone quit rates that reach 15-25%.[8] Behavioral interventions can be delivered in a variety of settings, which have been proven effective in smoking cessation interventions, including individual counseling, group counseling and proactive telephone counseling. These counseling interventions should provide patients with three essential elements to increase their chances of successful abstinence: 1) problem-solving skills training; 2) social support as part of treatment; and 3) help locating and securing social support outside of treatment. Clinicians can help their patients think about and identify situations that increase their risk of relapsing back to smoking, and develop stress management and coping strategies that will help them resist urges and maintain abstinence. Providing basic information about expected withdrawal symptoms and their time course will better prepare patients for success. Clinicians and counselors can provide social support during treatment by expressing concern and allowing open dialogue about the quitting process. Clinicians also can help patients identify and arrange additional social support in their environment (e.g., friends, co-workers and family members), and from trained professionals (e.g., quitline counselors).

Pharmacotherapy—First-Line Medications

Bupropion Sustained Release (Bupropion SR). Bupropion SR is available by prescription only and is the only non-nicotine medication approved by the U.S. Food and Drug Administration (FDA) for smoking-cessation treatment. It is marketed as Zyban for smoking cessation or Wellbutrin for depression. Bupropion has been shown to be effective for smoking cessation and well tolerated in a number of studies.[27-29] It is contraindicated in individuals with seizure disorders, eating disorders, or who used monoamine oxidase (MAO) inhibitors within the previous two weeks. The USPHS guideline recommends it as first-line pharmacotherapy for smoking cessation, and it is the only non-nicotine medication so designated. (*See Table 7.*)

Nicotine Replacement Therapies (NRTs). NRT products are available in various forms. The active ingredient in such products is nicotine. There is no evidence of increased cardiovascular risk with NRT.[8] The use of NRTs is contraindicated medically in cases of MI (within previous two weeks), serious arrhythmia, serious or worsening angina pectoris, and accelerated hypertension.

Nicotine Gum. Nicotine gum is available over the counter in 2-mg and 4-mg doses. It is absorbed best in a basic environment, and users should be advised to "park and chew" to achieve maxi-

Table 3. Assess—Determine Willingness to Make a Quit Attempt

ACTION
Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).
STRATEGIES FOR IMPLEMENTATION
Assess patient's willingness to quit: • If the patient is willing to make a quit attempt at this time, provide assistance (counseling and medications). • If the patient will participate in an intensive treatment, deliver such a treatment or refer to an intensive intervention. • If the patient clearly states he/she is unwilling to make a quit attempt at this time, provide a motivational intervention. • If the patient is a member of a special population (e.g., adolescent, pregnant smoker, racial/ethnic minority), consider providing additional information.

mum absorption. The dosage recommendation is to chew one piece every 1 to 2 hours for weeks 1 to 6, one piece every 2 to 4 hours for weeks 7 to 9, and one piece every 4 to 8 hours for weeks 10 to 12. The maximum dosage is 24 pieces per day. The recommended duration of treatment is 12 weeks.[30]

Nicotine Inhaler. Nicotine inhalers are available by prescription only. The recommended dosage of nicotine inhalers is 6-16 cartridges per day (each contains 10 mg of nicotine). The recommended duration of treatment is 12 weeks followed by a 6- to 12-week period of weaning. Therefore, six months is the maximum recommended length of therapy.[30]

Nicotine Lozenge. The new nicotine lozenge has been shown to have low abuse liability, not greater than the nicotine gum.[31] It is available in 2-mg and 4-mg doses and should be allowed to dissolve in the mouth without chewing or swallowing. Individuals who typically smoke their first cigarette within 30 minutes of awakening should use the 4-mg dose. Because it dissolves completely, it delivers 25-27% more nicotine than the nicotine gum. In clinical trials, it increased quit rates two-fold compared with placebo, reduced cravings and withdrawal symptoms, and temporarily suppressed weight gain.[32]

Nicotine Nasal Spray. Nicotine nasal spray is available by prescription only. Each 10-mL spray bottle contains 100 mg of nicotine (10 mg/mL). One dose of nicotine nasal spray (two sprays, one in each nostril) contains approximately 1 mg of nicotine. The recommendation is one to two doses per hour, which may be increased to a maximum of 40 doses per day for three months, followed by tapering of the daily dose. The recommended minimum dosage is eight doses per day, and the recommended duration of treatment is up to six months.[30]

Nicotine Patch. Nicotine patches are available both over the counter (OTC) and by prescription. The recommended OTC and prescription nicotine patch dosage is 21 mg/day for weeks 1 to 6, tapered to 14mg/day for weeks 7 and 8, and then tapered to 7 mg/day for weeks 9 and 10. Those smoking fewer than 10 cigarettes per day are advised to start at 14 mg/day instead of 21 mg/day. The recommended duration of treatment with nicotine patches is 8 to 10 weeks. Nicotine patches are available for 24-hour or 16-hour use.[30]

Pharmacotherapy—Second-line Medications

Based upon findings from the USPHS guideline panel, two medications were listed as second-line pharmacotherapies to be considered if first-line pharmacotherapies are not effective or are contraindicated.

Clonidine. Clonidine is an anti-hypertensive that has been shown in clinical trials to double quit rates compared with placebo. However, it has not been approved by the FDA for smoking cessation, nor has a specific dosing regimen been established. For these and other reasons (i.e., the side effect profile, a warning regarding abrupt discontinuation), it was recommended as a second-line agent by the guideline panel. Clinicians might consider using clonidine for patients with contraindications to using first-line medications or for patients who are unable to quit using first-line medications, but should be aware of the side effect profile and specific precautions and warnings regarding its use.

Nortriptyline. Nortriptyline is an anti-depressant that has been shown in a limited number of clinical trials to more than double quit rates compared with placebos. However, it has not been approved by the FDA for smoking cessation. The USPHS guideline panel recommended it as a second-line agent because of the limited number of studies, the lack of FDA approval for smoking cessation, and because of its side effect profile. Clinicians might consider using nortriptyline for patients who have contraindications to first-line medications or who were unable to quit smoking by using them. Clinicians should be aware of specific warnings and the side effect profile of this medication.

Multiple Therapies. Though combined NRT is not FDA approved currently, a number of studies have proven that combination therapy results in increased quit rates, and such combinations are recommended in the USPHS guideline. In addition, bupropion SR may be combined with any of the NRTs. In patients unable to quit using single therapy, combination therapy may be considered. Nicotine patch plus gum[33,34] or nicotine patch plus nasal spray[35] are more effective in promoting smoking cessation than a single NRT.

When to Refer to a Specialist

Despite health warnings and advice from physicians, a subgroup of smokers never quit. Difficulty quitting tobacco use has been associated with a number of characteristics, including a high level of nicotine dependence,[36] comorbid psychopathology,[37,38] and lower socio-economic status.[39] If one of these characteristics exists, referral to smoking-cessation specialists should be considered. A high level of nicotine dependence might be predicted by one of the following conditions: smoking more than 20 cigarettes per day; smoking within 30 minutes of awakening; finding it difficult to not smoke in situations and places where smoking is prohibited; and scoring within the high range on tests of nicotine dependence, such as the Fagerstrom Tolerance Questionnaire. Comorbid psychiatric problems—especially alcohol abuse and depression—might result in poor medication compli-

Table 4. Enhancing Motivation to Quit Tobacco—the 5 R's

RELEVANCE

Encourage the patient to indicate why quitting is personally relevant, being as specific as possible. Motivational information has the greatest impact if it is relevant to a patient's disease status or risk, family or social situation (e.g., having children in the home), health concerns, age, gender, and other important patient characteristics (e.g., prior quitting experience, personal barriers to cessation).

RISKS

The clinician should ask the patient to identify potential negative consequences of tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient. The clinician should emphasize that smoking low-tar/low-nicotine cigarettes or use of other forms of tobacco (e.g., smokeless tobacco, cigars, and pipes) will not eliminate these risks. Examples of risks are:

- *Acute risks*: Shortness of breath, exacerbation of asthma, harm to pregnancy, impotence, infertility, increased serum carbon monoxide
- *Long-term risks*: Heart attacks and strokes, lung and other cancers (larynx, oral cavity, pharynx, esophagus, pancreas, bladder, cervix), chronic obstructive pulmonary diseases (chronic bronchitis and emphysema), long-term disability and need for extended care
- *Environmental risks*: Increased risk of lung cancer and heart disease in spouses; higher rates of smoking by children of tobacco users; increased risk for low birth weight; sudden infant death syndrome; asthma; middle ear disease; and respiratory infections in children of smokers.

REWARDS

The clinician should ask the patient to identify potential benefits of stopping tobacco use. The clinician may suggest and highlight those that seem most relevant to the patient. Examples of rewards are:

- Improved health
- Improved taste of food
- Improved sense of smell
- Reduced expenses
- Improved self-image
- Improved smell in home, car, clothing, and breath
- No worrying about quitting
- Positive example for kids
- Healthier babies and children
- No worrying about exposing others to smoke
- Improved physical health
- Improved performance in physical activities
- Reduced wrinkling/aging of skin

ROADBLOCKS

The clinician should ask the patient to identify barriers or impediments to quitting and note elements of treatment (e.g., problem-solving, pharmacotherapy) that could address barriers. Typical barriers might include:

- Withdrawal symptoms
- Fear of failure
- Weight gain
- Lack of support
- Depression
- Enjoyment of tobacco

REPETITION

The motivational intervention should be repeated every time an unmotivated patient visits the clinic setting. Tobacco users who have failed in previous quit attempts should be told that most people make repeated quit attempts before they are successful.

ance. Almost 20% of heavy smokers have current alcohol problems[40] and nearly 40% of current smokers have a history of depression.[38,41] Persons who live below the poverty line (lower socio-economic status) are more likely to smoke than those who live at or above the poverty line.[1] Also, lower socio-economic status is associated with less access to cessation services, more environmental stressors, and exposure to other smokers in the social and work environment.

Special Challenges, Controversies, Pitfalls, Areas in Need of Research

Symptoms and Time Course of Withdrawal as Relates to Pharmacotherapy. While nicotine withdrawal symptoms vary from individual to individual, symptoms usually involve unpleasant effects, such as anxiety, irritability, difficulty concentrating, restlessness, impatience, hunger, tremor, racing heart, sweating, dizziness, nicotine craving, insomnia, drowsiness, headaches, digestive disturbances, and depression.[42] Withdrawal symptoms typically increase during the first week following abstinence, then steadily improve during the next four weeks. However, smoking withdrawal is variable among individual smokers, and some individuals experience symptoms that do not improve steadily, but instead either gradually improve or show very little improvement during the typical time course.[43] Individuals who experience withdrawal symptoms that increase or remain elevated during an extended period of time are at higher risk for relapse than those who have symptoms that steadily decline.[43,44] Such individuals should be considered for prolonged therapy and allowed to use NRT beyond the recommended time period to help prevent relapse to smoking.

Duration of Therapy. There is no consensus among experts about the optimum duration of pharmacotherapy for treating tobacco dependence. The recommendations regarding duration of therapy with nicotine replacement medications and bupropion as outlined in the *Physicians' Desk Reference (PDR)*[30] are based upon trials designed to determine effectiveness and safety of the medications, not necessarily maximum efficacy. Long-term use of pharmacotherapy (i.e., use beyond the recommended time period) might be an effective strategy for preventing relapse. For example, there is some evidence to suggest that though seven weeks of bupropion SR is effective for smoking cessation, a longer duration of treatment might prolong abstinence or time to relapse.[45]

Relapse Prevention (Risk Factors for Relapse). Most relapses occur early in the quitting

Table 5. Assist—Aid the Patient in Quitting

HELP THE PATIENT WITH A QUIT PLAN.

A patient's preparations for quitting (STAR):

- *Set* a quit date. Ideally, the quit date should be within 2 weeks.
- *Tell* family, friends, and co-workers about quitting and request understanding and support.
- *Anticipate* challenges to planned quit attempt, particularly during the critical first few weeks. These include nicotine withdrawal symptoms.
- *Remove* tobacco products from your environment. Prior to quitting, avoid smoking in places where you spend a lot of time (e.g., work, home, car).

PROVIDE PRACTICAL COUNSELING (PROBLEM SOLVING/SKILLS TRAINING).

- *Abstinence*—Total abstinence is essential. Not even a single puff after the quit date.
- *Past quit experience*—Review past quit attempts including identification of what helped during the quit attempt and what factors contributed to relapse.
- *Anticipate triggers or challenges in upcoming attempt*—Discuss challenges/triggers and how the patient will overcome them successfully.
- *Alcohol*—Drinking alcohol is associated highly with relapse. The patient should consider limiting/abstaining from alcohol during the quit process.
- *Other smokers in the household*—The presence of other smokers in the household, particularly a spouse or partner, is associated with lower abstinence rates. Patients should encourage significant others to quit with them. If others continue to smoke, the patient should ask them to smoke outdoors and not in the quitter's presence.

PROVIDE INTRA-TREATMENT SOCIAL SUPPORT.

Provide a supportive clinical environment while encouraging the patient in his or her quit attempt. Example: "My office staff and I are available to assist you."

HELP PATIENT OBTAIN EXTRA-TREATMENT SOCIAL SUPPORT.

Help patient develop social support for his or her quit attempt in his or her environments outside of treatment. Example: "Ask your spouse/partner, friends, and co-workers to support you in your quit attempt."

RECOMMEND THE USE OF APPROVED PHARMACOTHERAPY EXCEPT IN SPECIAL CIRCUMSTANCES.

Recommend the use of pharmacotherapies found to be effective in the USPHS Guideline. (*See Table 7.*) Explain how these medications increase smoking cessation success and reduce withdrawal symptoms. The first-line pharmacotherapy medications include bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch.

PROVIDE SUPPLEMENTARY MATERIALS.

- *Sources*—Federal agencies, nonprofit agencies, or local/state health departments.
- *Type*—Culturally/racially/educationally/age appropriate for the patient.
- *Location*—Readily available at every clinician's workstation.

Key: Buproprion SR = buproprion sustained release

Table 6. Arrange—Schedule Follow-up Contact

ACTION

Schedule follow-up contact, either in person or via telephone.

STRATEGIES FOR IMPLEMENTATION

Timing—Follow-up contact should occur soon after the quit date, preferably during the first week. A second follow-up contact is recommended within the first month. Schedule further follow-up contacts as indicated.

Actions during follow-up contact—Congratulate success. If tobacco use has occurred, review circumstances and elicit recommitment to total abstinence. Remind patient that a lapse can be used as a learning experience. Identify problems already encountered and anticipate challenges in the immediate future. Assess pharmacotherapy use and problems. Consider use or referral to more intensive treatment.

process. Primary care physicians should engage in relapse prevention with all former smokers because patients are at risk for relapse months, and even years, after the quit date. Relapse prevention is very important soon after quitting—especially within the first three months—and can be delivered by follow-up clinical visits, follow-up telephone counseling, or using proactive tobacco quitlines. Issues that should be discussed in an effort to prevent relapse include the benefits of cessation, any successes, and any problems encountered that threaten continued abstinence. Patients should be encouraged to seek help and to report promptly any difficulties (e.g., depression, medication side effects, strong withdrawal symptoms, or lack of social support). For patients at risk for relapse, consider a prolonged course of pharmacotherapy, beyond that recommended in the PDR.[46]

Special Populations (Gender, Adolescents, Pregnant Women, Race/Ethnic Minorities). Though research has demonstrated gender differences in smoking and cessation behavior, the USPHS guideline states that the same smoking-cessation interventions are effective for men and women and should be made available without regard to gender. Most smokers begin daily smoking as teenagers, before age 18. Many adolescent smokers report symptoms of nicotine dependence and experience withdrawal symptoms when trying to quit. Since nicotine replacement therapy is far safer than smoking, it should be considered for all smokers who need help quitting, including teens. Smoking during pregnancy is associated with serious risks to the pregnant smoker and the fetus. Although abstinence early in pregnancy will produce the greatest benefits, abstinence at any point during pregnancy is beneficial. Therefore, clinicians should offer effective smoking-cessation interventions to pregnant smokers at any and all prenatal visits. The USPHS guideline recommends that pharmacotherapy be considered when the likelihood of quitting—with its benefits for the expectant mother and fetus—outweighs the risks of the medication and continued smoking. Smoking-cessation treatments have been shown to be effective for various racial and ethnic minorities. Therefore,

Table 7. Pharmacotherapy

MEDICATION	DOSAGE	DURATION	PRECAUTION	ADVERSE EFFECTS
Bupropion SR	150 mg q am for 3 days; then 150 mg bid. (Begin treatment 1-2 wks pre-quit.)	7-12 wks Maintenance up to 6 months	Caution: Eating disorder Contraindications: Seizure disorder, use of MAO inhibitor in past 2 weeks	Insomnia, dry mouth
Nicotine gum	2-mg or 4-mg doses; Chew at least 1 piece q 1-2 hrs. (Acidic drinks like caffeine, juices, soda interfere with absorption.)	Up to 12 weeks	Caution: Unstable angina, 2 wks post-MI, serious arrhythmia	Mouth soreness, dyspepsia, hiccups (Proper technique is to "chew and park.")
Nicotine inhaler	Dosage is 6-16 cartridges/day. (Acidic drinks interfere with buccal absorption.)	Treat up to 6 months. Begin to taper after 3 months.	Contraindications: None	Irritation in mouth and throat, cough, rhinitis
Nicotine nasal spray	1 spray/nostril (1 mg nicotine), 1-2 doses/hour as needed	Up to 8 weeks; taper during 4-6 weeks	Caution: Unstable angina, 2 wks post-MI, serious arrhythmia Contraindications: Severe reactive airway disease	Nasal irritation
Nicotine patch	22 mg or 21 mg/24 hrs or 15 mg/16 hrs (If sleep disturbed, wear 16-hr patch when awake.) for up to 6 weeks, then taper	8 to 10 weeks	Caution: Unstable angina, 2 wks post-MI, serious arrhythmia	Local skin reaction
Nicotine lozenge (was not available when guideline was published)	2 or 4 mg (1 lozenge every 1-2 hrs for 6 weeks; 1 lozenge every 2-4 hrs during weeks 7-9; 1 lozenge every 4-8 hrs during weeks 10-12)	Up to 12 weeks	Precautions: Uncontrolled BP, recent heart attack or irregular heartbeat, stomach ulcers or diabetes	Nausea, hiccups, heartburn

Key: SR=sustained release; bid=twice daily; MAO=monoamine oxidase; MI=myocardial infarction; BP=blood pressure.

smokers from different racial/ethnic backgrounds should be offered effective interventions that are culturally relevant and appropriate.

Chronic Nature of Addiction. Tobacco dependence is a chronic disease associated with periods of abstinence and relapse that will require repeated systematic interventions. Studies have shown that it takes the average smoker four to five quit attempts before achieving smoking-cessation success.[26] Indeed, a significant number of former smokers have difficulty maintaining abstinence and relapse back to smoking even after use of pharmacotherapy. In the first year following cessation, relapse rates of 80% have been reported.[47,48] Therefore, physicians should think of tobacco dependence as a chronic disease to be managed similar to other chronic diseases—with ongoing rather than simply acute care. Factors that contribute to failed quit attempts should be addressed, and the patient should be encouraged to make another quit attempt as soon as possible. Some factors to consider are patient motivation, co-morbidities, stress, availability of social support, and use of medications.

New Medications—Approved for Use

Nicotine Lozenge. Nicotine lozenge might be a more acceptable form of oral nicotine replacement therapy than nicotine gum for patients who have difficulty chewing and parking the gum correctly. In a double-blind, placebo-controlled, randomized clinical trial, the nicotine lozenge was found to be safe and effective for

Table 8. Clinical Guidelines for Prescribing Pharmacotherapy for Smoking Cessation

WHO SHOULD RECEIVE PHARMACOTHERAPY FOR SMOKING CESSATION?

All smokers trying to quit except in the presence of special circumstances. Special consideration should be given before using pharmacotherapy with selected populations: those with medical contraindications, those smoking fewer than 10 cigarettes/day, those who are pregnant, and adolescent smokers.

WHAT FIRST-LINE PHARMACOTHERAPIES ARE RECOMMENDED?

All five of the FDA-approved pharmacotherapies for smoking cessation are recommended, including bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and the nicotine patch.

WHAT FACTORS SHOULD A CLINICIAN CONSIDER WHEN CHOOSING AMONG THE FIVE FIRST-LINE PHARMACOTHERAPIES?

Because of the lack of sufficient data to rank-order these five medications, choice of a specific first-line pharmacotherapy must be guided by factors such as clinician familiarity with the medications, contraindications for selected patients, patient preference, previous patient experience with a specific pharmacotherapy (positive or negative), and patient characteristics (e.g., history of depression, concerns about weight gain).

ARE PHARMACOTHERAPEUTIC TREATMENTS APPROPRIATE FOR LIGHTER SMOKERS (E.G., 10-15 CIGARETTES/DAY)?

If pharmacotherapy is used with lighter smokers, clinicians should consider reducing the dose of first-line pharmacotherapies.

WHAT SECOND-LINE PHARMACOTHERAPIES ARE RECOMMENDED?

Clonidine and nortriptyline.

WHEN SHOULD SECOND-LINE AGENTS BE USED FOR TREATING TOBACCO DEPENDENCE?

Consider prescribing second-line agents for patients unable to use first-line medications because of contraindications or for patients for whom first-line medications are not helpful. Monitor patients for the known side effects of second-line agents.

WHICH PHARMACOTHERAPIES SHOULD BE CONSIDERED WITH PATIENTS PARTICULARLY CONCERNED ABOUT WEIGHT GAIN?

Bupropion SR and nicotine replacement therapies, in particular nicotine gum, have been shown to delay, but not prevent, weight gain.

WHICH PHARMACOTHERAPIES SHOULD BE CONSIDERED WITH PATIENTS WITH A HISTORY OF DEPRESSION?

Bupropion SR and nortriptyline appear to be effective with this population.

SHOULD NICOTINE REPLACEMENT THERAPIES BE AVOIDED IN PATIENTS WITH A HISTORY OF CARDIOVASCULAR DISEASE?

No. Nicotine replacement therapies are safe and have not been shown to cause adverse cardiovascular effects. However, the safety of these products has not been established for the immediate (two-week) post-MI period, with serious arrhythmias, or in patients with severe or unstable angina.

MAY TOBACCO DEPENDENCE PHARMACOTHERAPIES BE USED LONG-TERM (e.g., 6 MONTHS OR MORE)?

Yes. This approach may be helpful with smokers who report persistent withdrawal symptoms during the course of pharmacotherapy or who desire long-term therapy. A minority of individuals who successfully quit smoking use ad libitum NRT medications (gum, nasal spray, inhaler) long-term. The use of these medications long-term does not present a known health risk. Additionally, the FDA has approved the use of bupropion SR for a long-term maintenance indication.

MAY PHARMACOTHERAPIES EVER BE COMBINED?

Yes. There is evidence that combining the nicotine patch with either nicotine gum or nicotine nasal spray increases long-term abstinence rates over those produced by a single form of NRT.

Key: SR=sustained release; NRT=nicotine replacement therapy;MI=myocardial infarction.

smoking cessation in low-and high-dependence smokers. The 2-mg lozenge had 2.1 greater odds, and the 4-mg lozenge had 3.7 greater odds of producing abstinence at six weeks compared with placebo. Significant treatment effects were maintained for a full year. The adverse events reported during use were moderate and comparable with those seen with nicotine gum.[32]

New Medications – Under Development

NicVaxä. NicVaxä is being tested in clinical trials by Nabi Biopharmaceuticals as a novel drug approach to help curb the cravings for cigarettes. Given intramuscularly, the vaccine is designed to trigger the immune system to make antibodies that attach to nicotine molecules. This vaccine-antibody complex is too large to cross the blood-brain barrier, thereby, blocking or hindering the effect of nicotine on the body. Preliminary animal studies have shown that the nicotine-specific antibodies produced by NicVaxä also reduced the effects of nicotine on the heart and on blood pressure.[49]

Rimonabant. Rimonabant is the first in a new class of drugs called selective CB1 blockers. The drug works by inhibiting the CB1 receptor, one of two receptors found in the endocannabinoid system (EC system), that are located in the brain and in other parts of the body. Associated with systems regulating the body's intake of food, the EC system also is involved in tobacco dependency. Chronic tobacco use over-stimulates the EC system creating an imbalance. By blocking the CB1 receptor, rimonabant helps restore balance to the EC system, resulting in reduced dependence on tobacco. Rimonabant, which is under development by Sanofi-Synthelabo, represents a potentially promising new treatment option that can help people stop smoking while curbing post-cessation weight gain.[50]

Varenicline. Varenicline is a new kind of medication being tested by Pfizer, Inc. for smoking cessation. It has the potential to ease cravings and withdrawal symptoms without being pleasurable or addictive. It works by attaching to the nicotine receptors in the brain and letting the brain think that nicotine is attached so individuals do not experience the unpleasant symptoms of nicotine withdrawal. Also, if a former smoker lapses and smokes a cigarette, the drug has the potential to reduce the sense of satisfaction associated with smoking.[51,52]

Conclusions

In conclusion, tobacco use remains the leading cause of preventable morbidity and mortality in the United States. Tobacco dependence is and should be treated as a chronic disease that requires systematic, ongoing management. Effective, evidence-based strategies exist for treating this costly disease, including pharmacotherapies and behavioral therapies. Also, new and better therapies are under development.

Primary care providers are well positioned to intervene with tobacco users by implementing the strategies recommended by the USPHS guideline to provide effective clinical interventions.

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Physician CME Questions

1. Which of the following medications is *not* one of the five FDA-approved medications recommended in the USPHS guideline as first-line pharmacotherapies for smoking cessation?
   a. Nortriptyline
   b. Nicotine patch
   c. Nicotine gum
   d. Nicotine inhaler
   e. Nicotine nasal spray

2. What are the 5 A's for intervening with tobacco users in the primary care setting?
   a. Ask, Accept, Assist, Arrange, Advocate
   b. Ask, Advise, Assess, Assist, Arrange
   c. Approach, Advise, Assist, Administer, Arrange
   d. Ask, Advise, Assess, Assist, Accommodate
   e. Ask, Acknowledge, Advise, Assess, Admonish

3. The 5 R's useful for motivating tobacco users to consider making a quit attempt include all of the following items *except:*
   a. risk.
   b. relevance.

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

c. reactions.
d. rewards.
e. roadblocks.

4. All of the following are essential components of behavioral therapy for smoking cessation and have been shown to increase long-term success *except:*
   a. problem solving/skills training.
   b. intra-treatment social support.
   c. extra-treatment social support.
   d. hypnosis.

5. Symptoms such as anxiety, irritability, difficulty concentrating, restlessness, impatience, insomnia, drowsiness, headaches, digestive disturbances, and depression are associated with which of the following?
   a. Nicotine withdrawal
   b. Nicotine toxicity
   c. Both nicotine withdrawal and nicotine toxicity
   d. Neither nicotine withdrawal nor nicotine toxicity

6. Based upon research involving the neurobiology of nicotine dependence, the basis of nicotine addiction is thought to involve nicotine's ability to activate the brain reward system by increasing the release of which neurotransmitter?
   a. Dopamine
   b. Norepinephrine
   c. Acetylcholine
   d. Serotonin
   e. β-endorphins

7. The presence of which of these conditions might indicate the need to refer to a specialist?
   a. Depression
   b. Female gender
   c. Patient not willing to quit within the next 30 days
   d. One prior unsuccessful quit attempt

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

CME Answer Key

1.a; 2.b; 3.c; 4.d; 5a.; 6.a.; 7. a.

In Future Issues:

Thyroid Disease

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Britain to Allow Over-the-Counter Sales of Zocor

The British government will soon allow over-the-counter (OTC) sales of Merck's simvastatin (Zocor), marking the first time any country has allowed the OTC sale of a statin. The drug lost its patent protection in England last year, and Merck is eager to make up for some lost revenues by entering the lucrative OTC market. It is likely the drug will be available in an OTC dose of 10 mg. Pharmacists will be asked to carry out a simple screening questionnaire on the spot to screen for appropriateness and safety. Not everyone is happy about the OTC switch however. An editorial in the British journal *Lancet* stated that there is insufficient evidence to justify the OTC switch and implied that the British government is simply trying to save money by defraying prescription drugs costs. Currently over 1.8 million patients in England take statins at a cost of over $1.1 billion per year.

FDA Rejects Plan B Bid

FDA regulators have rejected a bid from Barr Pharmaceuticals to market their "morning after pill" as an OTC. The product, called Plan B, contains 0.75 mg of levonorgestrel, a progestin commonly used in birth control pills. Plan B is marketed as an emergency contraceptive that can be used up to 72 hours after unprotected intercourse or suspected contraceptive failure. The decision by the FDA was somewhat surprising as it went against the recommendation the agency's own advisers who, last December, voted overwhelmingly in favor of the over-the-counter switch for Plan B. The decision prompted some groups to suggest that political pressure from the Bush administration was responsible for the denial. The FDA, however, stated in its rejection letter that they were concerned about the safety of the product for younger women, and kept the door open by suggesting that more data may prompt a reconsideration. In the meantime, Plan B is still available by prescription.

Recombinant Erythropoietin Products May Stimulate Tumor Growth

Two recent studies have raised the question of whether recombinant erythropoietin products may stimulate tumor growth in cancer patients. One study, published in the October 2003 *Lancet*, reviewed 351 adult patients with head neck cancer who were randomized to subcutaneous erythropoietin or placebo 3 times weekly prior to radiation therapy and continuing throughout radiation therapy. Patients treated with erythropoietin had improved hemoglobin concentrations, but otherwise had poor outcomes. Median locoregional progression-free survival was 745 days with placebo and 406 days with erythropoietin (relative risk, 1.62; [95% CI, 1.22-2.14]; P = .0008). Overall,

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In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

over the 4 years of study, 52% of placebo-treated patients died, compared to 61% of erythropoietin treated patients (RR 1.39; [95% CI, 1.05-1.82]; P = .02). A second study in Europe of erythropoietin in breast cancer patients was terminated early because patients receiving the drug had lower 12 month survival rates than patients receiving placebo (70% vs 76%; P = .0117). An editorial in the December 17th Journal of the National Cancer Institute reviewed this issue and raised the plausibility of the findings. The authors noted that erythropoietin receptors have been found on head and neck cancer cells, prostate cancer cells, and ovarian cancer cells, as well as breast, renal, and uterine cancer cells. They also noted that the preliminary data suggest that some of these cancers may proliferate in the presence of erythropoietin.

The editorial concluded by calling for more research into the possible relationship between erythropoietin and poor outcomes in the treatment of cancer patients. The FDA's Oncologic Drugs Advisory Committee recently met in May, and backed a proposal by Johnson & Johnson (makers of Procrit) and Amgen (makers of Aranesp) to study this issue. The exact design of these studies is still to be delineated, but both companies have pledged to collaborate on such research.

Rosuvastatin: Market's Most Potent Statin

Rosuvastatin (Crestor-Astra Zeneca) appears to be the most potent statin currently marketed. In a study of 3140 patients with CAD, atherosclerosis, or type 2 diabetes, patients were randomized to rosuvastatin 10 mg, atorvastatin 10 or 20 mg, simvastatin 20 mg, or pravastatin 40 mg for 8 weeks. Patients either remained on these treatments or were switched from other statins to rosuvastatin. The primary pinpoint was a LDL cholesterol of < 116 mg/dL. Significant improvement in LDL cholesterol goal achievement was found for patients who were switched to rosuvastatin 10 mg compared with patients who remained on atorvastatin 10 mg (86% vs 80%; P < 0.5), simvastatin 20 mg (86% vs 72%, P <.001), and pravastatin 40 mg (88% vs 66%, P < .0001). For patients who were switched from atorvastatin 20 mg to rosuvastatin 20 mg, the rate at goal was 90% vs 84% (P < .01) (*Am Heart J*. 2004;147:705-712). But while rosuvastatin appears to be the most potent statin, it may carry a higher dose related risk of muscle toxicity including myositis and rhabdomyolysis. Astra Zeneca has recently acknowledged 4 cases of rhabdomyolysis in patients who were taking 40 mg of rosuvastatin, and has urged physicians in England to avoid initial high dose therapy with the drug, instead starting at 10 mg and titrating with appropriate follow-up.

FDA Actions

Immunex Corp.'s etanercept (Enbrel) has been approved for use in patients older than the age of 18 with moderate-to-severe plaque psoriasis. Enbrel is currently marketed for use in patients with ankylosing spondylitis, psoriatic arthritis, moderate to severe rheumatoid arthritis, and juvenile rheumatoid arthritis. The expansion of indications to treat psoriasis was expected after 2 phases.

All studies showed improvement with treatment up to 1 year. Etanercept, which is a tumor necrosis factor inhibitor, joins the biologics alefcept (Amevive) and efalizumab (Raptiva) in the suddenly rather crowded market for the treatment of psoriasis.

The FDA has approved Indevus Pharmaceutical's trospium chloride (Sanctura), for the treatment of overactive bladder with symptoms of the urge urinary incontinence, urgency and frequency. The drug is a muscarinic receptor antagonist, and as such, has side effects that include dry mouth and constipation. It is, however, relatively well-tolerated with fewer drug-drug interactions than currently available medications.

Fondaparinux (Arixtra-Fonda BV), the synthetic selective factor Xa inhibitor, has been given the expanded indication for treatment of acute pulmonary embolism and acute deep venous thrombosis without PE when coadministered with warfarin. Previously, the drug had been approved for prevention of DVT in the setting of orthopedic surgery.

Salix Pharmaceuticals has received approval to market rifaximin (Xifaxan) for the treatment of travelers diarrhea caused by noninvasive strains of *Escherichia coli*. The drug is unique in that it is minimally absorbed (< 0.5%) after oral administration, and exerts its action only in the gut. It is not for use in patients with diarrhea associated with fever or bloody stools, or pathogens other than *E. coli*. The drug is approved for patients age 12 and older and appears to be well-tolerated. ■