Tobacco Use Disorder

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LEARNING OBJECTIVES

1. Justify tobacco use cessation efforts through patient education on the harms of continued use and the benefits of tobacco cessation.
2. Assess patient readiness to quit, and use appropriate counseling strategies (i.e., assess readiness to quit, use the "5 A's," the "5 R's," and/or "Ask-Advise-Refer") to help patients quit smoking.
3. Distinguish key information regarding common drugs used to help patients quit smoking.
4. Devise an appropriate, patient-specific pharmacologic and nonpharmacologic care plan for tobacco cessation, and adjust the plan for use in special populations.
5. Compose an evidence-based recommendation regarding the safety of e-cigarettes and their efficacy as smoking cessation therapy.

ABBREVIATIONS IN THIS CHAPTER

AE	Adverse effect
MI	Motivational interviewing
NRT	Nicotine replacement therapy
RD	Risk difference

Table of other common abbreviations.

INTRODUCTION

Epidemiology

Use of tobacco products remains the leading cause of preventable death in the United States (CDC 2019c). According to the 2017 National Health Interview Survey, an estimated 47.4 million U.S. adults currently use tobacco, including 24.8% of men and 14.2% of women (Wang 2018a). The prevalence of tobacco use is higher among minorities and those with a lower socioeconomic status. The prevalence of tobacco use is also higher among those who are uninsured (31%) or insured by Medicaid (28.2%) than among those with private insurance (16.2%). Regionally, the highest use of tobacco is in the Midwest (23.5%) and South (20.8%).

Of the tobacco products currently available, cigarettes continue to be most popular among adult users (14%), followed by cigars (3.8%), e-cigarettes (2.8%), smokeless tobacco (2.1%), and pipes (1%) (Wang 2018a). Despite the continued preference for cigarettes over other nicotine products among adult users, cigarette use continues to slowly trend downward, with 2017 marking the lowest prevalence reported since 1965 (Wang 2018a). A similar decreasing trend in tobacco use occurred with U.S. middle and high school students during 2011–2017 (Wang 2018b). However, e-cigarette use increased from 1.5% in 2011 to 20.8% in 2018 among high school students (Cullen 2018) and from 0.6% to 3.3% among middle school students during 2011–2017 (Wang 2018b). Preliminary evidence suggests that youth who use e-cigarettes are more likely to smoke traditional cigarettes at a later age than those who do not use e-cigarettes (Soneji 2017; Leventhal 2015; Primack 2015). Because of these worrisome trends in e-cigarette use, in 2016, the FDA finalized a rule that extends its regulatory authority to all tobacco products, including e-cigarettes

(FDA 2017). This rule also prohibits the sale of e-cigarettes to those younger than 18 years and requires a photo identification for purchase. The FDA proposed further restrictions on the sale of flavored e-cigarettes, menthol-flavored cigarettes, and flavored cigars, which typically appeal to younger consumers (FDA 2018). Although this proposal is still under review, over 50% of youth who use tobacco products use menthol cigarettes; therefore, further restrictions could have a significant impact.

Health Consequences

Data analyses are clear regarding the many long-term health consequences of tobacco use. Adults who quit smoking at age 25–34, 35–44, or 45–54 gained on average 10, 9, and 6 years of life, respectively, compared with those who continued to smoke (Jha 2013). According to the American Cancer Society, within 20 minutes of quitting smoking, heart rate and blood pressure begin to decrease (ACS 2019b). Just 2–3 weeks after quitting, lung function and blood flow improve. The risk of stroke decreases to the levels of a nonsmoker after just 2–5 years of continued cessation. After abstaining for 10 years, the risk of death caused by lung cancer is reduced by one-half, and after 15 years of cessation, the risk of coronary heart disease is equal to someone who has never smoked.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of tobacco-induced patient harm and the potential health consequences of long-term tobacco use
- General understanding of guideline-based management of concomitant cardiovascular diseases and their risk factors
- Knowledge of the drugs used to help with smoking cessation
- Basic principles of counseling for health behavior change, including motivational interviewing

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services, May 2008.
- U.S. Preventive Services Task Force. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2009;150:551-5.
- Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329.
- Rx for Change. Clinician-Assisted Tobacco Cessation (available with free registration).

PATIENT ASSESSMENT AND APPROACH TO COUNSELING

Almost 68% of current smokers report that they want to stop smoking, and 55.4% have tried to quit in the past year (Babb 2017). Pharmacists can play a key role in helping patients quit.

Successful intervention for smoking cessation begins with identifying current tobacco users and assessing their readiness to quit (AHRQ 2019). The U.S. Public Health Service treating tobacco use and dependence clinical practice guideline recommends the "5 A's" method for smoking cessation counseling (Fiore 2008). Key components of the 5 A's include (1) asking patients about tobacco use, (2) advising tobacco users to quit, (3) assessing patient readiness to quit, (4) assisting patients with quitting, and (5) arranging follow-up care (Fiore 2008).

5 A's Method

Ask

All patients should be asked about tobacco use at every encounter with a health care professional, and use status should be documented in the electronic medical record (Fiore 2008). Patients who received assistance from a clinician were 1.7–2.2 times more likely to quit than those who had not received clinician intervention. In addition, patients who receive tobacco interventions delivered by two or more types of clinicians are more than twice as likely to quit successfully. When asking about tobacco use, clinicians should consider that patients may be using non-cigarette products or several nicotine products (Fiore 2008). Therefore, the initial inquiry about tobacco use should include asking about these products in addition to cigarette use. For example, "Do you use any tobacco products, including e-cigarettes or smokeless tobacco?" might be an appropriate way to inquire. Box 1 provides additional information.

Advise

All identified tobacco users should be advised to quit in a compelling fashion (Fiore 2008). The clinician should try to personalize this message by referring to patient-specific health conditions that may be affected by smoking or motivations for cessation. This step should be delivered in a caring way to avoid damaging the patient-provider relationship.

Box 1. Assessing Tobacco Use History

Patients should be asked about their current tobacco use in addition to their past use and past quit attempts. The following are key questions when gathering a tobacco use history.

- Current tobacco use? Type(s)? Amount?
- Duration of tobacco use?
- Any changes in use recently?
- How many previous quit attempts?
- Most recent quit attempt? Duration of attempt?
- Methods used to help quit previously?
- Any previous use of medications to help quit? What worked? What did not work?
- What contributed to relapse during previous quit attempts?

Information from: University of Massachusetts Medical School. Center for Tobacco Treatment Research and Training. Clinician's Guide: Conducting an Intake, Assessment and Treatment Planning Session for Tobacco Cessation. 2010.

Assess

After advising patients regarding the benefits of smoking cessation, clinicians should ask patients about their desire to quit (Fiore 2008). During this stage, both readiness to quit and nicotine dependence should be assessed. If the patient is ready to quit, the clinician should help with the quit attempt planning and arrange for a follow-up. Motivational interviewing (MI) and the "5 R's" should be used to explore ambivalence if the patient is not ready to quit.

Assessing Readiness to Quit

Clinicians can use the transtheoretical model of change to determine the patient's current stage of change. Counseling strategies can then be tailored according to that stage (Prochaska 1983). The stages of change are precontemplation, contemplation, preparation, action, and maintenance (Prochaska 1997). Patients may move through the stages in a nonlinear manner and may transition to any stage at any time. For example, a patient may be in the preparation stage for a few weeks only to move into the contemplation stage because of a life stressor. To determine which stage patients are in, they can be asked when they envision themselves quitting (DiClemente 1991). Table 1 provides additional information regarding the transtheoretical model of change.

Assessing Nicotine Dependence

In addition to evaluating patient readiness to quit, the clinician should assess nicotine dependence because this can help guide the treatment plan. The Fagerström test for nicotine dependence provides a standardized instrument for assessing the intensity of physical addition to nicotine (Heatherton 1991). The higher the Fagerström score, the more intense the patient's physical dependence to nicotine and the more likely the patient will have withdrawal symptoms (Table 2).

Table 1. Transtheoretical Model of Change for Smoking Cessation

Stage	Signs	Strategies
Precontemplation	Not ready to quit Would like to quit after > 6 mo	Advise to quit Use MI and 5 R's Provide information about health consequences Offer support if patient decides to quit in the future
Contemplation	Would like to quit within 6 mo	Strengthen motivation Explore roadblocks Provide education
Preparation	Would like to quit within 1 mo	Set a quit date Develop a quit plan Discuss coping strategies
Action	Actively engaged in quit attempt	Modify quit plan as needed Congratulate successes Encourage continued abstinence
Maintenance	Quit within the past 6 mo	Offer encouragement and congratulations Provide relapse prevention strategies

MI = motivational interviewing.

Information from: Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot 1997; 12:38-48; Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol 1983;51:390-5; DiClemente CC, Prochaska JO, Fairhurst SK, et al. The process of smoking cessation: an analysis of precontemplation, contemplation and preparation stages of change. J Consult Clin Psychol 1991;59:295-304.

Table 2. Fagerström Test for Assessment of Nicotine Dependence

Question	Responses	Points
How soon after waking do you smoke your first cigarette?	Within 5 min	☐ 3
	5–30 min	☐ 2
	31–60 min	☐ 1
Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., church, library)?	Yes	☐ 1
	No	☐ 0
Which cigarette would you hate to give up?	First thing in the morning	☐ 1
	Any other	☐ 0
How many cigarettes a day do you smoke?	≤ 10	☐ 0
	11–20	☐ 1
	21–30	☐ 2
	≥ 31	☐ 3
Do you smoke more often in the morning?	Yes	☐ 1
	No	☐ 0
Do you smoke even if you are sick in bed most of the day?	Yes	☐ 1
	No	☐ 0
Score: 1 or 2 = low dependence 3 or 4 = low to moderate dependence 5–7 = moderate dependence 8+ = high dependence		

Reproduced with permission from: Heatherton TF, Kozlowski LT, Frecker RC, et al. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86:1119-27.

Assist

Assist the patient with developing a quit plan (Fiore 2018). The quit plan should be individualized and include a combination of practical counseling, support and encouragement, and, if appropriate, a plan for pharmacotherapy. According to the WHO, the "STAR" acronym can be used to remember key components of the quit plan (Box 2) (WHO 2019).

In addition to the components of the "STAR" acronym, clinicians should provide practical counseling to anticipate and problem solve potential roadblocks (Table 3 and Table 4).

Box 2. WHO STAR Acronym

- **S**et a quit date, ideally < 2 wk away
- **T**ell family and friends about quitting
- **A**nticipate challenges to the upcoming quit attempt
- **R**emove tobacco products from environment

Information from: World Health Organization (WHO). Toolkit for Delivering the 5 A's and 5 R's Brief Tobacco Interventions in Primary Care.

Arrange

Clinicians should arrange the initial follow-up, which should occur within 1 week of the quit date, followed by another follow-up contact within 1 month. The method of follow-up should be based on patient preference, but can be in person, by telephone, or electronically. Abstinence rates increase with an increasing number of follow-ups (Fiore 2008). Therefore, if desired by the patient and feasible for the clinician, more sessions should be targeted. During these sessions, the clinician should review the status of the current quit attempt, including any instances of slips, triggers for relapse, drug adherence, and available social support. Patients should be congratulated on successes during follow-up counseling and encouraged toward continued abstinence.

Ask-Advise-Refer

The 5 A's method can be modified for a brief intervention by simplifying to Ask-Advise-Refer. In this strategy, the clinician asks about tobacco use, advises patients to quit, and refers them to other resources or clinicians to provide

Table 3. Practical Counseling for Smoking Cessation

Practical Counseling	Examples
Identify situational triggers and brainstorm alternative methods to cope with stress	• See Table 4
Develop a strategy to address hand-to-mouth fixations	• Keep hands/mouth busy with gum, hard candies, etc. • Additional considerations: ◦ Lollipops provide benefit of a stick to keep hands busy and candy to keep mouth busy ◦ Cigarette-shaped objects may be particularly beneficial ◦ Consider pretzel sticks/nuts/popcorn if patient prefers something salty ◦ Consider vegetables (e.g., celery/carrots), calorie-free substitutes (e.g., ice, water), or non-food (e.g., flavored tooth picks, straws) if worried about weight gain ◦ Keep hands actively engaged in activity or work (e.g., art, sewing, fidget spinners)
Review how to respond to nicotine cravings	• Remind patients that cravings typically pass within a few minutes and become less frequent and less severe over time • Encourage patients to wait at least 1 min before smoking to try to talk themselves out of the cigarette; think on their reasons for wanting to quit for motivation • Remove cigarettes from house to create additional barriers • Remove reminders of smoking (e.g., ash trays, lighters, items that smell like cigarette smoke [or alternatively, deep clean these items]) • Distract yourself with a project, hobby, or distractive thinking • Consider as-needed NRT for breakthrough cravings
Discuss potential drug interactions	• Decrease the caffeine you consume because quitting tobacco can increase the effects of caffeine in your body by > 50%[a] and can worsen symptoms of nicotine withdrawal • Quitting can increase the concentration of several prescription drugs in the body, including warfarin; therefore, you should review your drugs with a pharmacist or physician before quitting
Compare the difference between slip and relapse	• A slip is smoking one or just a few cigarettes but can lead to a full relapse • Although slips should be avoided, they are a normal part of the quitting process and do not indicate failure • When a slip occurs, patients should be encouraged to contact their clinician to review the quit plan and coping strategies
Identify social support system	• Tell family and friends your reasons for quitting • Ask for check-ins from your support system on your quit date and for the first few weeks after quitting • If another household member also smokes, ask if they are interested in joining you in quitting • Share successes and struggles with your support team

[a]Swanson JA, Lee JW, Hopp JW, et al. The impact of caffeine use on tobacco cessation and withdrawal. Addict Behav 1997;22:55-68.
NRT = nicotine replacement therapy.

further assistance and arrange a follow-up. This allows for effective intervention in a short time and enables providers without clinical expertise in smoking cessation to screen for tobacco use.

Motivational Interviewing

Patients unwilling to quit smoking or unsure about their ability to quit may benefit from MI (Fiore 2008). Motivational interviewing is a patient-centered form of guiding that elicits and strengthens motivation for change (Miller 2012). The 2008 tobacco treatment guidelines recommend MI to help overcome the ambivalence in patients not currently ready to quit (Fiore 2008). According to a Cochrane review of 28 studies that used MI as an intervention for smoking cessation, compared with brief advice or usual care, MI increased the rate of successful quitting (RR 1.26; 95% CI, 1.16–1.36) (Lindson-Hawley 2015). In addition, increased engagement in tobacco cessation counseling and follow-up occurred after

Table 4. Practical Behavioral Strategies to Help Patients Overcome Common Smoking Triggers

Trigger	Sample Behavioral Strategies
First thing in the morning	• Change order of morning routine (e.g., shower/get dressed before having cigarette) • Avoid places where you typically smoke • Wake up 15 min later to eliminate time to smoke
With morning coffee	• Eat a breakfast or snack with coffee • Drink coffee somewhere you cannot smoke (e.g., in the house, the car, or a coffee shop) • Change coffee to tea or another beverage • Identify other means of waking yourself up (e.g., shower, morning exercise)
After meals	• Replace cigarette with new post-meal "treat" (e.g., mint, candy, small dessert) • Brush teeth or suck on lemon immediately after meal (some report these tastes reduce enjoyment of cigarettes) • Linger at table/avoid going outside • Clean table/kitchen as a distraction • Go for a walk after meals (will also help reduce weight gain)
When stressed	• Explain to patient that stress relief from smoking is largely because of removing oneself from stressful situations and deep breathing on cigarette for several minutes, so going outside and performing deep breathing exercises for several minutes may have similar effects • Identify other ways to de-stress (e.g., exercise, meditation or mindfulness, art/coloring books, music, bubble bath, positive self-talk or positive mental imagery, spending time with loved ones or pets) • Identify key stressors and avoid them, when possible • Eat well, exercise, and get plenty of sleep to prevent stress
When bored	• Resume past or develop new hobbies • Always have a means of distraction handy (e.g., a go-to game on cellphone or book of word puzzles) • Start new project that will require an extended period of work (e.g., clean, redecorate or renovate house, fix an old car, sew a blanket) • Fill extended periods at home with new activities in public (e.g., volunteering, socializing)
With alcohol	• Avoid/reduce alcohol consumption during first 2–4 weeks of quit attempt • Do not drink in places that allow smoking or with people who smoke • Remind patients that the more inebriated they become, the more difficult it will be to maintain their resolve not to smoke
Around others smoking	• Ask others not to smoke around you • Avoid places where others are smoking or remove yourself when they start smoking • If you live with other smokers, chances of success are much greater if you try to quit together
When driving	• Remove triggers (e.g., cigarette butts, cigarette smell) • Place cigarettes in trunk of car while driving • Change driving route to avoid subconscious triggers and require additional concentration • Sing to music, listen to books on tape
When on the telephone	• Do not go outside • Do not have cigarettes near
When taking a break from work	• Find other means of relaxation (e.g., close your eyes, have a snack, go for a walk) • Remain inside in an area where you cannot smoke
Before bed	• If patients are taking cessation drugs, remind them that there is less need to smoke before bed to reduce morning withdrawal • Find other means of relaxation (e.g., read, listen to music, drink tea)

Table 5. Examples of MI Techniques for Smoking Cessation

Patient case: R.R. is a 63-year-old man with a history of severe COPD who reports continued nicotine use (1 PPD) despite several recent hospitalizations for exacerbations. After advising the patient to quit, the pharmacist asks him if he has considered quitting. The patient reports he is not ready to set a quit date because of significant life stress (financial and health concerns). However, he expresses concern about his declining lung function and desire to stay healthy for his young grandchildren.

Skill	Examples
Open-ended question	• What have you learned so far about the connection between smoking and the health of your lungs? • If you were better able to manage your stress with other methods, what would be the potential benefits of quitting smoking? • What other strategies do you use to help manage your stress?
Affirmation	• Great job using your inhalers as prescribed! • You have already cut down from 30 cigarettes/day to 20 cigarettes/day. Good for you! • You've already been successful in the past when you tried to quit. You managed to quit for an entire month!
Reflection	• Your family is important to you and you would do anything in order to be there for them • This last hospitalization really scared you • You would be willing to consider quitting if you could find better methods for dealing with stress
Summary	• You are concerned about some significant stress in your life recently, particularly the financial and personal stress you've been feeling because of your worsening COPD, and this makes you hesitant to quit smoking. However, you mentioned that you know quitting smoking would help you stay out of the hospital and save you money, which would ultimately help decrease some of this stress. You are also concerned about maintaining your health so that you can be around for your family

COPD = chronic obstructive pulmonary disease; PPD = pack/day.

Information from: Miller WR, Rollnick S. Motivational Interviewing: Helping People Change, 3rd ed. New York: Guilford Press, 2012.

just a single session involving MI (Steinberg 2004). The core interviewing skills of MI include asking open-ended questions, affirming, reflecting, and summarizing (Miller 2012). These strategies are reviewed in Table 5.

5 R's Method

The principles of MI can also be applied while using the 5 R's method to enhance motivation. This method can increase the increased rates of future quit attempts (Carpenter 2004). The 5 R's – relevance, risks, rewards, roadblocks, and repetition – are to be used to motivate smokers to quit when they indicate they are not currently ready (Fiore 2008). First, ask the patient why quitting is personally relevant to help identify personal motivations to quit. Next, explore with patients their identified risks factors for continued smoking as well as the potential rewards for quitting. Patients should also be encouraged to brainstorm any roadblocks to quitting smoking and ways to overcome them. Examples of barriers often cited by patients include withdrawal symptoms, weight gain, fear of failure, stress relief from tobacco use, and being around other tobacco users. Clinicians should explore ways to address these barriers with the patient. The last "R," repetition, refers to the fact that this method should be repeated during future patient encounters.

GUIDELINE OVERVIEW

Several guidelines have been developed to provide recommendations for helping patients with tobacco cessation, though they have not been updated in recent years.

Clinical Practice Guideline for Treating Tobacco Use and Dependence: 2008 Update

The 2008 update on treating tobacco use and dependence guidelines was based on a systematic review and meta-analysis of 11 topics (Fiore 2008). In brief, the guidelines stress that smoking cessation interventions are effective across a wide range of patient populations, and clinicians should assess smoking status and willingness to quit at each patient encounter. If patients are interested in quitting, the guidelines recommend using NRT, varenicline, or bupropion, or a combination of these pharmacotherapy options. Counseling and other psychosocial interventions should be encouraged as well because the combination of pharmacotherapy and psychosocial intervention is more effective than either modality alone (Stead 2016).

USPSTF Recommendations

The U.S. Preventive Services Task Force (USPSTF) has also developed a guideline regarding tobacco cessation

interventions (USPSTF 2009). The two key recommendations from this guideline, both with grade A evidence, are as follows. (1) All adults should be asked about tobacco use and provided tobacco cessation interventions if they do use tobacco products. (2) All pregnant women should be asked about tobacco use and offered "augmented, pregnancy-tailored counseling" if they smoke. The compiled studies identify high-quality evidence that brief behavioral counseling (specifically, the guidelines discuss the 5 A's counseling strategy, "problem-solving guidance" to help smokers overcome barriers and develop a quit plan, social support, MI, readiness to change assessment, and telephone quitlines as counseling interventions shown helpful) and pharmacotherapy are effective in nonpregnant adults. Pregnant women are significantly more likely to quit if they receive smoking cessation counseling, particularly information tailored to pregnant smokers, and cessation at any point in the pregnancy significantly decreases harm to the mother and child.

National Comprehensive Cancer Network

More recently, the National Comprehensive Cancer Network released a smoking cessation guideline focused on helping patients with cancer (Shields 2016). The overall principles are similar to those of previous guidelines.

FIRST-LINE DRUGS

Nicotine Replacement Therapy

Nicotine replacement therapy promotes tobacco cessation by providing the patient with nicotine in order to reduce the withdrawal effects associated with abrupt cessation (Gomez-Coronado 2018). Using NRT is preferred to gradually reducing consumption of tobacco products for several reasons. Whereas nicotine is the primary addictive component, other substances in tobacco products cause much of the physical harm. Thus, NRT helps patients wean their nicotine consumption while limiting their exposure to harmful chemicals. Furthermore, NRT provides patients with nicotine but helps break the habit components of their addiction, such as a hand-to-mouth fixation, often developed with prolonged cigarette use.

Nicotine replacement therapy is available in five different dosage forms: patch, gum, lozenge, nasal spray, and inhaler (Lexicomp 2019; Rx for Change 2019). Table 6 provides key information regarding each formulation. In brief, a single patch slowly delivers nicotine throughout the day, whereas the other products are faster acting but require more frequent use to maintain sufficient nicotine levels to prevent withdrawal (Hartmann-Boyce 2018). In the United States, although the nasal spray and inhaler are available through prescription only, the patch, gum, and lozenge are available OTC (Lexicomp 2019).

A 2017 Cochrane review including 136 studies (n=64,640 patients) of NRT versus placebo determined that high-quality evidence supported the efficacy of NRT (Hartmann-Boyce 2018). The risk ratio (RR) of abstinence from any form of NRT versus placebo was 1.55 (95% CI, 1.49–1.61), including specific RRs of 1.49 (95% CI, 1.40–1.60) among 56 trials of nicotine gum, 1.64 (95% CI, 1.53–1.75) among 51 trials of nicotine patches, 1.52 (95% CI, 1.32–1.74) among eight trials of nicotine lozenges, 1.90 (95% CI, 1.36–2.67) among four trials of nicotine inhaler, and 2.02 (95% CI, 1.49–2.73) among four trials of nicotine nasal spray.

The adverse effect (AE) profile of NRT is usually more favorable than that of other smoking cessation options. Potential AEs include increased blood pressure, palpitations, lightheadedness, and nausea, which are more likely if the patient continues to use tobacco together with NRT (Lexicomp 2019; Rx for Change 2019). Nicotine patches offer once-daily use, likely leading to increased adherence compared with other dosage forms. Outside clinical trials, patients may have difficulty remaining adherent to the recommended frequency of the short-acting NRT products, particularly across the 10- to 12-week duration recommended. However, some patients may prefer the gum or lozenge because each not only provides nicotine, but also offers a distraction or routine to replace the behavioral patterns associated with smoking. In addition, NRT gum and lozenge both delay the weight gain associated with smoking cessation (Rx for Change 2019; Filozof 2004; Doherty 1996). In one study, among 79 participants, successful abstainers receiving placebo gained 3.7 kg at 90 days post-cessation, around 2 kg more than participants receiving 4 mg (1.7 kg, p=0.05) or 2 mg (2.1 kg, p=0.09) gum (Doherty 1996). Additional evidence suggests that weight suppression is greater with increased use of the gum, but once the gum is discontinued, the patient tends to gain weight similar to those not using the gum (Filozof 2004).

The inhaler may be desirable for some, given that it is the most similar to smoking a cigarette and can help with hand-to-mouth fixations, whereas the nasal spray may be desirable for others, given that it has the fastest onset of action (Drugs for Tobacco Dependence 2018). Conversely, certain comorbidities may make specific dosage forms less desirable, including chronic dermatologic conditions (patches), poor dentition or jaw disorders (gum), acid reflux or dyspepsia (gum or lozenge), asthma or bronchospastic conditions (inhaler), and nasal disorders or restrictive airway disease (nasal spray) (Rx for Change 2019). If the patch is chosen, patients should initially be encouraged to wear it for the full 24 hours, but if they have insomnia or bothersome dreams while wearing the patch, these symptoms may be alleviated by only wearing it while awake. However, given the higher likelihood of cravings and withdrawal effects on waking if the patch was not used overnight and the slow onset of the patch, another NRT product should be prescribed on waking to provide more immediate relief. Finally, many patients describe that the patch does not stick well, especially if they tend to sweat often. In this case, patients may apply medical tape over the patch to minimize this issue or consider other products.

Table 6. First-line Pharmacotherapy for Smoking Cessation

Generic Drug (brand name)	Mechanism of Action	Dosing	Patient Counseling	AEs and Precautions	Clinical Pearls
NRT patch (NicoDerm)	Binds nicotinic-cholinergic receptors	*Smoking > 10 cigs/day:* Apply 21 mg/day × 6 wk, then 14 mg/day × 2 wk, then 7 mg/day × 2 wk *Smoking ≤ 10 cigs/day:* Apply 14 mg/day × 6 wk, then 7 mg/day × 2 wk	Apply to hairless area of back, chest, arms Rotate application sites to reduce skin irritation Waterproof; may shower after applying Initially, use for 24 hr; if sleep disturbances too bothersome, take off before bed	AEs: *Patch:* Local skin reactions, insomnia, abnormal dreams *Gum or lozenge:* Mouth/throat irritation, dyspepsia, nausea, hiccups, jaw discomfort (gum only) *Inhaler-specific:* Mouth/throat irritation, dyspepsia, cough, hiccups, headache *Nasal spray:* Nasal/throat/ocular irritation, sneezing, cough, headache Precautions: *All NRT*: Caution use in patients with recent (≤ 2 wk) MI, arrhythmias, serious or worsening angina, pregnant, breastfeeding, adolescents *Patch-specific*: May exacerbate dermatologic conditions (e.g., psoriasis, eczema) or insomnia *Gum-specific:* Caution use in TMJ; may be less desirable for patients with missing teeth or significant dental work/dentures *Inhaler-specific*: Caution use in patients with asthma/bronchospastic diseases *Nasal spray–specific:* Caution use in patients with chronic nasal disorders or severe reactive airway disease	Patients should ideally completely quit smoking when they begin NRT Patients may state patch does not stick well, especially with sweating; applying medical tape over patch may help If patient cannot tolerate patch overnight, prescribe additional fast-acting NRT product to use on waking To increase effectiveness, use at least 9 gum/lozenge per day initially Dyspepsia, GI AEs, and efficacy may be improved through counseling on proper gum or lozenge technique For gum, lozenge, inhaler: Avoid food/beverages 15 min before or during use Scheduled use more effective than PRN because NRT has slower onset than cigs Fast-acting NRT may be used PRN in combination with patches to provide continuous nicotine with additional assistance during cravings NRT may be less likely to be covered by insurance plans given OTC availability; if not covered, may encourage patient to purchase 1 wk at a time and save cigarette money for next week's supply Nasal spray provides fastest onset Inhaler mimics hand-to-mouth routine; may be preferable for some, but for others, may be a barrier to overcoming this trigger
NRT gum (Nicorette)		If initial cig smoked within 30 min of waking, use 4 mg gum; otherwise, use 2 mg gum Weeks 1–6: Chew 1 gum q1–2hr (max 24 gum/day) Weeks 7–9: Chew 1 gum q2–4hr Weeks 10–12: Chew 1 gum q4–8hr	Crucial to use "chew and park" method to increase efficacy and reduce AEs. Chew until you notice peppery taste; then park between cheek and gum until peppery taste subsides. Repeat this process until it no longer tingles with chewing (~30 min)		
NRT lozenge (Nicorette)		If initial cig smoked within 30 min of waking, use 4-mg lozenge; otherwise, use 2-mg lozenge Weeks 1–6: Use 1 lozenge q1–2hr (max 5 lozenges q6hr or 20 lozenges/day) Weeks 7–9: Use 1 lozenge q2–4hr Weeks 10–12: Use 1 lozenge q4–8hr	To reduce AEs and increase efficacy, do not suck on lozenge like a mint or chew or swallow; instead simply park between cheek and gums and let it absorb buccally Occasionally rotate to different area of mouth		
NRT inhaler (Nicotrol)		Use 6–16 cartridges per day initially, and gradually taper over 6–12 wk; use at least 6 cartridges/day for the first 3–6 wk -May use for up 6 mo	DO NOT inhale into lungs like a cig; puff in short breaths because nicotine should be absorbed buccally Cartridge contents depleted after ~20 min of continuous puffing. If patient does not use complete cartridge, may continue to use open cartridge for up to 24 hr Best effect achieved with frequent continuous puffing		

(*continued*)

Table 6. First-line Pharmacotherapy for Smoking Cessation (*continued*)

Generic Drug (brand name)	Mechanism of Action	Dosing	Patient Counseling	AEs and Precautions	Clinical Pearls
NRT nasal spray (Nicotrol NS)		Initial: One or two doses per hour and taper over 4–6 wk It is not recommended to use more than 10 sprays per hour or 40 mg/day, or for more than 3 mo	2 sprays, 1 in each nostril contains 1 mg nicotine and constitutes one dose -Do not inhale through nose as spray is dispensed		Once-daily application of patch may be more desirable than the frequent dosing required of other NRT products; many patients have difficulty remaining adherent to recommended dosing of non-patch NRT products AEs may be more pronounced with continued smoking while using NRT products Most drug interactions from smoking come from the cigarette smoke as opposed to nicotine. As a result, though NRT has few drug interactions, cessation of smoking may alter the pharmacokinetics of various drugs, including warfarin, clopidogrel, and caffeine, among others
Varenicline (Chantix)	Partial α_4 β_2 nicotine receptor agonist	Days 1–3: 0.5 mg once daily Days 4–7: 0.5 mg twice daily Day ≥ 8: 1 mg twice daily Use for 12 wk May extend use to up to 6 mo, if needed For CrCl < 30 mL/min/1.73 m^2: Initiate 0.5 mg once daily and titrate to max dose of 0.5 mg twice daily For hemodialysis: Max dose of 0.5 mg once daily	Take with food and full glass of water to improve tolerability Effects will not be noticed immediately; begin taking varenicline at least 1 wk before quit date Report unexplained changes in mood to provider	*AEs:* Headache, nausea, vomiting, constipation, flatulence, insomnia, abnormal/vivid dreams, neuropsychiatric symptoms (e.g., anxiety, irritability, depression, suicidal ideation), CNS depression *Precautions:* Caution use in patients with PTSD, especially if night terrors present Caution use in patients with uncontrolled psychiatric comorbidities or suicidal thoughts (boxed warning now removed) Caution use in patients with seizures Caution use if pregnant or breastfeeding	Most effective monotherapy option Starter pack provides 0.5- and 1-mg tablets in daily dose blister pack to facilitate initial week dose titration May consider reduced dose if usual dose is not tolerated Brand name only; most expensive option on the basis of cash price, but is widely covered by insurance plans

Table 6. First-line Pharmacotherapy for Smoking Cessation (*continued*)

Generic Drug (brand name)	Mechanism of Action	Dosing	Patient Counseling	AEs and Precautions	Clinical Pearls
Bupropion SR (Zyban)	Not entirely understood; effects on dopamine and norepinephrine are thought to interfere with the reward pathway; also functions as a noncompetitive antagonist of nicotinic acetylcholine receptors	150-mg SR tablet once daily for 3 days, then 150-mg SR tablet twice daily for 7–12 wk Consider dose reductions for renal dysfunction (specific recommendations not provided) or severe hepatic dysfunction (for Child-Pugh score 7–15, prescribing information recommends max dose of 100 mg daily or 150 mg every other day) May use for up to 6 mo	Onset is delayed; begin at least 1 wk before target quit date Take second dose late afternoon/early evening to reduce insomnia	*AEs:* Insomnia, headache, agitation, weight loss, dry mouth, nausea, constipation, anxiety/nervousness, lack of concentration, tremor, seizures *Contraindications:* Seizure disorders or conditions that increase seizure risk (e.g., abrupt discontinuation of heavy alcohol or benzodiazepine use) Concomitant MAO inhibitors or bupropion (i.e., Wellbutrin for depression) therapy Bulimia or anorexia nervosa *Precautions:* Pregnant or breastfeeding Adolescents Treatment-emergent neuropsychiatric AEs Severe hepatic or renal impairment As with most antidepressants, the prescribing information includes warnings regarding increased suicidal ideation in patients with suicidal thoughts or risk of mania in patients with bipolar disorder; monitor closely after initiation or dose titration; EAGLES trial did not identify significant increase in neuropsychiatric effects or suicidality vs. placebo	If 300 mg/day is not tolerable, may continue at 150 mg once daily because efficacy has been shown at this lower dose May delay weight gain May be ideal for patients with comorbid, uncontrolled depression Functions as a CYP2D6 inhibitor Generic formulations available

AE = adverse effect; cig = cigarette; MAO = monoamine oxidase inhibitor; PRN = as needed; PTSD = posttraumatic stress disorder; q = every; Rx = prescription; TMJ = temporomandibular joint dysfunction.

Information from: Manufacturer's package insert; Lexicomp. Riverwoods, IL: Wolters Kluwer Health, 2019; Rx for Change. Clinician-Assisted Tobacco Cessation; Swanson JA, Lee JW, Hopp JW, et al. The impact of caffeine use on tobacco cessation and withdrawal. Addict Behav 1997;22:55-68.

Varenicline

According to the package insert, varenicline (Chantix) is a partial agonist of nicotinic acetylcholine receptors. Given its high affinity for these receptors and partial agonist effects, varenicline simultaneously inhibits nicotine from binding and reduces withdrawal effects. After an initial 1-week titration, varenicline is administered twice daily. Dose reductions are warranted for chronic kidney disease when the CrCl is below 30 mL/minute/1.73 m^2.

Varenicline has been more effective than bupropion or NRT in head-to-head trials (Cahill 2013). However, combination NRT may be similarly effective to varenicline alone, and combination varenicline and NRT or varenicline and bupropion may be more effective than varenicline alone (Anthenelli 2016; Baker 2016; Vogeler 2016; Chang 2015). However, evidence for the combination varenicline and NRT or varenicline and bupropion options is limited, and these combination therapies should be reserved for patients who have not responded to other options. A Cochrane review and meta-analysis similarly identified that varenicline was more effective than placebo (OR 2.88; 95% CI, 2.40–3.47), bupropion (RR 1.59; 95% CI, 1.29–1.96), and NRT monotherapy (OR 1.57; 95% CI, 1.29–1.91), but not combination NRT (OR 1.06; 95% CI, 0.75–1.48) (Cahill 2013).

Gastrointestinal AEs, headaches, and sleep disturbances, including abnormal/vivid dreams or insomnia, are well-established AEs associated with varenicline (Lexicomp 2019). Neuropsychiatric symptoms, including anxiety, irritability, depression, and suicidal ideation, have also been reported in clinical trials and in the varenicline prescribing information. The EAGLES trial mitigated concerns regarding the risk of neuropsychiatric AEs and suicide risk (Anthenelli 2016). This is discussed in greater detail in the Special Populations section that follows discussing patients with psychiatric comorbidities.

A 2011 meta-analysis raised concerns regarding a potential increase in cardiovascular risk associated with varenicline use (Lexicomp 2019; Singh 2011). Among 14 trials, including 8216 patients, serious adverse events occurred in 1.06% of patients receiving varenicline and 0.82% of patients receiving placebo (OR 1.72; 95% CI, 1.09–2.71). At the FDA's request, a 52-week nontreatment extension of the EAGLES trial assessed the cardiovascular safety profile of varenicline, the NRT patch, and bupropion. Varenicline did not increase the composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared with placebo during treatment (risk difference [RD] −1.13; 95% CI, −5.54–3.27) or at the end of the study (RD −0.99; 95% CI, −4.80 to 2.82) (Benowitz 2018). Furthermore, subsequent meta-analyses have not found an increased cardiovascular disease risk with varenicline (Sterling 2016; Chelladurai 2014). A 2017 meta-analysis of seven trials including 2809 patients compared varenicline, bupropion, or NRT with placebo in patients with established cardiovascular disease, finding varenicline the most effective treatment in this population (Suissa 2017). Compared with placebo, the RR was 2.64 (95% CI, 1.34–5.21), 1.42 (95% CI, 1.01–2.01), and 1.22 (95% CI, 0.72–2.06), respectively, for varenicline, bupropion, and NRT.

Bupropion Sustained Release

Bupropion is a dopamine and norepinephrine reuptake inhibitor initially marketed as an antidepressant and later found effective as a smoking cessation aid as well (Gomez-Coronado 2018). Bupropion's mechanism of action in smoking cessation is not entirely understood, though its effects on dopamine and norepinephrine may interfere with the reward pathway, and the drug also appears to function as a noncompetitive antagonist at the nicotinic acetylcholine receptors (Vogeler 2016). Bupropion is available in several formulations, but the formulation approved for smoking cessation is the 150-mg sustained release (SR) tablet. According to the package insert, bupropion should be administered once daily for 3 days, then twice daily for the remainder of therapy. On discontinuation, a taper off the drug is not needed. Severe liver or renal impairment can affect bupropion's pharmacokinetics, and dose reductions are advised in these situations. Epilepsy, bulimia, and anorexia are all considered contraindications for using bupropion.

Bupropion is more effective than placebo and similarly effective to NRT monotherapy (Cahill 2013). A meta-analysis of 36 studies identified the OR of smoking cessation with bupropion versus placebo as 1.82 (95% CI, 1.6–2.06) and bupropion versus NRT as 0.99 (95% CI, 0.86–1.13). Like NRT gum or lozenge, bupropion reduces cessation-associated weight gain by around 1–2 kg (Filozof 2004).

Several AEs occur with bupropion, including insomnia, headache, agitation, weight loss, dry mouth, nausea, constipation, anxiety, and lack of concentration (Lexicomp 2019). Seizures are a serious AE associated with bupropion because the drug reduces the seizure threshold. Although the aforementioned Cochrane review identified only a few seizures among 82 bupropion studies (six total in the bupropion groups vs. zero in the placebo groups), the drug should be avoided in patients with epilepsy or other factors that could increase their seizure risk (Cahill 2013). This meta-analysis also identified no significant excess in cardiovascular (RR 0.77; 95% CI, 0.37–1.59) or neuropsychiatric (RR 0.88; 95% CI, 0.31–2.50) AEs compared with placebo. This was corroborated by the EAGLES trial, which did not identify significant increases in neuropsychiatric AEs compared with placebo or active treatment in patient cohorts with or without psychiatric comorbidities (Anthenelli 2016).

Drug-Related Patient Counseling

Nicotine replacement therapy is most effective when used on a regular basis to prevent withdrawal, instead of as needed when cravings arise, because maximal nicotine blood and brain concentrations are reached significantly slower than

that with cigarettes themselves (Gomez-Coronado 2018). Whereas nicotine from cigarettes may reach the brain in only seconds, rapid-acting NRT delivers nicotine over minutes, and patches may take an hour or more (Molyneux 2004). Thus, patients should be counseled to take their NRT at regularly scheduled intervals in order to prevent withdrawal effects. Counseling on the appropriate administration technique such as rotating patch application sites and using the "chew and park" method for gum is important to improve tolerability and efficacy.

Although NRT products begin providing benefit on the first day of therapy, patients should be reminded that both varenicline and bupropion have a delayed onset and should be started at least 1 week before the desired quit date (Lexicomp 2019). An initial dose titration is also recommended for both varenicline and bupropion to improve tolerability, so patients should be counseled on the appropriate titration schedule. Varenicline should be administered with food to improve tolerability, whereas bupropion should not be administered immediately before bed to reduce the risk of insomnia. With both, patients should be encouraged to alert their provider of any significant changes in mood.

See Table 6 for additional product-specific counseling points, including how to use each product.

Combination Therapy

The guidelines specifically discuss the value of combination therapy and encourage clinicians to consider using several drugs in certain situations because many combinations have been shown effective in clinical trials (Fiore 2008). Specifically, the treating tobacco use and dependence guidelines identify sufficient evidence to recommend several combinations of several NRT products (patch plus gum, patch plus nasal spray, and patch plus inhaler), as well as the NRT patch plus bupropion. The guidelines also identify several small studies indicating the efficacy of combination NRT with nortriptyline, paroxetine, or venlafaxine versus placebo, but because the evidence of these combinations is quite limited and these drugs are not first line, the guidelines specifically recommend the combination of several NRT products or NRT plus bupropion preferentially.

Combination NRT

A Cochrane review and meta-analysis found combination NRT more effective with respect to sustained cessation of 6 months or longer than placebo (OR 2.73; 95% CI, 2.07–3.65), the NRT patch (OR 1.43; 95% CI, 1.08–1.91), NRT gum (OR 1.63; 95% CI, 1.21–2.2), and bupropion (OR 0.68; 95% CI, 0.5–0.91 for bupropion relative to combination NRT) (Cahill 2013). Combination NRT was similarly effective to varenicline (OR 1.06; 95% CI, 0.75–1.48 for varenicline relative to combination NRT). However, this added success associated with combination NRT relies on patient adherence to both NRT products, and evidence suggests that adherence to combination NRT is low. In fact, a 2018 study assessing adherence to the NRT patch plus NRT gum found that only 1.4% of patients were adherent to both their patch and their gum therapy every day over the 6-week follow-up after the target quit day (Schlam 2018).

NRT plus Bupropion

A separate Cochrane review, which included six trials, showed no significant difference in 6-month abstinence rates with the combination of bupropion and NRT versus NRT alone (RR 1.23; 95% CI, 0.67–2.26) (Hughes 2014). Thus, combination NRT or varenicline monotherapy is usually preferred to NRT plus bupropion, but this combination may be warranted in patients whose other options have failed.

Varenicline plus Bupropion

Several recent studies have also assessed combinations of varenicline with bupropion or NRT. Despite concerns regarding additive neuropsychiatric AEs, a 2016 systematic review identified four trials assessing combination varenicline and bupropion, finding it relatively safe and effective in each study, particularly in men, those smoking more cigarettes, and patients with higher nicotine dependency (Vogeler 2016). However, only one of the four studies included patients with psychiatric comorbidities, the patient population likely to be most at risk of these AEs (Issa 2013). Thus, additional studies are needed before using this combination routinely, and given the current evidence, the combination should be reserved for patients who have not responded to other options.

Varenicline plus NRT

With respect to varenicline and nicotine replacement, despite seemingly non-synergistic mechanisms of action (i.e., theoretically, varenicline would blunt the effects of NRT), several small studies have identified improved efficacy with the combination compared with varenicline alone. A 2015 systematic review and meta-analysis including three trials and 904 patients found the combination of NRT patch and varenicline more effective than varenicline alone in both the early outcomes of 4- or 12-week abstinence (OR 1.50; 95% CI, 1.14–1.97) and the late outcome of 24-week abstinence (OR 1.62; 95% CI, 1.18–2.23) (Chang 2015). Combination therapy resulted in numerically, but not statistically significantly, higher rates of nausea (OR 1.15; 95% CI, 0.85–1.56), insomnia (OR 1.27; 95% CI, 0.89–1.80), and abnormal dreams (OR 1.20; 95% CI, 0.60–1.72). One study reported skin reactions and, as expected, found this more likely with the combination than with varenicline alone (14.4% vs. 7.8%, p=0.03).

Factors Influencing Drug Selection

As previously discussed, a Cochrane review and meta-analysis determined the following regarding the relative efficacy: (1) NRT, varenicline, and bupropion were all more effective than placebo; (2) bupropion and NRT monotherapy were similarly

effective; (3) varenicline and combination NRT were more effective than bupropion or NRT monotherapy; and (4) varenicline and combination NRT were similarly effective (Cahill 2013).

Because each option can be effective, patient preference should be a significant component of the drug selection process, as should careful consideration of patient-specific factors and comorbid conditions. Given that bupropion is similarly effective to NRT but often has a greater risk of AEs, NRT is often preferred to bupropion in patients who have not previously tried pharmacotherapy unless a compelling indication exists for using bupropion, such as uncontrolled, comorbid depression. Although varenicline may have more AEs than NRT, its greater efficacy than NRT monotherapy is a consideration. Thus, in the absence of compelling indications for or against a specific therapy, combination NRT or varenicline may be preferred in previously untreated patients with no compelling indications for a specific therapy.

Posttraumatic stress disorder (varenicline), epilepsy, or other conditions that increase seizure risk (bupropion and, to a lesser extent, varenicline), uncontrolled psychiatric comorbidities, or active suicidal ideations make varenicline or bupropion less desirable than NRT. Patients who smoke more than 1 pack/day likely benefit more from varenicline or combination therapy, such as combination NRT or NRT plus bupropion. Because most patients require more than one quit attempt before sustained abstinence, many have tried smoking cessation aids in the past. In these situations, history of treatment success, failure, or intolerability to specific drugs also helps guide therapy decisions.

Cost may also play a role in treatment decisions. Varenicline is the most expensive option with respect to cash price, but it is widely covered by insurance companies. In contrast, although NRT has a relatively low cash price compared with varenicline, some insurance plans do not provide coverage because NRT is available OTC.

ALTERNATIVE DRUGS

Although not commonly used because of their less favorable AE profile and more limited evidence of their efficacy, several other drugs have been studied as tobacco cessation aids, though they lack labeled indications. Nortriptyline and clonidine are the two with the best evidence and recommended as second-line agents in the treating tobacco use and dependence guidelines for patients who do not respond to, do not tolerate, or have contraindications to each of the first-line agents (Fiore 2008).

Nortriptyline

The mechanism of action of the tricyclic antidepressant nortriptyline as a smoking cessation agent is unclear. Nortriptyline's effectiveness may result from producing noradrenergic action similar to nicotine, though several other potential mechanisms have also been proposed (Gomez-Coronado 2018; Hughes 2005).

When used for smoking cessation, nortriptyline should be started 10–28 days before the anticipated quit date at an initial dose of 25 mg once daily, titrating to a maximum of 75–100 mg/day, and continuing therapy for at least 12 weeks (Lexicomp 2019; Haggstram 2006). This total daily dose may be divided throughout the day, if needed, for tolerability. Specific recommendations for tapering after a smoking cessation attempt are not provided in the prescribing information, but tapering is advisable before discontinuing therapy (Hughes 2005). One potential taper schedule used in a recent study decreased nortriptyline from a maintenance dose of 75 mg/day to 50 mg/day for 4 days, followed by 25 mg/day for 3 days before discontinuation (Richmond 2013).

A 2014 Cochrane review evaluated six small trials of nortriptyline as a smoking cessation aid (Hughes 2014). Nortriptyline improved long-term smoking cessation rates compared with placebo (n=975 total participants; RR 2.03; 95% CI, 1.48–2.78). Among three trials directly comparing nortriptyline with bupropion, a meta-analysis had shown the efficacy of nortriptyline to be similar (n=417; RR of bupropion vs. nortriptyline 1.30; 95% CI, 0.93–1.82). Nortriptyline is usually associated with a less favorable AE profile than bupropion. However, the Cochrane review noted that in head-to-head studies, rates of AEs or treatment discontinuation were similar. Dry mouth (commonly reported, with rates as high as 85% in smoking cessation randomized controlled trials), constipation, nausea, and sedation are common with nortriptyline, and nortriptyline can be harmful in overdose (Hughes 2014, 2005). Because of these anticholinergic and sedating properties, nortriptyline is included in the Beers Criteria as a potentially inappropriate drug for older adults (AGS 2019). Furthermore, nortriptyline promotes weight gain, which may be particularly bothersome in patients already concerned about weight gain because of quitting smoking (Hughes 2005). However, these data are primarily from depression studies, because most trials of nortriptyline for smoking cessation did not report weight. In trials of nortriptyline for smoking cessation, dropout rates because of AEs were 4%–13%, but serious AEs were uncommon (one event among 506 total patients receiving nortriptyline in the Cochrane review) (Hughes 2014, 2005). No direct comparisons of nortriptyline with NRT or varenicline were identified, but pooled results from four trials found that nortriptyline significantly increased efficacy when it was added to NRT compared with NRT alone (n=1644; RR 1.21; 95% CI, 0.94–1.55) (Hughes 2014).

Clonidine

Clonidine, an α_2-agonist, has been used to ameliorate the withdrawal effects associated with cessation of tobacco, alcohol, or opioids (Gourlay 2004). Clonidine may improve the likelihood of smoking cessation by reducing the cravings, anxiety, restlessness, tension, and hunger associated with nicotine withdrawal.

A Cochrane review identified six placebo-controlled randomized controlled trials of clonidine for smoking cessation, three each of the oral and transdermal dosage forms, with at least a 12-week follow-up (Gourlay 2004). Overall, clonidine was more effective than placebo (n=776; RR 1.63; 95% CI, 1.22–2.18). Clonidine dosages used in these trials were 0.15–0.45 mg/day orally and 0.1–0.3 mg/day transdermally. For the oral dosage form, clonidine should be initiated at 0.1 mg twice daily and, if needed, titrated by 0.1 mg/day every 7 days to a maximum daily dose of 0.4 mg. The clonidine patch, which is applied weekly, should be initiated at 0.1 mg/day and increased to 0.2 mg/day after 1 week, if needed. Clonidine should be initiated 2–3 days before quitting with a recommended duration of 3–10 weeks, tapering the dose over the past few days of therapy to avoid clonidine withdrawal and rebound hypertension (Lexicomp 2019; Gourlay 2004). The necessary duration of clonidine may be shorter than for other cessation aids because its role is to provide relief of acute withdrawal effects, which typically last 3–4 weeks (Gourlay 2004).

Unlike the body of evidence for nortriptyline, in which the trials were of high quality, the authors of this Cochrane review noted significant sources of potential bias in the trials of clonidine for smoking cessation and rated the quality of evidence as poor (Gourlay 2004). Only one of the individual trials showed a statistically significant benefit with clonidine, and several trials notably lacked details regarding randomization and blinding procedures or failed to include biochemical verification of cessation or assessment of sustained abstinence. The Cochrane review also concluded that a high likelihood of AEs limits its usefulness. Common dose-dependent AEs include xerostomia, orthostatic hypotension, sedation, and dizziness. Like nortriptyline, clonidine is included in the Beers Criteria as a drug to avoid in older adult patients because of its high risk of CNS effects (AGS 2019). Clonidine should be reserved as a second-line agent for patients who are intolerant of varenicline, NRT, or bupropion or whose therapy with such agents has failed (Gourlay 2004). However, patients trying to withdraw from several drugs simultaneously or patients with significant agitation or anxiety with their tobacco cessation may have additional benefit from clonidine.

Patient Care Scenario

A 1 pack/day smoker returns to the clinic for a follow-up smoking cessation visit. You prescribed nicotine patches (21 mg × 6 weeks, 14 mg × 2 weeks, 7 mg × 2 weeks) 3 weeks prior, and he reports he is now 2 weeks smoke free. The nicotine patches are reducing the withdrawal effects he had in past quit attempts, and this is the longest he has ever gone without smoking. His only concern is that he has had difficulty sleeping over the past 3 weeks. He says he never had any difficulty sleeping before this. Which one of the following would be best to continue helping this patient in his quit attempt while mitigating his sleeping difficulties?

A. Change to nicotine gum therapy because this will cause less sleep disturbance than the nicotine patch.

B. Encourage him not to change his drug regimen, given that he is smoke free. Inform him that difficulty sleeping is common when quitting smoking but that it should wane within a few weeks.

C. Advise him to remove the patch each night before bed and prescribe as-needed nicotine lozenges.

D. Discuss changing to bupropion SR because this is the only first-line smoking cessation drug that does not usually cause sleep disturbances.

ANSWER

Answer C is best for this patient. Because he is having success with NRT and tolerating it relatively well, he should remain on NRT, if possible, particularly because his only concern is one that can likely be mitigated by optimizing his drug regimen. Although nicotine patches should initially be worn around-the-clock, if a patient has insomnia while wearing them, removing it before bed may resolve this AE. However, because the patch's onset of action is slow compared with other NRT products and first thing in the morning is often the most difficult craving to overcome, it is advisable to prescribe the patient a faster-acting NRT product (e.g., gum, lozenge, nasal spray, or inhaler) to be used on waking. Furthermore, evidence shows that combination NRT is more effective than NRT monotherapy, so Answer C is better than Answer A, though Answer A would be a possible alternative. Similarly, Answer D is a possible alternative, though it is less optimal for several reasons. Combination NRT is more effective than bupropion, and he has already had success with NRT therapy. In addition, bupropion has a delayed onset of action, so directly changing to bupropion would be less ideal in the middle of a successful quit attempt. The answer choice is also inaccurate, because bupropion also commonly causes insomnia. Finally, Answer B is not the most ideal because if the insomnia is a result of the NRT, it is not likely to resolve with continued use. Instead, his regimen can be optimized by maintaining his use of NRT but improving its tolerability.

1. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329.
2. Fiore MC, Jaén CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health & Human Services, May 2008.
3. Lexicomp. Riverwoods, IL: Wolters Kluwer Health, 2019.
4. Rx for Change. 2019. Clinician-Assisted Tobacco Cessation.

ADDITIONAL CLINICAL CONSIDERATIONS

Drug Interactions

Drug interactions should be considered when helping patients with their smoking cessation attempt. Whereas NRT and varenicline have few drug interactions, bupropion is a CYP2D6 inhibitor that may cause drug interactions (Lexicomp 2019). However, regardless of which drug is chosen, patients may experience the removal of drug interactions when quitting. The polycyclic aromatic hydrocarbons in tobacco smoke itself are inducers of hepatic CYP enzymes, particularly CYP1A2 (Lexicomp 2019; Rx for Change 2019). Thus, quitting smoking may alter the pharmacokinetics of drugs such as clozapine, olanzapine, warfarin, and clopidogrel. Smoking cessation increases plasma caffeine concentrations by more than 200% as well (Swanson 1997). Because the effects of caffeine toxicity may exacerbate those of nicotine withdrawal, heavy caffeine users should be advised to reduce their caffeine intake when quitting smoking. Another important drug interaction is that of smoking and estrogen-containing contraceptives. All smokers who want to use estrogen-containing contraception should be strongly advised to quit because of increased thromboembolic risk. Estrogen-containing contraceptives are contraindicated in women 35 and older who smoke 15 cigarettes or more per day (Curtis 2016).

Vaccinations and Screening

The CDC identifies smoking as a disease that significantly increases the risk of pneumonia and recommends that all smokers age 19–64 receive one dose of the pneumococcal polysaccharide (PPSV23) vaccination in addition to the routine vaccination that is recommended for all patients 65 and older (CDC 2019b). The USPSTF also recommends (grade B recommendation) annual screening for lung cancer with low-dose CT in adults age 55–80 with a 30 pack-year history of smoking unless they quit more than 15 years prior (USPSTF 2013), whereas the American Cancer Society provides similar recommendations but recommends a narrower screening window of patients age 55–74 (ACS 2019a).

NONPHARMACOLOGIC OPTIONS

Quitlines

One resource for helping patients with smoking cessation is the tobacco quitline. The tobacco quitline, 1-800-QUIT-NOW, is a national toll-free number operated by the National Cancer Institute that connects patients to a state-specific quitline (CDC 2019a; Fiore 2008). The free quitline uses several services to help tobacco users quit, including individual counseling, self-help materials, and free or discounted drugs.

Tobacco treatment counseling delivered by proactive telephone counseling increases abstinence rates compared with no counseling (Fiore 2008; Zhu 2002, 2000). In a study with the California Smokers' Helpline, cessation at 1 year was 9.1% in patients who received telephonic counseling plus a self-help packet compared with 6.9% in patients who just received a self-help packet with no counseling ($p<0.001$) (Zhu 2002). The greatest benefit was with three or more calls (Stead 2013). The best results occur when behavioral counseling delivered by quitline is combined with pharmacotherapy (Stead 2013).

In addition, many text or electronic messaging services are available to help through automated messages sent to the patient, many of which are tailored to specific patient populations. For example, smokefree.gov offers several text messaging programs tailored to specific populations, including pregnant women, teenagers, and veterans (Smokefree.gov 2019a, 2019b). Several free cellphone applications are also available, including "QuitGuide" and "quitSTART," which allow patients to track their smoking history and provide encouragement and tips during the cessation attempt.

Assisted Taper and QuitKey

Patients may also choose to slowly taper their tobacco use as a method of smoking cessation or preparation for smoking cessation. Options for a taper include self-regulating, changing to cigarettes with lower nicotine content, or using filters to decrease the inhaled nicotine content. Several tools help patients track their cigarette use to help with tapering, including cigarette logs or "pack tracks" – cigarette tracking tools that are similar in size to a pack of cigarettes and can easily be attached to pack for convenient tracking – though data analyses proving their efficacy are limited (ALA 2009).

Patients can also use assisted tapering devices such as the QuitKey to help with the tapering process (Riley 2002; Jerome 2000). QuitKey is a hand-held computer that creates a personalized plan for gradual reduction in cigarette use by tracking typical cigarette use over the first 7 days and then prompting nicotine users to slowly decrease cigarette use over the next 2–4 weeks (QuitKey 2019). Although QuitKey has been associated with improved cessation rates in two small studies, many phone apps are now available to provide assistance and may be more convenient for the patient (Riley 2002).

Financial Incentives

Programs that provide financial incentives or free drugs to incentivize quit attempts are another nonpharmacologic option. Financial incentives may include lottery tickets or prize draws, cash payments, vouchers, and the recovery of previously deposited money (Cahill 2015). Several studies have shown that using financial incentives as a motivation for smoking cessation resulted in a higher rate of sustained smoking abstinence (Halpern 2018, 2015; Tappin 2015). A Cochrane review showed an overall increase in short-term cessation rates using incentives, particularly with programs that used worksite-issued cash payments for cessation (Cahill 2015).

"Quit and Win" contests are another means of increasing motivation to initiate and maintain quit attempts using financial incentives. A Quit and Win contest is an initiative in which enrolled patients who successfully quit smoking for a specified period enter into a drawing to win a prize. Several Quit and Win studies have shown that using incentives such as cash prizes, vacations, or consumer goods as motivation for smoking cessation results in as high as an 8%–20% increase in quit rates, though a Cochrane review noted that most of these studies lacked sound control groups and had significant method limitations (Cahill 2011, 2008).

E-Cigarettes

A 2018 systematic evidence review concluded that changing from combustible tobacco products to e-cigarettes reduced short-term AEs of continued smoking (NASEM 2018). The CDC agrees that nicotine delivered by e-cigarettes is less harmful than smoking tobacco cigarettes, but long-term data on the risks of e-cigarette use are lacking. However, although likely safer than traditional cigarettes, e-cigarettes are not without risks. The vaping liquid used with e-cigarettes may contain carcinogenic compounds (Rubinstein 2018). Some patients using e-cigarettes may have greater nicotine exposure, and reports of nicotine toxicity associated with e-cigarettes are increasingly common, particularly in adolescents (Tegin 2018). According to a CDC study, calls to poison control centers related to e-cigarettes increased from 1 per month in September 2010 to 215 per month in February 2014 (Chatham-Stephens 2014). E-cigarettes are also a source of secondhand exposure to nicotine and other chemicals, and the risks of secondhand vapor are unknown (Hess 2017; Sleiman 2016).

Only limited evidence suggests e-cigarettes are effective as cessation aids (NASEM 2018; Hartmann-Boyce 2016). A 2016 Cochrane review identified little evidence of their effectiveness, with only one randomized controlled trial having cessation rates with e-cigarettes similar to NRT (RR 1.26; 95% CI, 0.68–2.34) (Bullen 2013). An additional randomized controlled trial compared e-cigarettes that contained nicotine with those that did not in current smokers who were not interested in quitting (Caponnetto 2013). This study found increased 6-month abstinence among users of nicotine-containing e-cigarettes.

A recent study assigned patients to a combination of behavioral support for at least 4 weeks with their choice of either NRT or second-generation e-cigarettes (Hajek 2019). In this trial, one of the most prominent studies to date of e-cigarettes for smoking cessation, among 886 participants, the 1-year abstinence rate was 18% in the e-cigarette group compared with 9.9% in the NRT group (RR 1.83; 95% CI, 1.30–2.58). However, this study had several significant limitations, including the lack of blinding and lower-than-expected success rate in the control group; most notably, 80% of participants who had successfully quit smoking were still using their e-cigarettes at the end of the 1-year follow-up, indicating that most had simply traded cigarettes for e-cigarettes.

SPECIAL POPULATIONS

Psychiatric Comorbidities

Individuals with psychiatric comorbidities are significantly more likely to use tobacco (32%) than adults without (23.3%) (CDC 2019d). There are many potential reasons for this, including patients using cigarettes to temporarily alleviate symptoms associated with psychiatric comorbidities or AEs of their medications, or to improve their focus or cognitive functioning, among others (CDC 2019d; Tsio 2013). These patients are also more likely to have barriers to quitting, including social or financial stressors or limited access to health care. This cohort may also face additional barriers to using tobacco cessation drugs, given their potential increased susceptibility to neuropsychiatric AEs.

Schizophrenia

Patients with schizophrenia are particularly vulnerable, with smoking prevalence up to 5 times higher than in the general population (de Leon 2005). Furthermore, patients with schizophrenia tend to smoke more heavily, have higher levels of nicotine dependence, and may have more psychological, cognitive, and social barriers to quitting than patients without schizophrenia (Tsio 2013; de Leon 2005).

A 2013 Cochrane review of 34 trials specifically focused on smoking cessation interventions for patients with schizophrenia (Tsio 2013). The authors concluded that bupropion had the most compelling evidence for use. Among seven trials, bupropion had greater efficacy than placebo at the end of treatment (RR 3.03; 95% CI, 1.69–5.42) and at 6 months (RR 2.78; 95% CI, 1.02–7.58), without significantly increasing neuropsychiatric AEs. Compared with placebo, varenicline also improved smoking cessation rates at the end of treatment (RR 4.74; 95% CI, 1.34–16.71) without significant differences in psychiatric AEs, though only two trials were included in this analysis. Among 144 total smokers receiving varenicline in these studies, two patients had suicidal ideation during these trials. Nicotine replacement therapy was not effective in this population. Two trials were also identified that suggested monetary rewards improve cessation rates in patients with schizophrenia, but evidence of long-term cessation was lacking.

Depression

Depression may also play an important role in cessation. People with depression are twice as likely to smoke, and uncontrolled depression may affect treatment choices or decrease a patient's success in abstaining (van der Meer 2013). Patients with current uncontrolled depression are often excluded from smoking cessation trials; thus, evidence of which treatment modalities are effective are limited compared with in the general population. A 2013 Cochrane

review identified 49 randomized controlled trials of smoking cessation interventions in patients with depression (van der Meer 2013). Adding a psychosocial mood management component, usually cognitive behavioral therapy, to standard smoking cessation interventions was effective in patients with past (RR 1.41; 95% CI, 1.13–1.77) and current (RR 1.47; 95% CI, 1.13–1.92) depression.

Data analyses assessing specific pharmacotherapy in this patient population, though limited, favor bupropion. Bupropion had numerically, but not statistically significantly, greater efficacy than placebo (RR 1.37; 95% CI, 0.83–2.27) in five small trials (n=410) of patients with current depression and greater efficacy than placebo (RR 2.04; 95% CI, 1.31–3.18) in four small trials (n=404) of patients with past depression. A separate Cochrane review that focused on using antidepressants for smoking cessation found nortriptyline and bupropion more effective than placebo in helping patients quit smoking, but no significant association between the efficacy of these drugs and the history of depression (Hughes 2014). In this same review, selective serotonin reuptake inhibitors did not increase smoking cessation rates alone (four trials, n=1594; RR 0.93; 95% CI, 0.71–1.22) or in combination with NRT (three trials, n=466; RR 0.70; 95% CI, 0.06–1.82). In the trials included in the Cochrane review, current use of antidepressants was typically an exclusion criterion for entering the study (Hughes 2014). Comorbid anxiety may affect the treatment choice as well, given that CNS stimulation and anxiety are relatively common AEs of bupropion (Lexicomp 2019). Similarly, in patients with bipolar depression, antidepressants may increase the risk of mania or hypomania, and additional monitoring of the patient's mood is warranted. In the trials included in this Cochrane review, bipolar depression was typically listed as an exclusion criterion; hence, the study's results cannot be extrapolated to that population.

After release of the Cochrane reviews, a landmark randomized controlled trial assessed the safety and efficacy of NRT, bupropion, and varenicline in patients with and without psychiatric comorbidities (Anthenelli 2016). In this EAGLES trial (which included 8144 subjects, 4116 of whom had psychiatric comorbidities), varenicline was more effective than placebo (OR 3.24; 95% CI, 2.56–4.11), bupropion (OR 1.74; 95% CI, 1.41–2.14), and the NRT patch (OR 1.62; 95% CI, 1.32–1.99) within the psychiatric cohort, whereas bupropion (OR 1.87; 95% CI, 1.46–2.39) and the NRT patch (OR 2.00; 95% CI, 1.56–2.55) were both more effective than placebo. Furthermore, in the psychiatric cohort, the risk of composite neuropsychiatric AEs was not significantly increased with varenicline (6.5%; RD 1.59; 95% CI, −0.42 to 3.59) or bupropion (6.7%; RD 1.78; 95% CI, −0.24 to 3.59) compared with placebo (4.9%). Specifically, the risk of suicidal ideation was similar across all treatment groups in both the psychiatric and nonpsychiatric cohorts, and the only completed suicide occurred in the placebo group. This prompted the FDA to remove the boxed warning from the varenicline and bupropion SR packaging regarding serious mental health AEs associated with using these drugs to help people quit smoking (FDA 2016). However, patients with currently uncontrolled psychiatric comorbidities were excluded from the EAGLES trial, so these results cannot be extrapolated to all patients with psychiatric comorbidities.

Pregnancy

Smoking cessation is an important modifiable factor associated with reducing pregnancy-related complications. Cigarette smoking during pregnancy can cause intrauterine growth restriction and is associated with poor fetal neurodevelopment, low birth weight, preterm birth, and miscarriage (Coleman 2015). Up to 46% of smokers try to quit smoking before or during pregnancy, but most (60%) resume smoking within a year after pregnancy (Chun 2019; Colman 2003).

Primary treatment for this population involves psychosocial intervention (USPSTF 2009). Women who are pregnant are commonly excluded from clinical trials because of concerns for fetal harm. Thus, data are sparse on the safety and efficacy of the common drugs within this population (Coleman 2015; USPSTF 2009).

Psychosocial or behavioral interventions help women in late pregnancy stop smoking, leading to improved health outcomes for the infant after birth, according to a 2013 Cochrane review (Chamberlain 2013). Key psychological interventions studied include counseling, health education, feedback, incentives, social support, exercise, and dissemination of counseling. Strong evidence supports the efficacy of counseling (RR 1.44; 95% CI, 1.19–1.73) and incentives (RR 2.36; 95% CI, 1.36–4.09) for smoking cessation compared with usual care. Limited evidence supports the use of health education (RR 1.20; 95% CI, 0.85–1.70) and feedback (RR 1.29; 95% CI, 0.75–2.20), though these were not statistically significantly more effective in meta-analyses. The effects of social support, exercise, and widespread dissemination of counseling on smoking cessation are less clear.

To date, data are limited supporting NRT, bupropion, or varenicline in this population, and these are not considered first-line therapy (ACOG 2017; Coleman 2015). Behavioral therapy plus NRT during late pregnancy may reduce smoking rates by up to 40% (Coleman 2015). No significant difference in AEs was found between NRT and placebo. Expert consensus supports that NRT should be safer than continued smoking, though additional studies are needed to confirm this. If NRT is used, it should be provided under close supervision and after weighing the risk-benefit (ACOG 2017). Of note, NRT drugs are metabolized more quickly during pregnancy, may be less effective at standard dosages, and are recognized as potential fetal toxins (Coleman 2015). A single study with 11 participants comparing bupropion with placebo noted the benefits of bupropion in smoking cessation and tolerable AEs (Stotts 2015). Limited information on varenicline can be derived from one retrospective surveillance study (n=434), which found that the risk of congenital malformation from

varenicline-exposed pregnancy was 2.25% in the studied population (Richardson 2017).

Adolescents

Most smokers (80%) begin smoking or become nicotine-dependent during adolescence (Chun 2019). The earlier a smoker begins smoking, the more susceptible to diseases that individual will be (Klein 2013). The primary goal is to prevent smoking or to promote cessation as early as possible in this population.

At present, few interventions have been found effective or superior in preventing young people from smoking (Fanshawe 2017). A 2017 Cochrane review of tobacco cessation interventions for young people found psychosocial intervention to be the only treatment with significant evidence of its efficacy in this group. A meta-analysis of nine randomized controlled trials showed that adolescents treated with behavioral therapy were less likely to start smoking (RR 0.82; 95% CI, 0.72–0.94; number needed to treat [NNT] 52) and more likely to quit smoking (RR 1.34; 95% CI, 1.05–1.69; NNT 13) (Peirson 2016). Studies using group counseling showed some efficacy in preventing adolescents from smoking, whereas individual counseling and text messaging–based intervention had no effect (Fanshawe 2017).

No drug is preferred or recommended (Fanshawe 2017). Some small studies assessed either NRT or bupropion, but neither was significantly more efficacious than controls in the same Cochrane review (NRT RR 1.11; 95% CI, 0.48–2.58; bupropion RR 1.49; 95% CI, 0.55–4.02). Despite lack of evidence for the effectiveness of NRT, in patients unsuccessful with psychosocial support, cautious use of NRT may be considered, given its relative safety (Chun 2019). However, sale of OTC NRT is restricted to individuals 18 years and older. Thus, access to NRT may be a barrier for adolescents, given that they must obtain a prescription for NRT (Karpinski 2010). Currently, neither bupropion nor varenicline has an approved indication for use in adolescents (Lexicomp 2019). In 2018, a small phase IV study of varenicline in adolescents failed to reach its primary end point of 4-week continuous abstinence at study weeks 9–12 (ClinicalTrials.gov 2019; Pfizer 2018). Although a complete report of the study has not yet been published, the FDA updated the varenicline prescribing information to specify that it is not recommended in patients 16 or younger (FDA 2019a, 2019b).

Prevention and cessation of smoking in adolescence is a public health priority because of the increased lifelong health risk associated with early smoking. Further studies on using pharmacotherapy agents are warranted, but psychosocial intervention remains the primary option for preventing smoking and smoking cessation for adolescents.

Non-cigarette Nicotine Use

There are many forms of smokeless tobacco, including chewing tobacco or snus, in which tobacco is placed in the mouth, and snuff, in which tobacco is sniffed through the nose, among others. Relative to cigarettes or other forms of smoked tobacco, smokeless tobacco is less dangerous, particularly to the lungs, but can still lead to nicotine addiction and cause significant harm (Ebbert 2015). These harms include an increased incidence of myocardial infarction, stroke, gingival recession, oral cancer, esophageal cancer, and pancreatic cancer (CDC 2016; Piano 2010). In 2010, smokeless tobacco caused more than 250,000 deaths worldwide (Siddiqi 2015).

Smokeless tobacco was suggested previously as an alternative to help patients quit smoking, but patients should be informed that it is no longer recommended, given the increased risk of harm. At least one study has shown that changing from smoked tobacco to smokeless tobacco caused a higher rate of death from any cause (HR 1.08; 95% CI, 1.01–1.15) than abstaining from tobacco after quitting (Henley 2007).

A 2015 Cochrane review on drug therapy to help smokeless tobacco users quit, which included 34 trials and over 16,000 patients, found that varenicline increased smokeless tobacco cessation (RR 1.34; 95% CI, 1.08–1.68) but that bupropion provided no benefit (RR 0.89; 95% CI, 0.54–1.44) at 6 months (Ebbert 2015). Similarly, the nicotine patch (RR 1.13; 95% CI, 0.93–1.37) and nicotine gum (RR 0.99; 95% CI, 0.68–1.43) did not provide any benefit in cessation, though the data analyses were limited. Conversely, nicotine lozenges increased smokeless tobacco cessation rates (RR 1.36; 95% CI, 1.17–1.59). Behavioral support is also encouraged together with pharmacotherapy to improve the likelihood of long-term tobacco abstinence.

ROLE OF THE PHARMACIST

Pharmacists can play a crucial role in tobacco cessation and are uniquely positioned to screen patients for tobacco use. Not only are pharmacists trained to counsel patients on the drugs used for smoking cessation, but they can also play a key role in drug selection and provision of behavioral counseling.

Pharmacists interested in obtaining advanced tobacco cessation training can seek certification as a Certified Tobacco Treatment Specialist (ATTUD 2019). Several accredited trainings exist nationally that cover the Association for the Treatment of Tobacco Use and Dependence (ATTUD) core competencies, which include tobacco knowledge and education, counseling skills, assessment interview, treatment planning, pharmacotherapy, relapse prevention, diversity and specific health issues, documentation and evaluation, professional resources, law and ethics, and professional development. In addition, the Association for Addiction Professionals, in collaboration with the ATTUD, recently established a National Certificate in Tobacco Treatment Practice (NAADC 2018).

Practice Points

- **Ask all patients at each encounter about their smoking status, and strongly advise those who smoke to quit.**
- **Except for a few cohorts, most notably adolescents and pregnant women, all patients who are ready to quit should be offered a combination of counseling and pharmacotherapy to assist with their quit attempt.**
- **Many counseling strategies help people quit smoking. The guidelines recommend the 5 A's approach to help patients quit, as well as the 5 R's and/or MI to motivate smokers who are currently unwilling to quit.**
- **Three classes of medications are considered first line for smoking cessation: NRT, varenicline, and bupropion. Combinations of these agents, usually several NRTs or NRT plus bupropion, are also viable options.**
- **Meta-analysis has shown a hierarchy of effectiveness of these drugs, with varenicline or combination NRT therapy similarly effective and more effective than NRT monotherapy or bupropion. NRT monotherapy, bupropion, or bupropion plus NRT are similarly effective and are significantly more effective than placebo.**
- **Key considerations that may dissuade a clinician from using specific medications include posttraumatic stress disorder or a history of bothersome nightmares (varenicline), epilepsy or other conditions that predispose to seizures (bupropion), end-stage liver or kidney disease (bupropion), bulimia or anorexia (bupropion), uncontrolled psychiatric conditions or active suicidal ideations (bupropion or varenicline), chronic skin conditions (NRT patches), temporomandibular joint dysfunction (NRT gum), severe reactive airway disease (NRT nasal spray), asthma (NRT inhaler), or arrhythmia or myocardial infarction less than 2 weeks prior (all NRT).**
- **Use of electronic cigarettes is associated with health concerns, though the overall risks are likely less than with traditional cigarettes. However, evidence is limited proving that e-cigarettes significantly improve tobacco cessation.**

CONCLUSION

Tobacco use significantly increases morbidity and mortality risk. Guidelines recommend assessing tobacco use status for all patients at each encounter, and promoting tobacco cessation should be a top priority of clinicians when caring for patients who use tobacco products. Except for a few cohorts, most notably adolescents and pregnant women, all patients who are ready to quit should be offered a combination of counseling and pharmacotherapy to help with their quit attempt.

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Self-Assessment Questions

1. A 70-year-old woman who recently lost her husband to lung cancer is referred to your pharmacotherapy clinic for untreated depression and help with smoking cessation. She smokes 1 pack/day but is ready to make a quit attempt within the next 2 weeks. Her medical history includes hypertension, hypothyroidism, and hyperlipidemia. Which one of the following is best to recommend for this patient?

   A. Nortriptyline 25 mg daily titrated to 75 mg daily over 3 weeks for total of 12 weeks of therapy, then taper dose to 50 mg daily for 4 days followed by 25 mg daily for 3 days
   B. Nortriptyline 25 mg daily titrated to 75 mg daily over 3 weeks for total of 12 weeks of therapy in addition to a nicotine replacement therapy (NRT) patch 21 mg for 6 weeks, then 14 mg for 2 weeks, then 7 mg for 2 weeks
   C. Bupropion SR 150 mg once daily for 3 days, then 150 mg twice daily for the remainder of 12 weeks of therapy
   D. Bupropion SR 150 mg twice daily for 11 weeks, then decrease to bupropion SR 150 mg once daily for 1 week

2. A physician wants to initiate a patient on a nicotine transdermal patch but is unclear of the dose the patient should start on and asks for your assistance. Which one of the following questions would be best to ask in order to make the appropriate recommendation?

   A. How many cigarettes does this patient smoke per day?
   B. What is his CrCl?
   C. How soon after waking does this patient smoke his first cigarette?
   D. Has he previously used nicotine transdermal patches?

3. A patient with contraindications to bupropion has not previously tolerated NRT or varenicline but wants to try clonidine. Which one of the following is best to recommend regarding clonidine use for smoking cessation in this patient?

   A. Clonidine should be initiated 3–4 weeks before the quit date because it requires a slow titration to the recommended dose.
   B. Clonidine should be initiated on the same day that the patient quits as it does not require dose titration.
   C. Four weeks of clonidine therapy may be sufficient because its primary role is to relieve nicotine withdrawal symptoms, which usually wane within 2–4 weeks.
   D. Ten weeks of clonidine therapy may be sufficient because its primary role is to relieve nicotine withdrawal symptoms, which usually wane within 2–3 months.

4. A patient arrives in the clinic for her initial smoking cessation visit. She smokes 3/4 pack/day. Discussion reveals that she smokes her first cigarette mid-morning after dropping her children off at school and smokes most cigarettes during the afternoon while they are at school; these cigarettes while she is bored at home are her biggest struggle. When discussing what helps her avoid cigarettes, she notes that she has begun volunteering at the school some days and that she can easily avoid cigarettes all day while volunteering. She also notices that she has had several bad respiratory tract infections recently and smokes much less when she is feeling sick. Which one of the following best reflects this patient's level of nicotine dependence?

   A. Low
   B. Low to moderate
   C. Moderate
   D. High

5. A male patient is exploring the idea of quitting smoking but is not ready to quit within the next 30 days. Which one of the following is best to recommend for this patient?

   A. Arrange an appointment with a smoking cessation expert who can convince the patient to quit smoking.
   B. Be firm with the patient, letting him know how much he is hurting himself and others around him by smoking to persuade him to quit.
   C. Recommend that he starts taking varenicline today to reduce his cravings so that he may be ready to quit sooner.
   D. Strongly advise him to quit, and use the 5 R's to increase his motivation to quit.

6. A patient presents to a pharmacist-managed warfarin clinic. She began using the nicotine patches this week to quit smoking. So far, she has remained smoke free and feels confident she can remain smoke free long term with the help of the patches. Which one of the following is the most likely impact of this change on this patient's warfarin therapy?

   A. Effects of a new drug interaction between nicotine patches and warfarin, which may affect her INR, will need to be monitored.
   B. Removal of a drug interaction between her cigarette smoking and warfarin therapy may change her INR and require a warfarin dose adjustment.

C. This will not affect her INR until she finishes her nicotine patches because the patches contain the same interacting drug (nicotine) as the cigarettes.
D. This will have no effect because neither cigarette smoking nor nicotine patches have a drug interaction with warfarin.

7. In your ambulatory care clinic, you provide smoking cessation assistance to a patient with bipolar disorder. This patient has previously not responded to either nicotine replacement monotherapy or combination NRT, so you are considering prescribing bupropion or varenicline. Which one of the following statements best reflects the most likely outcome of these drugs, according to the EAGLES trial results?

   A. Varenicline therapy would be significantly more efficacious than nicotine patches but not significantly more efficacious than bupropion.
   B. Varenicline would have significantly higher rates of moderate or severe neuropsychiatric adverse effects (AEs) than placebo.
   C. Bupropion and varenicline would produce similarly moderate or severe neuropsychiatric effects, and this likelihood would not be significantly greater than placebo.
   D. Bupropion would produce significantly higher rates of moderate or severe neuropsychiatric AEs than placebo.

Questions 8 and 9 pertain to the following case.

A.P. is a 51-year-old man (height 70 inches, weight 79 kg [175 lb]) who wants to quit smoking. He arrives in your clinic today seeking assistance with quitting smoking. A.P. has smoked 1 pack/day for 35 years. He made one quit attempt several years ago. He used nicotine patches for 14 days. During this time, he reduced his cigarette consumption significantly but could not totally quit. He ended his quit attempt after a death in the family and has not tried to quit again since then. A.P.'s medical history includes a myocardial infarction (3 years ago), situational depression, hyperlipidemia, congestive heart failure, allergic rhinitis, epilepsy, migraines, gastroesophageal reflux disease, posttraumatic stress disorder, and type 2 diabetes. His laboratory test results include SCr 0.9 mg/dL, ALT 14 IU/L, AST 19 IU/L, A1C 9.2%, TC 170 mg/dL, LDL 88 mg/dL, HDL 42 mg/dL, and TG 200 mg/dL. His home drugs include atorvastatin 20 mg daily, ranitidine 150 mg twice daily, metformin 500 mg twice daily, carvedilol 3.125 mg twice daily, lisinopril 20 mg daily, furosemide 20 mg twice daily, loratadine 5 mg daily, levetiracetam 1500 mg twice daily, prazosin 5 mg at bedtime, and sumatriptan 100 mg as needed for migraines.

8. Given his medical history and current drug regimen, which one of the following is best to recommend initiating in A.P.?

   A. Varenicline 0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily
   B. Bupropion SR 150 mg once daily for 3 days, then 150 mg twice daily
   C. Nortriptyline 25 mg daily initially, titrated to 75 mg daily, if needed
   D. NicoDerm patches 21 mg daily × 6 weeks, then 14 mg daily × 2 weeks, then 7 mg daily × 2 weeks PLUS Nicorette 2 mg gum as needed for breakthrough cravings

9. A.P. has never received a pneumonia vaccine or been screened for lung cancer. Which one of the following is best to recommend for A.P. regarding pneumonia vaccines and lung cancer screening?

   A. Provide a pneumococcal conjugate vaccine (PCV13) pneumonia vaccine in the clinic today. No other pneumonia vaccine is indicated until he turns 65. He should be screened for lung cancer every 5 years until he turns 80.
   B. Provide a PPSV23 pneumonia vaccine in the clinic today. No other pneumonia vaccine is indicated until he turns 65. Lung cancer screening is not currently recommended for A.P.
   C. Provide a PCV13 pneumonia vaccine in the clinic today and a PPSV23 pneumonia vaccine 1 year later. He will then be indicated for further pneumonia vaccination when he turns 65. He should be screened annually for lung cancer until he turns 74.
   D. A.P. does not need a pneumonia vaccine until he turns 65. He should be screened annually for lung cancer until he turns 80.

10. A 60-year-old woman with type 2 diabetes (A1C 8.9%), hepatic cirrhosis (Child-Pugh score 15), hypertension (blood pressure in clinic 125/78 mm Hg), and depression (PHQ-9 [Patient Health Questionnaire] score 4) would like help with quitting smoking. She smokes 1 pack/day; she has previously tried and could not tolerate varenicline because of severe headaches. Which one of the following is best to recommend for this patient?

    A. Bupropion SR 150 mg once daily for 3 days; then 150 mg twice daily
    B. NicoDerm patches 21 mg × 6 weeks, 14 mg × 2 weeks, 7 mg × 2 weeks plus Nicorette gum 2 mg as needed for breakthrough cravings
    C. Nortriptyline 25 mg daily initially, titrated to 75 mg daily, if needed
    D. Paroxetine 20 mg daily initially, titrated to 50 mg daily, if needed

Questions 11 and 12 pertain to the following case.

R.R. is a 68-year-old man who presents to your pharmacotherapy clinic for drug review. While completing the initial intake questionnaire, R.R. identified that he currently smokes 1 pack/day in addition to using e-cigarettes on a daily basis while at work. He reports a 40-year history of using cigarettes and a 1-year history of using e-cigarettes.

11. R.R. has been thinking about quitting recently because of the loss of his father secondary to lung cancer. However, he is concerned about dealing with stress without cigarettes. When asked about when he would imagine himself quitting, R.R. reports he would like to quit by his next birthday (about 4 months from now). Which one of the following stages of the transtheoretical model best describes R.R.'s current willingness to quit using tobacco?

    A. Contemplation
    B. Preparation
    C. Precontemplation
    D. Action

12. R.R. is now 1 week away from his quit date and has worked with you to develop a quit plan in addition to completing behavioral interventions. He feels confident about his upcoming quit date and has a strong support system to encourage his success. When arranging his follow-up, which one of the following best describes the ideal time to schedule future visits?

    A. In 3 days
    B. In 3 days and again in 7 days
    C. In 7 days and again in 1 month
    D. In 1 month

13. A 62-year-old man has a medical history of diabetes, hypertension, anxiety, hyperlipidemia, and tobacco use disorder. He was referred to you for tobacco cessation counseling by collaborative practice agreement. The patient has smoked about 1 pack/day of cigarettes for the past 40 years and recently began using e-cigarettes as well, with the plan to taper his cigarette use. He has been considering completely quitting cigarette use because he would like to begin training for a marathon race. However, the patient has several concerns about quitting, including stress management and weight gain. Which one of the following would best initiate a discussion about his anticipated barriers to a cessation attempt while fostering commitment to change?

    A. "Tell me about some other methods besides cigarettes that you have used in order to manage stress in the past."
    B. "What have you heard so far about the potential to gain weight during a quit attempt?"
    C. "You have been dealing with a lot of stress recently and you are concerned that quitting could contribute to even more stress."
    D. "You are really looking forward to running this marathon and you know that quitting would enable to you train harder."

14. During a counseling session with a patient who wants to quit smoking, the patient reports an interest in using e-cigarettes to quit. The patient has already tried nicotine patches and varenicline and would like to try something else. Which one of the following is the best response to give this patient?

    A. "E-cigarettes can be used to quit smoking as long as you use vaping liquid with minimal or no nicotine and plan to slowly taper use."
    B. "The CDC recommends e-cigarettes as a safer alternative to tobacco-containing cigarettes, making them an appropriate cessation aid."
    C. "Because e-cigarettes are not FDA regulated, they should never be recommended to patients as a cessation aid."
    D. "Currently, e-cigarettes are not FDA approved as a smoking cessation aid, and it is recommended that you use an approved option."

15. During an appointment, a patient mentions that he is worried about how his tobacco use is affecting his health; however, he cannot see himself quitting anytime soon because he has significant life stress. Which one of the following counseling tools would be most useful in this patient situation?

    A. 5 A's
    B. STAR acronym
    C. 5 R's
    D. Transtheoretical model