

A Comprehensive Approach to Tobacco Dependence Interventions

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Tobacco smoking remains the leading preventable cause of death and illness in the United States. Smoking cessation is particularly relevant for individuals with chronic obstructive pulmonary disease because it is known from multiple studies that individuals who quit smoking experience an initial improvement in pulmonary function, a decreased rate of normal age-related decline in FEV₁, a lower risk of hospital admission, and improved survival. Tobacco dependence must be recognized as a chronic disease, and comprehensive treatment for the tobacco-dependent patient with chronic obstructive pulmonary disease begins with a physician's inquiry into smoking and encouragement to quit, followed by an assessment of the level of dependence and the severity of withdrawal symptoms during previous quit attempts. Combination pharmacotherapy is recommended for the initial treatment of most smokers, especially those with moderate to high baseline levels of tobacco dependence. The patient's history, combined with his or her personal preference, can guide the clinician in initiating an appropriate treatment regimen. Given the chronic nature of tobacco dependence, clinicians must anticipate relapses and the need for recurrent, long-term follow-up. Comprehensive tobacco treatment consultation should be sought whenever possible for patients with high levels of tobacco dependence and multiple relapses or failed quit attempts. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:481-8)

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The use of combustible tobacco products is causally linked to chronic obstructive pulmonary disease (COPD), lung cancer, tuberculosis, pneumonia, asthma, and cardiovascular disease, as well as many other noncardiopulmonary diseases.¹ Since 1965, there have been more than 20 million estimated premature deaths caused by smoking and exposure to secondhand smoke. Similarly, the Surgeon General estimates that if current trends continue, an additional 5.6 million US individuals currently younger than 18 years will die prematurely as a result of smoking.¹ Despite a significant decline in the number of adult smokers in the US over the past 50 years, approximately 18% of the US population continues to smoke.² The Centers for Disease Control and Prevention estimated that between 2000 and 2004 there were 443,000 premature deaths, 5.1 million years of potential life lost, and \$96.8 billion annual productivity losses in the United States.³ Moreover, the most recent evidence suggests that the health toll of smoking is even worse than previously noted, with links to deaths from renal failure, breast and prostate cancer, infections, and various other respiratory diseases.⁴

Smoking cessation is particularly relevant for individuals with COPD because it is known from multiple studies that individuals who quit smoking experience an initial improvement in pulmonary function, a decreased rate of normal age-related decline in FEV₁, a lower risk of hospital admission, and improved survival.⁵⁻⁹ Despite being equally motivated to quit smoking compared with healthy smokers, patients with COPD typically suffer from a higher degree of tobacco dependence, smoke more cigarettes per day, and have a more difficult time quitting smoking.¹⁰ Consequently, they represent a unique population that may require intensive treatment to gain control over the compulsion to smoke.

This review will discuss standard therapies for tobacco addiction, will provide the clinician with a relevant approach to evaluation and treatment, and will briefly consider areas of uncertainty, including the public health controversy surrounding the use of electronic cigarettes (e-cigs) and snus.

CHRONIC DISEASE MODEL FOR TOBACCO DEPENDENCE

One of the greatest challenges in treating tobacco dependence is the degree to which cigarettes are addictive. Nicotine, the major addictive component of tobacco, is delivered to the pulmonary circulation and reaches the arterial circulation and brain within seconds after inhalation.^{11,12} After reaching the brain, nicotine binds to nicotinic cholinergic receptors and causes release of multiple neurotransmitters including dopamine, glutamate, and gamma-aminobutyric acid. The net biologic effects are feelings of pleasure, satisfaction, heightened mood and concentration, and relief from stress and anxiety. Furthermore,

Abbreviations used

COPD- chronic obstructive pulmonary disease
e-cigs- electronic cigarettes
FDA- Food and Drug Administration
FTND- Fagerström Test for Nicotine Dependence
NRT- nicotine replacement therapy

other additives and constituents of smoke such as monoamine oxidase inhibitors produced from acetaldehydes potentiate the level of tobacco addiction by reducing the metabolism of dopamine.^{13,14} Following prolonged and recurrent tobacco smoking, tolerance, desensitization, and upregulation of nicotine receptors occurs, which leads to craving, addiction, and withdrawal symptoms when nicotine is no longer present.^{15,16}

Multiple studies have shown high relapse rates among smokers attempting to quit.¹⁷⁻¹⁹ Strong and long-lasting cravings and other symptoms of withdrawal are commonly implicated in disrupting quit attempts and causing relapses.^{20,21} Given the difficulty of quitting and the frequency of relapses, tobacco dependence must be viewed as a chronic disease. Just as conditions such as COPD, asthma, diabetes, and hypertension are chronic conditions prone to exacerbation, tobacco dependence is a long-term condition that must be managed through episodes of relapse and remission. Recognition that relapses are not indicative of patient or provider failure, but instead reflect a common part of the course of the illness, can allow patients and health care providers to focus on refining the treatment plan and arranging regular follow-up.

CLINICAL INTERVENTIONS FOR SMOKING CESSATION

Brief clinician interventions

Brief physician advice is the most important first step in promoting smoking cessation and has been shown to significantly increase long-term quit rates.^{22,23} Utilizing smoking status as a vital sign is recommended because it has been shown to significantly increase recognition of smokers in the clinical setting.²⁴ The advice provided and the approach to initiating management will differ depending on whether a smoker is willing to quit or not. For smokers who are unwilling to quit, motivational interviewing is a technique that has been shown to be effective in assisting smokers in quitting, either alone or in combination with pharmacotherapy.²⁵⁻²⁷ Motivational interviewing uses nonconfrontational counseling and expression of empathy to encourage smokers to consider changing their behaviors.^{22,28} The purpose of this counseling is to assist smokers in moving from a precontemplative stage to a contemplative stage of change by highlighting the benefits of quitting and empathizing with the smoker's ambivalence. An acknowledgment and exploration of patient concerns regarding quitting such as fear of weight gain or withdrawal symptoms may help ease fears of making a quit attempt and address barriers to quitting.

Another concept that has gained recognition is the calculated "lung age," which has shown promise in motivating smokers with chronic lung disease to stop smoking.^{29,30} *Lung age* is defined as the age of the average person who has an FEV₁ equal to that of the individual. Because people who smoke experience a more rapid decline in FEV₁ than do nonsmokers, a smoker's lung age will be higher than his or her chronologic age. A

multicenter randomized controlled trial provided smokers with spirometry results either as a raw number or as measured by their lung age.²⁹ Participants were then advised to quit smoking and given access to a local smoking cessation service. Those randomized to the lung age group had a significantly higher quit rate at 12 months than did the FEV₁ raw number group. The mechanism by which this effect occurred was not entirely clear because subjects with worse lung age were no more likely to quit than were subjects with normal lung age in either group. However, the study was not powered to detect differences among people with varying severity of lung disease. A more recent meta-analysis of 15 clinical trials studied the efficacy of providing additional biomarkers to motivate individuals to quit smoking.³¹ There was no evidence that providing carbon monoxide level, spirometry, or genetic susceptibility to lung cancer increased smoking cessation rates in this meta-analysis.

More recent evidence has begun to emerge that initiating treatment and encouraging a more gradual reduction in smoking among patients willing to cut down but not yet ready to quit may also be beneficial and improve long-term quit rates.³²⁻³⁹ Counseling and pharmacotherapy can be effective for this group of smokers, and consequently these patients should be approached and treated in a similar manner as those who are ready to stop smoking.^{27,32,37,40}

For smokers who are ready to quit, the clinician should offer support and facilitate setting a quit date, ideally within the next 2 weeks.²² An evaluation of the level of tobacco dependence and the history of withdrawal symptoms is useful in determining a treatment plan, followed by a discussion of treatment options (reviewed below) and arrangement of follow-up.

Assessing the level of tobacco dependence and withdrawal symptoms

Assessment of a smoker's severity of tobacco dependence is one of the most important steps taken before initiating appropriate treatment. Individuals with higher levels of dependence will require more intensive interventions to achieve smoking cessation and need to be identified before treatment is started. The Fagerström Test for Nicotine Dependence (FTND) is one of the most commonly used tools for assessing the severity of tobacco dependence (see [Table I](#)).⁴¹ The test is a 6-item scale, and its total score is closely related to biochemical measures of intensity of smoking.⁴¹ The questions from this scale focus on how quickly a person smokes after waking ("time-to-first cigarette"), intensity of smoking, and smoking patterns during the day. An analysis of the relationship between smoking cessation success and the FTND in individuals enrolled across multiple smoking cessation clinical trials found that the "time-to-first cigarette" in the morning item was the strongest predictor of cessation outcome.⁴² These findings suggest that those who smoke their first cigarette within 5 minutes of waking have the highest levels of tobacco dependence and are likely to require the most intensive treatment to ensure a successful attempt at cessation. Assessing the patient's level of dependence is a critical step in determining the appropriate initial therapy because those with higher levels of dependence are less likely than those with lower levels of dependence to succeed without combination therapy.

A second important step is assessing the severity of withdrawal symptoms from previous quit attempts, and on each subsequent visit after a quit attempt is made. Common symptoms include

TABLE I. Fagerström Test for Nicotine Dependence*⁴¹

Questions	Answers	Points
How soon after you wake up do you smoke your first cigarette?	Within 5 min	3
	6-30 min	2
	31-60 min	1
	After 60 min	0
Do you find it difficult to refrain from smoking in places where it is forbidden, eg, church, at the library, and in cinema?	Yes	1
	No	0
Which cigarette would you hate most to give up?	The first one in the morning	1
	All others	0
How many cigarettes/day do you smoke?	10 or less	0
	11-20	1
	21-30	2
	31 or more	3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

*Classification of dependence: 0-2, very low; 3-4, low; 5, moderate; 6-7, high; 8-10, very high.

craving, dysphoric mood, anxiety, irritability, insomnia, increased appetite, or weight gain (Table II). Patients should be queried about these symptoms routinely to assess the efficacy of the treatment plan. Withdrawal scales such as the Minnesota Nicotine Withdrawal Scale can also be used to quantify withdrawal symptoms and are predictive of relapse and continued tobacco smoking.^{43,44} At least 3 trials have found craving and other withdrawal symptoms to be causes of relapse within the first 30 days of quitting.^{20,21,45} Furthermore, aggressive suppression of withdrawal symptoms using combination pharmacotherapy and higher than standard doses when necessary improve treatment outcomes and increase continuous smoking abstinence rates at 3 and 9 months.⁴⁶⁻⁴⁸ Taken together, these data indicate the crucial importance of assessing and treating withdrawal symptoms intensively in the initial period after a smoking cessation attempt.

Available therapy

Multiple trials and meta-analyses have demonstrated the efficacy of counseling, pharmacotherapy, and combination therapy for smoking cessation among people willing to quit (see Table III).^{22,49-52} We will briefly review strategies for counseling and Food and Drug Administration (FDA)-approved pharmacotherapies for tobacco dependence and will integrate this information with patient evaluation to develop a practical approach to treatment. Except where noted, the data presented below are in concordance with the US Department of Health and Human Services 2008 Tobacco Use and Dependence Treatment Guidelines.⁵³

Counseling. Studies have consistently found that long-term quit rates improve significantly with counseling, with more intensive interventions having a greater impact. Counseling can be provided by any health care provider, a tobacco treatment specialist, or through referral to a telephone smoking Quitline (1-800-QUIT-NOW). Counseling is most effective when the

TABLE II. Common tobacco withdrawal symptoms

Craving for cigarettes
Irritability, frustration, or anger
Anxiety
Difficulty concentrating
Increased appetite or weight gain
Depressed or sad mood
Insomnia or sleep problems

provider expresses empathy, inquires about stressors and triggers for smoking, focuses on patients' concerns about the smoking cessation process, and discusses the benefits of treatment. Emerging evidence suggests that "gain-framed" statements (ie, "Quitting smoking is beneficial to your health.") are preferable to "loss-framed" statements (ie, "Smoking is harmful to your health.") when treating adult smokers.⁵⁴ Consequently, focusing on the positive elements of smoking cessation may promote quit attempts and success. Thus, even if only for a few minutes, counseling is a critical component to successful tobacco dependence treatment.

Nicotine replacement therapy. Nicotine replacement therapy (NRT) involves the delivery of nicotine through transdermal, oral, or inhalational routes and has been shown to be effective as monotherapy or as part of combination therapy for smoking cessation. There are 5 approved NRTs: patch, gum, lozenge, nasal spray, and inhaler. All NRTs deliver nicotine more slowly compared with tobacco smoking, and consequently have less addiction potential.

Among NRTs, the nicotine patch delivers nicotine most gradually throughout a 24-hour period. Although the patch can be used as monotherapy, it is less effective than varenicline and should typically be used as part of combination therapy.⁵¹ Initial dosing is typically a 21-mg patch for those smoking more than 10 cigarettes daily and a 14-mg patch for those smoking 10 or fewer cigarettes daily. Dosing may need to be titrated on the basis of initial response to therapy; fear of overdose is common, and causes both clinicians and patients to underestimate how much NRT is most appropriate. Dose escalation may be appropriate if withdrawal symptoms are poorly controlled.⁵⁵ The minimum treatment duration is 8 weeks, but longer durations of therapy are safe and may be necessary for more dependent smokers.^{56,57} The patch is safe in patients with stable cardiovascular disease and does not increase the risk of acute cardiovascular events, including in patients who continue to smoke.⁵⁸⁻⁶⁰

The most common adverse effects of the patch include local skin reactions that are usually self-limited, insomnia, or vivid dreams. Skin reactions can typically be managed with topical steroids and by rotating the patch site. The patch should be avoided in those with severe inflammatory dermatologic conditions or who develop intractable skin irritation related to use. For individuals who experience sleep disturbance, the patch can be removed before bedtime to reduce symptoms. The most common signs and symptoms of nicotine toxicity that may occur with concurrent use of other nicotine-containing products include nausea, vomiting, dizziness, anxiety, and heart palpitations.

Other forms of NRT deliver nicotine more rapidly compared with the patch, but slower than a tobacco cigarette. The nicotine

TABLE III. Pharmacotherapy

Medication	Dosing	Initial treatment duration	Adverse effects	Contraindications
Long-acting drugs				
Nicotine patch	If >10 cigarettes/d → 21-mg patch daily; if ≤10 cigarettes/d → 14-mg patch	8 wk	Local skin reactions, insomnia and/or vivid dreams	Pregnancy,* severe skin conditions
Varenicline	0.5 mg daily × 3 d, then 0.5 mg twice a day × 4 d, then 1 mg twice a day	12 wk	Nausea, insomnia, vivid dreams. Rare cases of agitation, changes in behavior, and suicidal ideation	Pregnancy, use cautiously in patients with psychiatric illness
Bupropion sustained release	150 mg daily × 3 d, then increase to 150 mg twice a day	7-12 wk	Insomnia, dry mouth. Lowers seizure threshold	Pregnancy, seizure disorder, eating disorder. Use of an MAO inhibitor in the past 14 d
Short-acting drugs				
Nicotine gum	4-mg piece if smoking ≥25 cigarettes/d, otherwise 2-mg piece. Use every 1-2 h PRN	12 wk	Mouth soreness, hiccups, dyspepsia, jaw ache	Pregnancy, unstable angina or arrhythmias
Nicotine lozenge	4-mg lozenge if smoking first cigarette within 30 min of waking, otherwise 2-mg lozenge. Use every 1-2 h PRN	12 wk	Nausea, hiccups, heartburn, headache, cough	Pregnancy, unstable angina or arrhythmias
Nicotine inhaler	1 puff PRN, up to 6-16 cartridges/d	24 wk	Mouth and throat irritation, cough, rhinitis	Pregnancy, severe reactive airway disease, unstable angina or arrhythmias
Nicotine nasal spray	1 spray each nostril, every 1-2 h PRN	12-24 wk	Nasal irritation, nasal congestion, change in sense of smell and taste	Pregnancy, severe reactive airway disease, severe nasal disease, unstable angina or arrhythmias

MAO, Monoamine oxidase; PRN, *pro re nata* (when necessary).

*The 2008 Tobacco Treatment Guidelines suggest that pregnant smokers should be encouraged to quit without medication and should be offered intensive behavioral counseling support at the first prenatal visit and throughout the course of the pregnancy.⁵³ Nicotine replacement products are FDA pregnancy class D agents. Varenicline and bupropion are FDA pregnancy class C agents.

gum and lozenge deliver nicotine through the oral buccal mucosa. The gum can be chewed as either 2-mg or 4-mg pieces and can be used as needed every hour. Proper technique must be used in order for the gum to have effect. The gum must be chewed until a flavored taste is sensed, and then held between the cheek and buccal mucosa. When the taste wears off, the gum should be chewed again until taste returns and again parked between the cheek and buccal mucosa. This process should be repeated for 30 minutes to allow absorption. Long-term use of the gum is safe, and the addictive potential is low. The gum has also been shown to delay weight gain after smoking cessation in a dose-response manner. Common adverse effects are typically mild and include mouth soreness, hiccups, dyspepsia, and jaw ache. The nicotine lozenge comes in similar doses compared with the gum and should be allowed to dissolve in the mouth rather than chewing or swallowing. Its benefits and adverse-effect profile are similar to those of the gum.

The nicotine nasal spray and inhaler are available by prescription, and, like other NRTs, can be used alone or in combination with other medications. The main advantage of the nasal spray over other NRTs is that it produces more rapid and higher peak nicotine levels (although still less than tobacco smoking). Local irritation of the nose and throat are common adverse effects. Both products are safe and can be used in combination with the patch.

Varenicline. Varenicline is a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor⁶¹ that has been shown to be

effective as monotherapy or as part of combination therapy for smoking cessation. Varenicline should typically be started at least 1 week before the anticipated quit date, with a target dose of 1 mg twice daily.⁵³ Treatment is typically continued for at least 14 weeks, and is well-tolerated and efficacious for up to a year.^{62,63}

The most common adverse effects of varenicline include nausea, difficulty sleeping, and vivid dreams. Nausea can be mitigated by advising patients to take the medication on a full stomach. In 2008, the FDA added a warning on the basis of reports of suicidal ideation, changes in behavior, and depressed mood that occurred with varenicline use in patients with underlying psychiatric illness, and these patients may require a higher level of monitoring. Several subsequent meta-analyses have shown that the overall likelihood of severe neuropsychiatric reactions is both very low and not statistically different than controls, even in patients with preexisting comorbid psychiatric conditions.⁶⁴⁻⁶⁶

Bupropion sustained release. Bupropion sustained release is an antidepressant that presumably acts as a neuronal reuptake inhibitor of dopamine and norepinephrine and has been shown to be effective as monotherapy or as part of combination therapy for smoking cessation.⁶⁷ Bupropion should be started at least 1 to 2 weeks before the target quit date at a dose of 150 mg daily and titrated up to 150 mg twice daily. The minimum duration for treatment is typically 7 to 12 weeks, but as is the case with varenicline, longer courses (up to 6 months) of therapy are safe and appropriate for some smokers. Because it can delay weight gain after quitting smoking, bupropion may be a good choice for

individuals who are obese and/or concerned about weight gain. It may also be a good choice for individuals with comorbid depression because it is approved as an antidepressant. The most common adverse effects associated with bupropion are insomnia and dry mouth. There is a 1 in 1000 risk of seizures associated with bupropion use, and thus the medication should be avoided in those with underlying seizure disorders or alcohol dependence.⁶⁷ Other contraindications to use include eating disorders or use of a monoamine oxidase inhibitor in the past 14 days to avoid potentially toxic drug-drug interactions.

Combination therapy. Combination therapy for smoking cessation is more effective than monotherapy in the treatment of tobacco addiction.⁵¹ There are no specific evidence-based algorithms to guide the optimal selection of a first-line regimen, but multiple regimens are known to be effective. Combinations of both long- and short-acting drugs can be used and have a high effectiveness (ie, nicotine patch plus lozenge, gum, or nasal spray), as well as 2 or more long-acting drugs (ie, nicotine patch plus bupropion).^{68,69} A recent randomized trial using varenicline found that the drug was more effective when used in combination with the nicotine patch than when used alone.⁷⁰ The optimal choice of initial therapy will depend on the patient's comorbidities, degree of drug dependence, and preference on the basis of experience.

Approach to treatment

The initial approach to treatment involves assessing the patient's motivation to quit, the degree of tobacco dependence as measured by the FTND, the history of withdrawal symptoms, and the success or difficulty with any methods used during previous quit attempts. Given the evidence that behavioral and pharmacologic therapies for smoking cessation improve quit rates even among individuals who are not yet motivated to quit, all smokers should be offered treatment regardless of whether they want to quit smoking.^{33,34,39,71}

Consistent with the most recent 2008 tobacco treatment guidelines,²² smokers are commonly advised to set a quit date and attempt to quit smoking abruptly with the aid of treatment. Although this practice may work for some, many smokers cannot quit immediately. For these individuals, smoking cessation is a more gradual process that starts with a reduction in daily cigarette use. Previous studies suggest that the gradual approach to smoking cessation can be efficacious.^{33,36,37,72}

For all patients, with the possible exception of those with the lowest levels of tobacco dependence (FTND score ≤ 3), combination pharmacotherapy in addition to counseling is the best initial treatment. A long-acting drug such as the nicotine patch, varenicline, or bupropion should be prescribed on the basis of patient's comorbid conditions, preference, and adverse-effect profile. This medication should be continued regardless of whether the patient continues to smoke, and adherence to therapy should be assessed at each visit. The long-acting drug is then combined with a second short-acting NRT such as the nicotine gum, lozenge, nasal spray, or inhaler. The short-acting NRT is used as needed to treat cravings and withdrawal symptoms because it can deliver nicotine more rapidly. Nonadherence to therapy is an important barrier to successful quitting, and patients should be advised to continue with prescribed treatments even if they continue to smoke.

The critical second step in the treatment process is the assessment of nicotine withdrawal symptoms, adherence, and treatment efficacy. The inability of the initial treatment regimen to suppress withdrawal symptoms is likely to prevent a successful quit attempt, particularly for those with high levels of tobacco dependence or a history of severe withdrawal. It is important to recognize that a lack of response to initial therapy does not represent a treatment "failure." Rather, it indicates that the initial treatment regimen is inadequate and needs to be intensified. Patients should be advised to continue with the long-acting medication and increase the frequency of use of the short-acting NRT if they are not already consuming maximum doses. They should also be prescribed a second long-acting medication of a different class to augment the therapeutic effect, as long as contraindications to therapy are not present. This process continues at each follow-up visit until withdrawal symptoms are controlled and the patient has stopped smoking.

An alternative strategy for highly tobacco-dependent patients or those who suffer severe withdrawal symptoms is to refer early to a comprehensive tobacco treatment service if available. This may allow for more time-intensive treatment and close monitoring of the patient's progress.

AREAS OF UNCERTAINTY AND CONTROVERSY

Electronic cigarettes

E-cigs are battery-operated devices that heat and aerosolize a liquid solution that typically contains nicotine. The emergence of e-cigs has produced significant controversy in the public health community, with some viewing them as a disruptive technology with the potential to make tobacco smoking obsolete and others seeing them as threatening to renormalize smoking, and reversing much of the progress made in tobacco control over the past 50 years.⁷³ In spite of this debate, there is little available evidence to support benefits or harms of e-cigs. Early toxicology data found that e-cigs contain harmful compounds including carbonyls and nitrosamines, although in much lower levels than does tobacco smoke.^{74,75} However, because these products have been in widespread use for less than 10 years, long-term health risks remain unknown. There is limited data supporting the efficacy of e-cigs in promoting smoking cessation and reduction.⁷⁵⁻⁷⁷ The largest trial randomized 657 smokers to nicotine e-cig, placebo e-cig, or nicotine patch.⁷⁷ Quit rates at 6 months were low in all groups and not statistically different (7.3% with nicotine e-cigs, 5.8% with nicotine patches, and 4.1% with placebo e-cigs). There were no differences in adverse events between groups. The study was limited by the use of early generation e-cig products with probable ineffective nicotine delivery, low quit rates, and limited statistical power.

Given the currently limited evidence for the efficacy and safety and the lack of FDA regulation, we do not recommend the use of e-cigs for the initial treatment of smoking cessation. For smokers who inquire about e-cigs for smoking cessation, we recommend advising them to quit smoking using behavioral and FDA-approved pharmacologic therapies described here. As noted above, quitting smoking often takes multiple attempts and ongoing management and treatment efforts. However, smokers who have failed to quit smoking after multiple attempts using FDA-approved therapies or who cannot tolerate these therapies because of adverse effects but have had success in cutting down or quitting tobacco smoking using e-cigs can be reasonably

advised to continue using the e-cig in the short term if it helps them abstain from tobacco. They should be educated about the absence of safety data of long-term e-cig use, and attempts should be made to wean off the e-cig for chronic users.

Snus

Snus is a form of smokeless tobacco that is placed under the lip and delivers nicotine and other chemicals through the oral mucosa. Although awareness and use of snus in the United States is low,⁷⁸ the product is widely used in Sweden, where multiple correlational lines of evidence have linked snus use to lower rates of tobacco smoking.^{79,80} Likewise, Swedish men, a significant fraction of whom use snus, have been noted to have the largest reduction in smoking prevalence and smoking-related diseases between 1976 and 2002.⁸¹ As a result, interest in snus as a treatment for smoking cessation and harm reduction has developed. Snus contains carcinogens such as tobacco-specific nitrosamines and heavy metals, although in lower quantities than does smoked tobacco and North American style smokeless tobacco products (thought to be due to differences in manufacturing and storage techniques).⁸¹ Unlike other smokeless tobacco products, snus has not been definitively linked to increased risk of cancers of the oral mucosa, head, and neck, possibly related to the lower nitrosamine levels.^{82,83} An industry-funded randomized placebo controlled trial found that point prevalence smoking abstinence was significantly higher in the snus group at week 6 (18.4% vs 8%; $P = .03$), but not at week 28.⁸⁴ Adverse events were mild but more common in the snus group and included nausea, dyspepsia, gingivitis, hiccups, and dizziness.

Given the currently limited evidence for efficacy and safety and the availability of many other FDA-approved therapies, we do not recommend the use of snus for smoking cessation. For smokers who inquire about snus for smoking cessation, we recommend advising them to quit smoking using behavioral and FDA-approved pharmacologic therapies described in this review. Smokers who have failed to quit smoking after multiple attempts using FDA-approved therapies or who cannot tolerate these therapies because of adverse effects but have had success in cutting down or quitting tobacco smoking using snus can be reasonably advised to continue using snus in the short term if it helps them abstain from tobacco. They should be educated that although these products are safer than smoking cigarettes, snus and other forms of smokeless tobacco contain carcinogens and can cause harm. Cessation from all forms of tobacco should always be strongly recommended, supported, and treated.

CONCLUSIONS

Tobacco smoking remains the leading preventable cause of death and illness in the United States. Comprehensive treatment for the tobacco-dependent patient begins with a physician's inquiry into smoking and encouragement to quit, followed by an assessment of the current level of dependence and the severity of withdrawal symptoms during previous quit attempts. Combination pharmacotherapy is recommended for the initial treatment of the vast majority of smokers and is particularly important for those with high baseline levels of dependence. The patient's history combined with his or her personal preference can guide the clinician in initiating an appropriate treatment regimen. Clinicians must recognize tobacco dependence as a chronic disease and anticipate relapses and the need for recurrent, long-term follow-up. Comprehensive tobacco smoking cessation

service consultation should be sought whenever possible for patients with high levels of tobacco dependence and multiple relapses or failed quit attempts.

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