Smoking Cessation

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KEYWORDS

• Smoking • Cessation • Treatment • Pharmacotherapy

KEY POINTS

- Smoking is the major risk factor for lung cancer and contributes to risk for heart disease and many other conditions.
- Although the risks of smoking and the benefits of cessation are well recognized, for both generalist and specialist physicians, smoking cessation is often not a priority.
- Cigarette smoking should be regarded as a chronic relapsing disease.
- Optimal treatment requires a long-term approach, combining pharmacologic and nonpharmacologic interventions and close interactions between patient and clinician.

INTRODUCTION

Cigarette smoking is one of the major preventable causes of morbidity and mortality worldwide. It is the major risk factor for the development of chronic obstructive pulmonary disease (COPD) in the developed world and follows only indoor air pollution in the developing world. Smoking is the major risk factor for lung cancer and contributes to risk for heart disease and many other conditions. The adverse effects of smoking have been recognized at least since 1604,[1] and the overwhelming evidence linking smoking to disease was first reviewed in a Surgeon General's report in 1964.[2] The benefits of cessation are also well established and were the subject of a Surgeon General's report in 1990[3] and of a new report due in 2014.

Although the risks of smoking and the benefits of cessation are well recognized, for both generalist and specialist physicians, smoking cessation is often not a priority. This situation is unfortunate because more than 70% of adult smokers want to quit and interventions can help. Most have tried many times in the past. This situation often leads to a sense of futility, both for the smoker and the clinician. Undertreatment helps sustain this unhappy scenario. However, first-line smoking cessation interventions are not difficult, and all clinicians should be able to offer them to their patients.

The approach to cigarette smoking is to regard it as a chronic relapsing disease.[4] The role of the clinician is to help smokers achieve abstinence (remission), recognizing that relapses may occur. The proper model might be lymphoma, in which remissions are always regarded as successes and relapses are not failures but rather occasions that should lead to aggressive retreatment. In this article, the physiologic basis for smoking is reviewed and then both pharmacologic and nonpharmacologic approaches to treatment are addressed, with a discussion of practical issues.

PHYSIOLOGY OF SMOKING

There is a traditional view that regards smoking as a lifestyle choice and a habit. The decision to begin smoking is a choice, and in that context, it is a lifestyle choice. However, almost all smokers

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Clin Chest Med 35 (2014) 165–176

http://dx.doi.org/10.1016/j.ccm.2013.11.002

begin smoking in adolescence.[5] The choice to begin smoking is influenced by numerous social factors, which include not only the behaviors of family and friends but the promotion of smoking through advertising and public image. Smoking behavior is also strongly influenced by other social factors, including accessibility and cost.[6–8] Thus, although smoking is (in part) a lifestyle choice, it is clearly more than that. An alternative description is that it is a dangerous behavior, for which a susceptible population is at risk. Public health initiatives that are designed to influence smoking initiation among youth were initiated in the United States in the mid-1990s. These initiatives have had major impact on smoking prevalence.[9] Although public health initiatives are not reviewed here, they should be a part of any tobacco control program.

Nicotine is the most important psychologically active drug in tobacco, although there are others that are less well understood. Nicotine is a cholinergic agonist that acts specifically on a subset of cholinergic receptors, which have been classified as nicotinic receptors.[10,11] Nicotinic receptors are ion channels that are homopentamers or heteropentamers, which bind 2 ligand molecules.[12] The other major class of cholinergic receptors is muscarinic receptors, which are 7 membrane spanning G-protein coupled receptors that bind a single ligand molecule. Humans have 17 genes that code for distinct nicotinic receptor component chains, resulting in many potential pentamers. However, only a few play biological roles. Nine α and 3 β receptors are expressed in the brain. However, the (α4)(β2) complex, which can incorporate other subunits, including α5, α6, or β3, is believed to be a modulator of the effects of nicotine, and the $(\alpha4)_3(\beta2)_2$ subunit is believed to be particularly important in nicotine addiction. In support of the concept, deleting the β_2 receptor in mice eliminates behavioral responses to nicotine, whereas mutations in the gene can result in markedly increased sensitivity to nicotine[12] and the $(\alpha4)_3(\beta2)_2$ subunit is believed to be particularly important in nicotine addiction. In support of the concept, deleting the β_2 receptor in mice eliminates behavioral responses to nicotine, whereas mutations in the gene can result in markedly increased sensitivity to nicotine.[13]

By binding to the $(\alpha4)_3(\beta2)_2$ receptor, nicotine modulates the release of dopamine, which is a key mediator of pleasure and reward and plays a central role in the physiology of drug self-administration.[14] In particular, the release of dopamine is believed to mediate the euphoria associated with nicotine and many other addicting drugs. Nicotine also modulates the release of neurotransmitters in addition to dopamine and initiates both positive and negative feedback pathways, which may involve both changes in receptor expression and formation of neural connections. The overall effect in most individuals is an increase in nicotine self-administration together with a change in behavior (ie, addiction). These alterations can be long lasting. In rats, in utero exposures persist to adult life.[15] Adolescents may be particularly at risk for long-term alterations induced by nicotine.[16] These long-term effects may account for the persistent risk of relapse, which may be lifelong, which characterizes many addictions, including cigarette smoking. For this reason, an abstinent smoker is correctly regarded as in remission and at risk for relapse.

Some individuals, estimated at about 15% in the United States, are not addicted. Sometimes termed chippers, these individuals may smoke episodically and seem to not be fully addicted but may not be entirely normal either.[17,18] The physiologic basis for chippers is unclear, but may be related to genetic factors. It is an important point for the clinician, because this kind of behavior is well known to the general public and frequently confounds understanding of addiction.

Consistent with smoking being an addiction to nicotine, smokers adjust nicotine intake. If supplemental nicotine is provided, consumption is generally reduced.[19] Alternatively, if a smoker is obliged to reduce the number of cigarettes smoked, most maintain nicotine intake by altering the way in which individual cigarettes are smoked.[20] However, smoking is more than just an addiction to nicotine. Many cigarettes are smoked in social settings or habitually in association with other behaviors. In this regard, nicotine can augment the acquisition and persistence of conditioned behavior.[21] A smoker wishing to quit, therefore, must deal with both the biological effects caused directly by nicotine as well as with conditioned behaviors that likely have been potentiated by nicotine.

Nicotine is volatile. As a result, when air is sucked through the tip of a cigarette, the heated air causes nicotine in the unburned tobacco to volatilize. As the air passes through the cigarette, it cools, and the nicotine condenses on smoke particles, resulting in an aerosol that is about 1 μm in size, ideally suited to reach the alveolar space. Because nicotine is also lipid soluble in its neutral form, it can rapidly cross the alveolar space into the pulmonary capillary blood, reaching the brain in 15 to 20 seconds after a puff. The euphoric effects of nicotine depend in part on the kinetics: a rapid increase in levels at the receptors in the brain is associated with a greater hit. After absorption, nicotine redistributes into other body spaces,

which leads to rapid decreases in arterial levels after smoking a cigarette is completed.[22] Nicotine is then metabolized, primarily in the liver by CYP450 enzymes, which lead to the formation of cotinine.[23] The nicotine half-life in the blood is 2 to 4 hours, so with continuing smoking throughout the day, nicotine levels increase. They are lowest in the early morning, and consistently, most addicted smokers report that the most potent cigarette is the first one smoked in the morning. Individuals who do not smoke within an hour of arising may not be heavily addicted. In contrast, heavily addicted smokers smoke within minutes of arising. This clinical observation forms a key part of the Fagerstrom Index, which is a widely used measure that assesses nicotine addition (**Table 1**).[24] The importance of nicotine kinetics in mediating its psychoactive effects is the basis for nicotine replacement as an aid for smoking cessation (see later discussion).

Table 1
Items and scoring for Fagerstrom test for nicotine dependence

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

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. Copyright © 1991 KO Fagerstrom.

APPROACH TO A QUIT ATTEMPT

As noted earlier, smoking should be regarded as a primary addictive disorder.[4] Seventy-five percent of Americans wish to quit, but only 3% achieve prolonged abstinence in any year, indicating both the involuntary nature of the established addiction and the substantial need for treatment.[25] It is recommended that smoking status and willingness to quit be assessed at every health care visit.[4,26,27] However, individual readiness to quit (**Table 2**) is likely variable and may be related to acute health care events that may have no direct relationship to smoking.[28] Clinicians, therefore, must be prepared to exploit these windows of opportunity during which cessation attempts are made and may have greater success. To find these opportunities, the clinician must assess smoking status, hence the rationale for the recommendation for assessment at each visit.

The National Cancer Institute recommends using a 5-part approach, termed the 5As,[4,26,27] which follow the stages of change model. These stages are to ask patients about their smoking status, to assess their willingness to make a quit attempt, to advise smokers to stop, to assist them in their stop smoking efforts, and to arrange for follow-up visits to support the patient's efforts.

Routine inquiry about smoking may also favorably affect achievement of abstinence. In this regard, self-efficacy, the self-judged likelihood of success, seems to be a strong predictor of both success in a quit attempt[29] and the likelihood of subsequent relapse.[30] Failure to inquire about smoking is believed to send messages to the patient: that the physician does not care if the patient smokes; that the physician does not have an effective intervention; and that the physician does not

Table 2
Stages of change model for smoking cessation

Precontemplation	Not interested in quitting, likely unresponsive to direct intervention
Contemplation	Considering quitting, likely receptive to physician advice
Preparation	Actively preparing to make a quit attempt
Action	Quit attempt in progress
Maintenance	Avoidance of relapse (after a 6-mo remission)

Data from Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. Prog Behav Modification 1992;28:183–218.

think that the patient can quit, all of which can compromise self-efficacy. In support of the approach for routine assessment using the 5 As strategy, meta-analysis suggests that simple advice to quit from a clinician has a small but significant effect at boosting quit attempts and cessation.[27]

Quit attempts should be approached with the same strategy as inducing remission from lymphoma. Each treatment attempt should be given an optimal chance of success. In general, this strategy requires a combination of both pharmacotherapy, which can address some of the physiologic aspects of addiction, and nonpharmacologic approaches which can address the conditioned responses and other behavioral aspects of smoking. A staged approach, in which a person tries to quit on their own and, if unsuccessful, interventions of gradually increasing intensity are tried, is a misguided approach. Pharmacoeconomic analyses suggest that more intense programs are more cost-effective, because the less intense programs, which cost less, have less benefit.[31]

Whether smokers should quit with gradual reduction or tapering or with a sudden stop (eg. cold turkey) remains controversial. For most smokers, gradual cutting down can have initial success. First, a smoker can eliminate discretionary cigarettes that are smoked out of habit rather than to derive nicotine. As reduction proceeds, smokers can alter smoking behavior to maintain nicotine intake. However, as reduction continues, the smoker may begin to experience tobacco withdrawal symptoms. Rather than suffer prolonged discomfort, many taperers gradually return to their customary cigarette levels and do not succeed in quitting. In contrast, abrupt abstinence is often acutely stressful and leads to tobacco withdrawal symptoms. However, within a few weeks of total abstinence, complete abstainers experience less frequent cigarette cravings than taperers and are less prone to relapse. Nevertheless, some smokers may benefit from a tapering program,[32–34] and this can be used for selected individuals.

Most smokers are aware, at least in general, about the health hazards of smoking. In general, educational programs have proved disappointing as a means to achieve smoking abstinence.[4,26,27] Nevertheless, education about smoking is still regarded as useful, particularly when the information addresses specific patient concerns.

Group counseling programs to aid smoking cessation are available from several commercial and voluntary health organizations. Content generally includes lectures, group interactions, exercises on self-recognition of one's habit, some form of tapering method (leading to a quit day), development of coping skills, and suggestions for relapse prevention. Programs sponsored by voluntary health organizations are generally the best cost value,[4,26,27] but are generally available only in large metropolitan areas and often on a sporadic basis. One-year success rates associated with group counseling programs are in the 15% to 35% range,[4,26,27] although the success rates likely reflect selection bias (ie, participants may be more motivated to quit).

Smoking cessation strategies are generally the same for special populations, including patients with COPD. In this regard, all 3 approved medications (nicotine replacement therapy [NRT], bupropion and varenicline) have been assessed in COPD and efficacy has been shown.[35–37] The hospital setting is an appropriate venue to begin treatment. Withdrawal symptoms are uncommon in the hospital, perhaps because of the enforced abstinence and unavailability of cigarettes. Follow-up after discharge seems to be particularly important for quit attempts initiated in the hospital.[38] Psychiatric comorbidities are not a contraindication to smoking cessation intervention. The cessation attempt does not compromise treatment of psychiatric disease, and successful abstinence can be achieved in that setting.[4,26,27]

STRATEGY FOR THE QUIT ATTEMPT

The greatest quit rates are achieved when nonpharmacologic support is combined with pharmacotherapy. The more extensive the support, the greater the success. However, many smokers do not accept referral to a group program. Limited counseling in the office can be provided to these individuals. In addition, telephone quit lines, which have shown efficacy,[39] are available toll-free and at no cost in many countries, including the United States and Canada. In the United States, the phone number is 1-800-Quit Now. Support can be found via the internet using smokefree.gov. Clinicians should encourage their patients to make use of these resources.

Several agents are available for pharmacotherapy. Selection of an agent should be based on past experience and individual patient issues. Nicotine Replacement Therapy (NRT) is often used as a first-line agent, because many clinicians have more experience with it and it has fewer adverse effects. The patch-plus regimen is often used, because of its increased efficacy, particularly for individuals who are more heavily addicted (Fagerstrom scores $\geq$7).[4,26,27,40] In contrast, an individual with a history of depression may be best treated with bupropion.[41] Individuals who achieved abstinence with an agent, but later

relapsed, can be retreated with the same agent, but with specific attention to prevention of relapse. The details of specific agents are discussed later. NRT is generally started on the target quit date. Bupropion and varenicline are started 1 week before the quit date. Success has also been reported with varenicline started 1 to 5 weeks before the quit date.

A follow-up visit should be scheduled 10 days to 2 weeks after the quit date. This strategy allows assessment of adverse effects. However, the major reason for the visit is that it improves success rates, allowing the clinician to provide support to prevent relapse.

There are 4 specific issues that the clinician should anticipate with each quit attempt: withdrawal symptoms, cravings, depression, and weight gain. The clinician should prepare an action plan for each of these issues for each patient undergoing a quit attempt.

Withdrawal symptoms (**Box 1**) are experienced to a variable degree by most smokers undergoing a quit attempt. The symptoms generally peak within 72 hours then decrease gradually over the next 3 to 4 weeks. Common strategies that may help with withdrawal symptoms include increased levels of activity, deep breathing exercises, avoidance of high-risk situations, and use of other oral products (eg, cinnamon gum or chewable candies). Urges to smoke and withdrawal symptoms are greater when there is ready availability of cigarettes. As a result, it is important to remove all the cigarettes and smoking paraphernalia from the environment and to avoid situations in which cigarettes are provided by others.

Cravings to smoke are a feature of withdrawal. However, unlike the other symptoms, cravings can persist for years and are often precipitated by behaviors previously associated with smoking. Generally, they decrease markedly in frequency but can still be intense. Cravings are times at which there is risk for relapse. Use of alcohol, which is often associated with smoking, can both precipitate craving and increase the risk of relapse.

Depression is experienced by many smokers during the first 3 months after cessation and is associated with a higher rate of relapse.[42] For most, the depression is mild and transient. For others, it may require treatment. Smoking has increased prevalence among individuals with depression, and both nicotine and other components of cigarette smoke have modest antidepressant effects. Some of the depression associated with cessation, therefore, may be an uncovering of a preexisting depression and may require counseling or pharmacotherapy.

Weight gain is a particularly difficult problem associated with smoking cessation.[4,26,27] Rapid weight gain for 6 to 8 weeks after cessation is common. A more gradual gain may follow. On average, 10 years after cessation, weight is increased 4.4 kg and 5.0 kg for men and women, respectively. Although the health risks associated with postcessation weight gain are unknown, they are likely surpassed by the health benefits of stopping smoking.

Box 1
Nicotine withdrawal symptoms (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*)

- Dysphoric or depressed mood
- Insomnia
- Irritability, frustration, or anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Decreased heart rate
- Increased appetite or weight gain

PHARMACOTHERAPY

Three classes of medication are approved as aids to smoking cessation (nicotine replacement, bupropion [Zyban, also sold under the trade name Wellbutrin to treat depression], and varenicline [Chantix]) and 2 others are available off-label (nortryptiline and clonidine), which have documented efficacy and are recommended as alternative therapies in current guidelines.[4,26,27,40]

NRT

There are 5 NRTs: lozenges, polacrilex (gum) and transdermal systems, which are available over the counter (OTC), and nasal spray and a nicotine inhaler, which are available with a prescription. Other nicotine preparations, including nicotine toothpicks and e-cigarettes, have been developed and marketed as consumer products. Their efficacy and safety in smoking cessation remain undetermined, and their use, particularly that of e-cigarettes, is controversial (see later discussion under harm reduction). There were initial reports of cardiac events when NRT products were used with concurrent smoking, which led the US Food and Drug Administration (FDA) to recommend against this practice. However, the FDA recently (April, 2013) removed this warning from the OTC

formulations. These initial concerns are widely known by the general public, often inaccurately, and the current recommendations should be provided before the quit attempt.

NRT is usually started on a scheduled quit day, after which the smoker should be completely abstinent. If a smoker has some lapses, but is still interested in quitting, the quit attempt should continue. The concept is to replace nicotine to reduce the intensity of withdrawal. However, smokers' experience withdrawal symptoms, albeit with less intensity (see **Box 1**). The 5 approved formulations have similar 2-fold increases in quit rates over placebo when used alone.[4,26,27,43] They differ pharmacokinetically.[44] The transdermal systems provide the slowest delivery of nicotine but maintain steady state levels throughout the day. The other formulations, which can be administered ad lib, allow episodic dosing.

Nicotine polacrilex gum

Nicotine polacrilex gum is now commercially available OTC in 2-mg and 4-mg forms. The nicotine is bound to a resin and is released with chewing. Consequently, the rate of chewing influences nicotine delivery. At low pH nicotine is ionized, which prevents its absorption across the buccal mucosa. Thus, acidic foods or beverages can impair delivery of nicotine from the gum. The nicotine-containing saliva must be retained in the mouth as long as possible, because the nicotine must be absorbed across the buccal mucosa. If swallowed, the nicotine can cause local irritation of the stomach and can be absorbed. However, high first-pass metabolism in the liver limits blood nicotine levels. If chewed properly, blood levels peak after about 30 minutes[44] and achieve blood nicotine levels at less than 40% of customary smoking. A fixed dosage regimen rather than ad lib usage may have better success,[45] perhaps because it can produce higher blood nicotine levels. Some recommend that a smoker use 1 piece of gum every 1 to 2 hours for the first 6 weeks, followed by gradual reduction over 6 weeks. The long-term use of gum at times of craving to prevent relapse is also recommended. Some smokers can use sufficient gums to sustain nicotine addiction without smoking. Although this practice is not an approved use of NRT, it is recommended by some clinicians (see later discussion under harm reduction).

Nicotine gum is generally less effective in general practice and unsupervised settings than in clinical trials. This situation may be because of improper use of the gum, because chewing is important to its efficacy. Adverse effects of nicotine polacrilex gum include local effects (temporomandibular joint [TMJ] disease, trauma to dental appliances, sore jaw, oral irritation or ulcers, and excess salivation), effects from swallowed nicotine (hiccups), and effects from systemic absorption of nicotine (nausea, vomiting, abdominal pain, constipation, diarrhea, palpitations, and headache). Nicotine polacrilex gum is not recommended for those with poor dentition or who have dental appliances.[40]

Nicotine polacrilex lozenge

A nicotine polacrilex lozenge is also available OTC. Chewing is not required, but acid food or beverages impair absorption, as with gum. The lozenge is similar to the gum with regard to dosing, absorption, and duration of therapy.[46] Because it is not chewed, the lozenge does not share the problems related to TMJ disease or dental appliances. Other side effects are similar to those of gum.

Transdermal nicotine

Several transdermal patch delivery systems are available OTC. They are easy to use and maintain steady nicotine levels for 12 to 24 hours, achieving nicotine blood levels roughly 40% to 50% of a smoker of 30 cigarettes/d.[44] Perhaps because of the ease of use, transdermal nicotine systems have shown efficacy in the primary care setting.[28,47] The recommended duration of patches varies by product, but a minimum of 4 weeks of therapy is probably required to help achieve long-term abstinence.

Most commonly, patches are worn at night. This strategy provides a level of nicotine when a smoker awakes. This is a time when relapse is particularly likely, both because the low nicotine levels are associated with withdrawal and because smokers are familiar with the increased effect of a cigarette smoked on awakening. Both are likely reduced by maintaining nicotine levels during the night. However, nocturnal nicotine may disturb sleep, causing either vivid dreams or insomnia. Long-term use of the patch has not been observed, which suggests that the slow kinetics of nicotine delivery with transdermal systems is insufficient to sustain addiction.[48] As previously noted, early concerns about increased cardiac risk among individuals who smoked while wearing the patch have not been substantiated. In contrast, because patches lead to reduced smoking, they may decrease cardiac events.[49–51]

Nicotine inhaler

The nicotine inhaler is a plastic nicotine-containing cartridge that fits on a mouthpiece. Nicotine is not effectively delivered to the lungs, because the particle size is too large, but it is deposited and absorbed through the buccal mucosa. This

situation results in pharmacokinetics that resemble nicotine polacrilex. Blood levels can be about one-third of conventional smoking but depend on frequency of use. Usual dosing is 6 to 16 cartridges per day for 6 to 12 weeks, followed by gradual reduction over 6 to 12 weeks. The inhaler recapitulates many actions associated with smoking: preparation of the device, oral stimulation, inhalation, and so forth. Thus, it may be effective for smokers in whom these behaviors are particularly strongly conditioned. The inhaler may cause irritation of the throat and mouth and may precipitate bronchospasm in individuals with reactive airways as well as cause the adverse effects associated with the lozenge.

Nicotine nasal spray

The nasal spray delivers nicotine to the nasal mucosal, through which it is absorbed. It has the most rapid pharmacokinetics of the currently available nicotine replacement formulations, but nicotine delivery is still slower than that of a cigarette.[44] Nasal irritation is common, particularly when initiating therapy. Recommended dosing is 1 to 2 sprays per hour, with a maximum of 80 sprays per day for the first 3 months. Because the spray delivers large amounts of nicotine rapidly, it may be particularly useful for heavily addicted smokers. It may also have a greater risk of nicotine overdose and may have a greater potential to sustain a long-term addiction.

Combinations of NRT

The patch-plus regimen,[52,53] which combines a transdermal system with an ad lib NRT, has become common practice, although its use is off-label. This approach provides a baseline of nicotine replacement but also increases nicotine dosing at times of urges. Because combination of a transdermal system with an ad lib modality has been shown to increase quit rates,[4,26,27,47,54] it is recommended by some as initial therapy.[40]

Bupropion

Bupropion is used both as an antidepressant (trade name, Wellbutrin). It is also effective as an aid for smoking cessation (trade name, Zyban).[4,26,27,55] It is thought to act by potentiating dopaminergic and noradrenergic signaling. It is important not to prescribe bupropion under both names to an individual, because overdosage can result.

Bupropion approximately doubles quit rates compared with placebo. In 1 trial, individuals with a history of depression seemed to benefit from bupropion but did not with nicotine replacement, suggesting that bupropion may be a superior initial choice in these individuals.[41] Combination of nicotine replacement with bupropion seems to be more effective than either agent alone.

Recommended dosing is 150 mg daily for 3 days, followed by 150 mg twice daily. Steady state levels are achieved after 6 to 7 days, and thus, the target quit date should be approximately a week after the start of therapy. The 150-mg once-daily dose was nearly as effective as 150-mg twice daily.[56,57] As a consequence, many practitioners use the lower dose routinely. The appropriate duration of therapy has not been established. A 7-week course was the basis for regulatory approval, although a 12-week course is now commonly recommended. With prolonged therapy, secondary quits increase. Thus, therapy for 1 year results in more quits than therapy for 7 weeks.

The most common adverse effects are dry mouth, insomnia, agitation, and headache. An increase in blood pressure may occur, particularly when used in combination with NRT. Bupropion reduces seizure threshold, and a seizure risk of 0.1% has been reported. Because of its effects on seizure threshold, buproprion is contraindicated among those predisposed to seizures, or with anorexia nervosa or bulimia.

In 2008, concerns were raised for both bupropion and varenicline (see later discussion) with regard to a "possible association [with] suicidal events."[58] Because the benefits of smoking cessation were believed to outweigh any potential risks, the medicines were not withdrawn from the market, but a black box warning related to potential neuropsychiatric effects was added to the label. This warning states that patients and their caregivers should be alerted to the possibility of neuropsychiatric symptoms, and patients should be monitored for changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts. Common practice is reassessing patients 3 to 7 days after the quit day. This strategy allows for both monitoring of adverse effects and the provision of additional support for the quit attempt. In this context, a second visit has been shown to greatly improve success.[4,26,27]

Varenicline

Varenicline is a partial agonist at the (α4)(β2) nicotinic receptor.[59] As a result, it partially activates the receptor, thereby reducing withdrawal symptoms. It also prevents nicotine from acting, thus reducing the rewarding and reinforcement effects associated with nicotine. This effect may help prevent a lapse from becoming a full relapse. Both reduction in withdrawal symptoms and reduction in the rewarding effects of smoking a cigarette have been reported in clinical trials.[60–63] Varenicline consistently improves success in quitting

compared with placebo by an effect of 2-fold to 4-fold.[4,63]

Dosing is started at 0.5 mg orally once daily for 3 days, followed by 0.5 mg twice daily for 4 days and then 1 mg twice daily for 3 months. Treatment of a total of 6 months was associated with reduced relapse. A quit date is usually recommended for 1 week after starting medication. However, using a quitting window from 1 to 5 weeks had success that was comparable with a fixed quit rate.[64,65] The increased flexibility of this regimen may be helpful in exploiting windows of opportunity when patients are seen for another problem, and when motivation to make a quit attempt may be high.

The most common adverse reactions associated with varenicline are nausea, insomnia, visual disturbances, syncope, and skin reactions. The dose titration described earlier reduces nausea.[66] Varenicline has the same boxed warning as bupropion, indicating that patients and their caregivers should be alerted to the possibility of neuropsychiatric symptoms, and patients should be monitored for changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts.[58] Clinical trials have failed to confirm psychiatric adverse effects, although they cannot be fully excluded.[67] One meta-analysis[68] reported a significant increase in cardiovascular events with varenicline. However, this analysis excluded studies with no events, a methodological flaw.[69] A subsequent meta-analysis,[69] which included all available studies, found no difference between varenicline and placebo. Current recommendations are that patients taking varenicline should be alert for development of new or worsening symptoms of cardiovascular disease.[70] Accidental injuries from falls and vehicular accidents have also been associated with varenicline.[71] As a result, the FDA has issued an advisory regarding operating heavy machinery while using varenicline.[72]

Off-label agents

Two off-label medications have documented efficacy for smoking cessation. Nortriptyline is a tricyclic antidepressant. Its efficacy in aiding smoking cessation is supported by both individual studies and meta-analyses.[55,73] The US Department of Health and Human Services (DHHS) guidelines recommend nortriptyline as a possible second-line agent for clinicians familiar with its use.[4,26,27] Major adverse effects of nortriptyline include drowsiness and dry mouth. As with other tricyclics, central nervous system and cardiovascular effects, including arrhythmias, may occur.

Clonidine is an α_2-adrenergic agonist used to treat hypertension. Several clinical trials have shown trends toward efficacy as an aid to smoking cessation, which is supported by a meta-analysis.[74] DHHS guidelines suggest that it can be considered by practitioners familiar with its use.[4,26,27] The most common important adverse effects are drowsiness, fatigue, dry mouth, and postural hypotension.

Smoking cessation has some associated risks. Depression may occur, as was discussed earlier. Exacerbations of ulcerative colitis have been reported to be increased after cessation.[75] Less well established are anecdotal reports that asthma may worsen after cessation, although smoking generally makes asthma worse.[76] Smoking leads to glucocorticoid resistance in asthma, and smoking cessation is generally associated with improvement in asthma.[77] Similarly, some individuals report worse cough and sputum with cessation. However, clinical studies have reported dramatic reductions in cough and sputum after cessation.[78,79]

HARM REDUCTION

Cigarette smoke contains up to 6000 components, which are generated by the complex chemical processes associated with curing and pyrolysis of the tobacco.[80] Nicotine is not among the most important toxic compounds in smoke. This factor has led to the concept that nicotine addiction could be addressed by nicotine replacement using a preparation that does not include the health-compromising toxins. This approach, termed harm reduction, is inherently controversial, because it involves supporting an addiction and, potentially, the use of less toxic tobacco products.[81,82]

As noted earlier, many smokers sustain an addiction to nicotine with NRT, most commonly nicotine polacrilex. Most clinicians view pharmacologic grade nicotine as less hazardous than smoking and, if smoking is the alternative, find this acceptable. The e-cigarette is more controversial. There are many e-cigarettes available. Their nicotine delivery is unregulated. In addition, the various products also contain many flavorants and other additives, the toxicity of which is unknown. Thus, the potential benefits of using e-cigarettes compared with conventional cigarettes is unknown, although it is likely that the e-cigarette delivers considerably less of most toxins. However, e-cigarettes may have other health issues. Because they are seen as a safer alternative to smoking, there are concerns that many smokers who would have quit opt to use e-cigarettes. Worse, some individuals may start using e-cigarettes because of their perceived

lack of harm. After becoming addicted, these individuals may be at an increased risk for smoking conventional cigarettes.

Harm reduction with tobacco products is even more controversial. Several cigarette-like tobacco products that do not burn or burn very little tobacco have been developed. The personal and public health effects of these products are unknown. Snus is an unfermented tobacco product that is used orally and is not burned. It is widely used in Scandinavia, where it has been associated with dramatic reductions in risk of many cigarette-associated diseases.[83–86]

Because snus is a tobacco product produced and marketed as a consumer product, there is no experience with its use in a treatment setting.

SUMMARY

Cigarette smoking should be regarded as a chronic relapsing disease. However, it is a disease that can be effectively treated in many cases. Optimal treatment requires a long-term approach combining pharmacologic and nonpharmacologic interventions and close interactions between patient and clinician.

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