ABSTRACT

Cigarette smoking should be considered a chronic and relapsing disease, with chronic obstructive pulmonary disease (COPD) as one of its complications. Understanding of the physiologic underpinnings of addiction and smoking cessation may help clinicians appreciate not only the difficulties of smoking prevention and cessation but also the potential for future therapies that target these specific pathophysiologies. This article considers 4 elements of smoking as a primary prevention strategy, including (1) smoking initiation and the function of dopaminergic pathways in the brain as a key to nicotine addiction, (2) smoking cessation and the role of various nicotine replacement therapies, (3) relapse prevention and the permanent alteration of brain susceptibility to addiction seen in long-time smokers, and (4) harm reduction techniques and the impending political and social implications of the new “safer” cigarettes. Large studies have convincingly demonstrated that smoking cessation can preserve lung function and alter the natural history of COPD. By improving our understanding of the biology underlying the complex and difficult “quitting” behavior, clinicians will be in a better position to help their patients stop smoking and, thereby, lower the risk for COPD as well as for the many other diseases caused by cigarette smoking.


Most reviews of new targeted therapies for diseases begin with an outline of the key pathophysiologic mechanisms and then typically continue with detailed descriptions of aberrant biomolecular pathways and new pharmaceutical treatments targeting those specific pathways. With chronic obstructive pulmonary disease (COPD), however, smoking is the prime mechanism of disease, and smoking cessation is the most important and efficacious intervention. Large studies have convincingly demonstrated that smoking cessation can preserve lung function and alter the natural history of the disease.

In this review, therefore, the biology and behavior of smoking addiction and cessation will be outlined, and the potential for targeted interventions at key points will be described. Just as a greater understanding of disease genetics and cell biology is leading to improved targeted therapies for many diseases, including COPD, recent insights into nicotine metabolism, brain physiology, addictive behavior, and social policy are leading to novel smoking cessation strategies based on the underlying early pathophysiology of the harmful dependence. Specific tips to help patients quit smoking are also summarized here, along with a bibliography of practical resources for more information.

Clinicians would agree that smoking cessation is the highest priority for management of patients with COPD. But clinicians also realize that nicotine is extremely addictive, that many patients fail in their efforts to quit, and that different quitting strategies work for different patients. By considering the array of factors that contribute to the smoking addiction and, in many patients, to severe COPD, clinicians will be better positioned to customize smoking cessation plans with higher rates of success.
THE STAGES OF COPD

Understanding the natural history of COPD helps to identify the best points for therapeutic intervention. As shown in the adaptation of the classic Fletcher and Peto graph, lung function— as indicated by the forced expiratory volume in 1 second (FEV₁)—increases into early adulthood and then begins to diminish naturally with age. In cigarette smokers, the rate of this lung function loss is accelerated (Figure 1). Of course, individuals vary in their starting amounts of lung function; as is true with bone density, more is better. But as pointed out by Burrows, in some smokers and in others at elevated risk, the drop in FEV₁ is even more accelerated, often punctuated by sharp exacerbations that contribute to a more rapid decline. These individuals with highly accelerated declines in lung function most often come to the attention of clinicians. Typically, the diagnosis of COPD is made when patients are in their mid-to-late 50s or 60s and have presented with dyspnea on exertion.

While smokers typically lose lung function at about twice the average rate as nonsmokers, approximately 10% to 15% of smokers are eventually diagnosed with COPD. Such a statistic does not imply that the other 85% of smokers are free of major health risks. In fact, most smokers lose lung function, although they may not complain of symptoms nor be diagnosed. As many clinicians realize, however, patients with early-stage COPD often avoid any level of exertion that might cause symptoms. Thus, this self-induced restriction in activity, not any inborn protection from disease, may keep many patients from being officially diagnosed with COPD. Importantly, all-cause mortality is increased in all of those patients with diminished lung capacity. Most of the increased mortality is due to heart disease. This relationship, therefore, may reflect elevated susceptibility to smoking damage, causing both lung function loss and coronary artery disease. Alternatively, airway inflammation may contribute to cardiovascular disease.

Whatever the reason for the underdiagnosis of COPD, those patients with asymptomatic or early-stage COPD cannot be neglected. Not all patients with high cholesterol will suffer from atherosclerosis-related events, and not all smokers will develop symptomatic COPD. But the risk must still be addressed. As recommended by the Lung Health Education Program and by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), more aggressive use of lung function testing (especially spirometry) will be critical in diagnosing early COPD. In the latest GOLD guidelines, even those individuals who have normal spirometry but have chronic COPD-like symptoms, such as cough or sputum production, are now classified with a new diagnostic stage (Stage 0: At Risk) and need clinical attention.

The starting point for patients with any level of COPD is risk reduction; for most patients, smoking cessation, a risk reduction strategy proven effective at any stage of disease, is mandatory. As outlined in the remaining sections, smoking cessation is a multidimensional intervention. If clinicians are to appreciate not only the sheer human difficulty to quit smoking but also the potential for future targeted behavioral, societal, or pharmaceutical aids to improve such efforts, they must be aware of the multiple factors that determine why smoking cessation efforts succeed or fail.

SMOKING INITIATION

About 80% of patients with COPD are cigarette smokers, so smoking initiation should be the first element of risk reduction to be addressed. Most evidence...
indicates that if individuals do not start smoking by 30 years of age, then they have a relatively low chance of ever becoming a smoker. In fact, most people start smoking in childhood or during adolescence, which suggests that COPD is a geriatric complication of a primary pediatric disorder. One review of US survey data from the 1980s indicated the incidence of smoking initiation increased rapidly in individuals after age 11, reached a peak in individuals 17 years to 19 years of age, and declined rapidly in individuals up to age 25, and declined more gradually thereafter. About 15% of nonsmokers become smokers in each of those peak initiation years. The initiation rates were generally similar among races but much higher in those individuals with less than a high school education. In current years, the peak of smoking initiation has shifted to even younger ages.

Approximately 50% of those individuals who try cigarette smoking become long-term smokers, with recent studies suggesting that about half of the susceptibility to chronic cigarette smoking is genetic. The likely mechanism of genetic predisposition to cigarette smoking involves nicotine addiction and dopaminergic transmission in the brain. Nicotine— as with opiates, ethanol, cocaine, and amphetamines— modulates dopamine release. Nicotine binds to specific nicotinic receptors, including those receptors in the mesolimbic-dopaminergic system (controlling motivational behavior and reward) and those projecting into the locus ceruleus (controlling vigilance and arousal). When these receptors are activated, dopamine is released from the presynaptic vesicles and binds to 1 of 5 varieties of postsynaptic membrane-spanning dopamine receptors. Researchers posit that this pathway in the mesolimbic reward system functions as a learning for pleasurable sensations.

In smokers, this pathway may be overstimulated, or coopted, to create a state of physiologic dependence. Several researchers are now looking for interindividual differences in the various proteins along this complex brain reward pathway to explain why some people become addicted to nicotine. For example, in one of the first studies of this pathway Noble et al found that cigarette smokers are twice as likely to have the less prevalent A1 allele of the D2-dopamine receptor (DRD2) than are nonsmokers. Although this small study (354 Caucasian men and women) was subject to the usual limitations of any association study, it highlights the potential for finding an inherited basis for substance abuse problems.

Clearly, DRD2 is not “the smoking gene.” Addiction to cigarettes and the development of COPD may involve a complex polygenic inheritance. Over 50 different genes (eg, coding for dopamine receptors, dopamine reuptake proteins, dopamine metabolizing enzymes) may contribute to the risk of smoking, and none of these genes will account for more than 3% of the 50% variance due to genetic effects. Nonetheless, all of these genes may affect smoking behavior and risk and may explain why some patients are chain smokers and other patients never started smoking. Another genetically variable pathway that may affect smoking initiation involves nicotine metabolism. The CYP2A6 enzyme is a mixed-function, liver P-450 oxidase that metabolizes about 70% of the nicotine taken in during smoking. A research group has found that approximately 12% of 164 tobacco-dependent smokers had the null allele (ie, inactive form) of CYP2A6, as compared to about 20% of 184 nonsmokers who had tried cigarettes (P < .04). These results support the hypothesis that the inability to metabolize nicotine reduces the likelihood of a smoking habit (ie, the individuals become ill when they smoke). Interestingly, the researchers also showed that the smokers with null CYP2A6 smoked fewer cigarettes per day, indicating the need for fewer cigarettes to attain the desirable nicotine blood level. Recent studies in Japan show that smokers with the null mutation for this nicotine-metabolizing gene smoke fewer cigarettes per day and also have lower rates of lung cancer than is expected, based on the number of cigarettes smoked, as compared to those smokers with other CYP2A6 genotypes. Preliminary data from this same group indicate that lung function is better in those patients who have a limited capacity to metabolize nicotine.

While the genetic underpinnings of nicotine addiction are intriguing, therapy or counseling based on such factors are obviously years or decades in the future. At present, the only well-documented factor to impact smoking initiation is much more prosaic: money. A study in Canada showed that as cigarette prices nearly tripled from 1985 through 1990 (mostly due to increased taxation), the number of cigarettes smoked per year dropped markedly—from about 3500 per year to about 2500 per year for adults, to almost 1000 per year for teenagers. Even more gratifying was the drop in the percentage of teenaged smokers over this same time period (Figure 2).

Despite the evidence of efficacy, increasing taxes on cigarettes remains a complicated social issue.
Canada, for instance, the tax was eventually rescinded because of concerns about smuggling of less expensive cigarettes from the United States and related concerns about increased gang activity and violence. The price-per-pack issue is also currently influenced by the increased numbers of new manufacturers who can offer the product for a lower price, since they are not subject to the retroactive tax associated with the large tobacco company lawsuit settlement. Although the price issue is complex, money remains the single best pressure point for measurably reducing teenaged smoking initiation. While antitobacco campaigns in states such as California have had some success in smoking cessation in adults, the impact among adolescents has been much less. Recent reports, however, suggest that comprehensive public health campaigns are beginning to reduce smoking among high school students. Increasing the public’s awareness of COPD will also contribute to public willingness to raise the price of cigarettes. Clinicians can help in these efforts by screening more at-risk patients with spirometry and by advocating higher cigarette taxes and comprehensive tobacco control programs at a local and national level.

**SMOKING CESSATION**

If smoking initiation cannot be stopped, then the next best solution is smoking cessation. About two thirds of all adults and adolescents actually want to quit smoking, but there is a high failure rate even in this willing majority.

Nicotine replacement is one of the best-known strategies for weaning patients from cigarettes. The rationale for nicotine replacement is to provide a steady-state blood level of nicotine that will prevent withdrawal symptoms. Most smokers crave the rapid rise in drug that is most prominent from the first cigarette of the day. As with most addicting drugs, the rapid bolus of nicotine to the brain causes euphoria and may also contribute to the biochemical and cellular mechanisms of addiction. Smokers try to avoid withdrawal effects by smoking another cigarette after blood levels decline, often keeping a steady-state nicotine level at about 40 ng/mL by continual smoking.

Nicotine replacement products cause lower peak nicotine levels so the reinforcing psychological euphoria is missing (and possibly the reinforcing addictive mechanism as well, although this is more speculative). Although the pharmacokinetic profile of each replacement product is unique and probably related to its addiction potential (Table 1), all of these products work essentially the same way: prevent withdrawal by providing a baseline steady-state concentration of nicotine. When patients no longer have this physiologic craving, they have begun to change their behavior, to learn how to deal with situations without smoking, and to become a nonsmoker.

The various delivery systems for nicotine replacement allow patients to choose an option that matches their preferences and lifestyle. Currently, all nicotine replacement products appear to boost the quit rate by 1.5 to 2 times as compared to that of a placebo. Product differences involve pharmacokinetics and the related potential for addiction, which appears to be lowest for the patch, higher for the gum and the inhaler, and highest for the spray. In fact, concerns over addiction with the spray, which provides a peak nicotine level in 10 minutes (identical to a cigarette), probably explain why this product is not available over-the-counter. A new lozenge formulation for nicotine replacement is also available, although less data about it have been published.

Combinations of the replacement products may also eventually improve the dismal abstinence rates for
smokers trying to quit. One recent long-term study showed the combination of a nicotine patch (for 5 months) plus the nicotine spray (for 1 year) was about twice as effective at stopping smoking than was the nicotine patch plus placebo spray. The combination regimen, which allowed patients to acutely boost their baseline nicotine levels with the spray, led to abstinence rate of 27% at 1 year and 16% at 6 years, as compared to 11% at 1 year ($P = .001$) and 9% at 6 years ($P = .077$) in the patch-only group.

Such results highlight the potential benefits of creative combinations of nicotine replacement products but also remind clinicians of the extreme difficulty of smoking cessation even in motivated individuals. Clearly, other targeted pharmaceuticals to attack the addiction pathways in the mesolimbic system would be welcome. Bupropion, an antidepressant that primarily affects dopamine metabolism, has been used in conjunction with nicotine replacement with some success. Other agents such as nortriptyline and clonidine, which work via different mechanisms, may also work as smoking cessation drugs.

Comprehensive strategies for smoking prevention and cessation are beyond the scope of this article, but the 5-step checklist recommended by the US Public Health Service (USPHS) provides a good practical framework for intervention (Table 2). Guidelines published by GOLD, by the USPHS, and by the Agency for Health Care Policy and Research should be consulted. At a minimum, clinicians in their everyday practice should recall the following recommendation by the joint National Heart, Lung, and Blood Institute/World Health Organization committee (GOLD) based on these guidelines:

“Even a brief, 3-minute period of counseling to urge a smoker to quit can be effective, and at the very least this should be done for every smoker at every visit.”

### Relapse Prevention

Relapse prevention should be considered as a distinct component of smoking cessation because the physiologic mechanisms underlying abstinence may vary from patient to patient. These underlying differences make it more difficult for certain patients to quit, a fact perhaps reflected in the 70% to 85% quit rates typically seen in the early weeks of smoking cessation programs versus the 20% to 23% success rates seen at 1 year.

The complete process of nicotine addiction usually requires a long period of smoking before becoming completely established. Certainly there is variation among individuals, but on average the mature adult habit may require approximately a decade. Presumably, during this period cellular and biochemical alterations in the brain structure are elicited, and

### Table 1. Pharmacokinetics of Nicotine Replacement Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Time to Max (minutes)</th>
<th>Steady State Level (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td>500</td>
<td>20</td>
</tr>
<tr>
<td>Gum</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Inhaler</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Nasal Spray</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Cigarette</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>

### Table 2. Strategies to Help Patients Quit Smoking

1. **ASK** Systematically identify all tobacco users at every visit. Implement office-wide system that ensures that tobacco-use status is queried and documented for each patient at each clinic visit.
2. **ADVISE** Strongly urge all tobacco users to quit. In a clear, strong, and personalized manner, urge every tobacco user to quit smoking.
3. **ASSESS** Determine willingness to make a quit attempt. Ask all tobacco users if they are willing to make a quit attempt at this time (eg, within the next 30 days).
4. **ASSIST** Aid the patient in quitting. Help the patient with a quit plan; provide practical counseling; provide extratreatment social support; help patient obtain extratreatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. **ARRANGE** Schedule follow-up contact, either in person or by telephone call.

Adapted from GOLD, as adapted from USPHS.
some of these alterations may be very long lasting or permanent, even with cessation. Thus, when addicted individuals quit smoking—even if they have completed acute withdrawal but then relapse—they quickly resume their fully addicted behavior. Within days, they return to their original habits. Thus, relapse is not the same process as initiation.

To prevent relapses or readdiction in these most vulnerable individuals, several targeted treatments are now being tested. In general, the rationale for these treatments is to block the effects of nicotine in the most relapse-prone individuals and, thereby, abort the rapid descent back into addiction. The classic scenario involves the ex-smoker in the bar who, after a rough day and a few drinks, loses his inhibitions and smokes half a pack of cigarettes. If the nicotine in those cigarettes could be blocked before reaching the permanently primed brain receptors, the full and rapid relapse might be prevented. In animal studies, 2 strategies have been evaluated for their ability to block nicotine in such situations: nicotine vaccines and nicotine antagonists (eg, mecamylamine). Various versions of these strategies are now entering clinical trials.

For clinicians today, tracking the early clinical progress of any such antinicotine treatments is perhaps less vital than simply understanding the key concept that the nicotine-addicted brain is deeply and permanently altered. As such, cigarette smoking should be viewed as a chronic and relapsing disease. And, as with cancer therapy, after induction of the remission, the remission must be consolidated. With our increasing insights into the biochemistry of the addicted brain, we are closer to achieving such longer-term consolidations in smoking cessation.

One “pearl” for the clinician involves the interaction of alcohol and smoking. Many smokers not only drink but often drink in situations closely associated with smoking. Relapses are often associated with this concurrent alcohol use, perhaps because alcohol erodes resolve or perhaps because of biological interactions in the addicted individual. Cautioning an ex-smoker about the hazards of relapse while drinking has been suggested.

HARM REDUCTION

If all attempts to prevent smoking initiation and to promote smoking cessation (without relapse) fail, then an attempt at harm reduction may become the next best strategy. This strategy of designing and providing “safer” cigarettes or using other means to effectively reduce the amount of cigarettes smoked is controversial. As with needle exchange programs or methadone maintenance for heroin addicts, some critics say that a program that assumes continuation of a bad behavior such as smoking should not be funded. In response to this criticism, the Institute of Medicine recently prefaced its evaluation of harm reduction approaches for smoking by stating that “harm reduction explicitly assumes continuation of the undesired behavior... and aims to lower the total adverse consequences.” Harm reduction, in other words, involves continued exposure to harmful substances in tobacco and continued (albeit potentially reduced) exposure to related disease, and is meant only for individuals who are so addicted that they cannot quit smoking.

There are actually several possible approaches to harm reduction in smoking and COPD. Inhibition of the CYP2A6 enzyme mentioned earlier, for example, is an approach that might eventually limit the number of cigarettes smoked. A drug that inhibited nicotine metabolism might be beneficial since fewer cigarettes would be needed to sustain a given nicotine blood level. Partial nicotine replacement (ie, using a patch or another replacement device but still smoking the occasional cigarette) is another strategy for reducing overall intake and, thereby, mitigating overall harm.

The most commonly discussed current strategies for harm reduction, however, involve reduction of toxin exposure in the cigarettes themselves. Low-tar and low-nicotine cigarettes, unfortunately, do not seem to help. We tested individuals who switched to low-tar/low-nicotine cigarettes and found that the level of inflammation in the lung (as measured by bronchoscopies and alveolar macrophage concentrations) actually increased in these smokers. Apparently, smokers simply used more of the low-tar/low-nicotine cigarettes in order to achieve the desired nicotine level. Smokers who used nicotine gum and reduced smoking had a significant drop in lung inflammation.

Completely redesigned “low-risk” cigarettes, such as the Eclipse (R. J. Reynolds Tobacco Company), are the latest attempt at harm reduction. These cigarettes burn an ingredient other than tobacco to liberate the nicotine within the unburned processed tobacco leaf. In the Eclipse, the heat source at the end of the cigarette is charcoal. Since the pyrolysis of tobacco generates most of the harmful chemicals in the usual cigarette, the Eclipse is engineered to avoid these toxins and deliver “cleaner”
nicotine to the lung. In our clinic we have demonstrated that the level of lower respiratory tract inflammation can be reduced by switching heavy (>40 cigarettes/day) smokers to the Eclipse. This change was statistically significant and was evident within 2 months of switching to the low-risk cigarette.25

These preliminary results are mentioned only to help make a few final points about harm reduction. First, clinicians must become aware of safer cigarette approaches because these cigarettes will soon be available nationally. Second, these cigarettes seem to be less harmful than a regular cigarette. Third, low-risk cigarettes do carry complications, specifically, touting them as less harmful than a regular cigarette might discourage smoking cessation and encourage smoking initiation. Thus, the arena of harm reduction for tobacco-induced disease is controversial, not only medically but also politically and socially. The wide-scale introduction of a safer cigarette may easily erode long-standing public health campaigns and eventually decrease cessation and increase initiations among those individuals who are unaware of the low-risk product. The fragile societal momentum against cigarette smoking is at risk. Regulation may be needed to balance the potential benefit of this new product for highly selected patients versus the potential for harm to the public health as a whole. Nevertheless, such products may have benefits for the continuing smoker.

Finally, as will be discussed in the final issue of this Advanced Studies in Medicine series, reversing the pathophysiology of COPD itself is another harm reduction technique with applications for specific patients. With these new anti-inflammatory, antiprotease, and antiapoptosis strategies, the fundamental triggers for emphysema and chronic bronchitis will be attacked. While such targeted therapies are clearly necessary for those individuals already suffering from COPD, the controversial question related to harm reduction may also apply to these agents: If we can eliminate the diseases of smoking (not just COPD but lung cancer, heart disease, and the many others) while allowing people to continue smoking, should we? Until researchers solve the dilemma of diseases associated with smoking, smoking cessation must remain the paramount goal for clinicians every time they see a patient who smokes—and who is, therefore, at high risk for COPD.

Conclusion

A century ago, lung disease—tuberculosis—was the number 1 killer in the United States. The intervention with the largest impact on tuberculosis mortality was not drugs or improved medical care but a vigorous public health campaign, as will be true today for COPD—currently the fourth leading cause of death in the United States.26 Developing targeted therapies for COPD is necessary and commendable, but only a renewed determination to study, refine, and improve smoking cessation efforts will halt and eventually reverse the powerful momentum of the COPD epidemic.

References