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Pharmacotherapy for Nicotine Dependence[1]

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ABSTRACT Approximately 50% of long-term cigarette smokers die prematurely from the adverse effects of smoking, including on cancer, cardiovascular disease, lung disease, or other illness. This risk can be substantially reduced by smoking cessation, with greater benefits occurring the earlier in the smoking career that cessation occurs. However, cessation provides benefits at any stage, including after the onset of smoking-related disease, by improving the prognosis and quality of life. Clinicians can have a significant impact on reducing tobacco use by their patients by following the US Public Health Service Clinical Practice Guidelines. Proven strategies include structured methods of advising cigarette smokers to quit and guidance to facilitate their efforts, as well as the use of various pharmacotherapies. Pharmacotherapies for tobacco dependence include nicotine replacement medications in the form of gum, transdermal patch, lozenge, sublingual tablet, nasal spray, and vapor inhaler formulations. The only nonnicotine medication that has been approved by the US Food and Drug Administration is bupropion. Combination therapies, long-term medication therapies, and harm reduction strategies may further improve outcome with approved medications. Further, new medications such as varenicline and rimonabant are likely to reach tobacco users who are refractory to current treatments. Increasing the treatment options, increasing availability, and reducing the perceived cost of these medications may have an additional public health impact. (*CA Cancer J Clin 2005;55:281–299.*) *© American Cancer Society, Inc., 2005.*

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INTRODUCTION

In 2002, an estimated 45.8 million adults in the United States were current cigarette smokers; of these, an estimated 37.5 million (81.8%) smoked every day, and 8.3 million (18.2%) smoked some days. Among those who smoked every day, an estimated 41.2% reported that they had stopped smoking for at least 1 day during the preceding 12 months because they were trying to quit.[1]

Cigarette smoking causes approximately 440,000 deaths annually in the United States or 18.1% of all deaths nationwide.[2,3] As shown in Table 1, 155,789 (about 35%) of these smoking-related deaths were caused by cancer among smokers. However, cigarette smoking is a major contributor to cardiovascular and lung disease; approximately 56% of cigarette smokers die from these conditions and about 9% die from other causes.[2]

Reduction of health risks by smoking cessation (relative to continued smoking) varies across medical condition. For example, pregnant women reduce the risks of smoking-related pregnancy complications to almost the nonsmoker level if they quit during the first trimester.[4,5] The reduction in risk of cardiovascular disease-related death decreases precipitously at 6 months to 2 years.[5] The risk reduction for lung diseases and various cancers is less pronounced and more gradual to accrue. Improvements in lung function can be seen as soon as 1 year after cessation, and with sustained abstinence, the age-related decline in lung function returns to that of never smokers.[5] Significant risk reduction for cancers after cessation

[1]JEH, RVF, and ARB consult on tobacco-dependence treatment products through Pinney Associates to GlaxoSmithKline Consumer HealthCare. JEH also has a financial interest in a new nicotine replacement product. JEH was supported in part by the Robert Wood Johnson Foundation Innovators Awards Program at the Johns Hopkins University School of Medicine. Additional support to JEH, RVF, and ARB was provided by Pinney Associates.

TABLE 1 Annual Neoplasm Deaths, Smoking-attributable Mortality by Type of Neoplasm in the United States, 1995–1999

Neoplasms	Male	Female	Total
Lip, oral cavity, pharynx	3,873	1,264	5,137
Esophagus	6,280	1,613	7,893
Pancreas	3,065	3,415	6,480
Larynx	2,525	602	3,127
Trachea, lung, bronchus	80,571	44,242	124,813
Cervix, uteri	—	552	552
Urinary bladder	3,699	1,053	4,752
Kidney, other urinary	2,799	236	3,035
Total	102,812	52,977	155,789

From the Centers for Disease Control and Prevention, 2002.[2]

can be seen in 5 to 15 years, though the risk generally does not appear to reach the level of never smokers.[5] In fact, even if a person develops smoking-caused disease, they benefit from cessation by generally improved prognosis, medication response, and quality of life.[6] Although the vast majority of tobacco-related deaths in the United States are due to cigarette smoking, all forms of tobacco are deadly and addictive. Cigar smokers carry a generally lower risk of lung disease although their risk can be comparable to cigarette smokers if they inhale, which many do.[7,8] Smokeless tobacco users (eg, "snuff" and "chewing tobacco") have increased risk of head and neck cancer as well as very high risks of oral dental diseases.[9,10] Furthermore, about 40,000 nonsmokers die each year in the United States as a consequence of their involuntary exposure to environmental smoke.[2]

Because of the morbidity and mortality associated with tobacco use and the substantial benefits of cessation, it is vital that all clinicians make a concerted effort to motivate tobacco users to cease their use of tobacco and to assist in their cessation effort. Specifically, the Clinical Practice Guideline on Treating Tobacco Use and Dependence[11] published by the Public Health Service offers the following recommendations to intervene with tobacco users willing to quit: *ask* the patient if he or she uses tobacco, *advise* him or her to quit, *assess* willingness to make a quit attempt, *assist* him or her in making the quit attempt, and *arrange* for follow-up contacts to prevent relapse. In a meta-analysis, it was shown that brief advice to quit smoking from a clinician increases cessation rates by 30%.[11] It should be noted that the critical role of the physician is to initiate the discussion about the importance of quitting smoking and not necessarily to provide all of the elements of appropriate counseling. These elements can be provided either by referral to a clinic with extensive experience in treating tobacco dependence or by a knowledgeable assistant.

The guidelines[11] also state that pharmacotherapy should be offered to "all smokers trying to quit, except in the presence of special circumstances. Special consideration should be given before using pharmacotherapy with selected populations: those with medical contraindications, those smoking fewer than 10 cigarettes per day, pregnant/breastfeeding women, and adolescent smokers." For first-line pharmacotherapies, the guidelines[11] recommend all of the US Food and Drug Administration (FDA)-approved medications, which include nicotine replacement medications and the antidepressant bupropion. For second-line therapies, clonidine and nortriptyline are suggested. The current review will discuss the rationale behind the use of pharmacotherapies, nicotine replacement medications, nonnicotine medications, and how efforts can help individuals to substantially reduce their risk of disease, disability and premature death, as well as contribute to overall improved public health.

Because the majority of people who are advised to quit may not do so in the near term, many doctors and other health professionals undoubtedly underestimate the power of their own guidance in getting their patients ready to eventually try to quit and to be successful when they do.[11–13] The data reviewed in the guidelines indicate that advice alone is important, and advice plus assistance and follow up, are effective for many tobacco users,[11–13] and highly cost-effective when compared with therapies for other medical disorders.[14] Although pharmacotherapies for smoking cessation can essentially double the rates of successful quitting relative to placebo, the absolute rates of cessation remain quite low. This should not discourage the clinician from recommending these pharmacotherapies, but rather the clinician should be aware that several quit attempts may be required before long-term cessation is achieved.

RATIONALE FOR USE OF PHARMACOTHERAPIES TO TREAT TOBACCO DEPENDENCE

Most widely marketed cigarettes, including those labeled as "light" cigarettes, deliver 1.2 to 2.9 mg of nicotine as tested under standards of the Massachusetts Department of Health. The typical pack-per-day smoker absorbs 20 to 40 mg of nicotine each day, achieving plasma concentrations of 23 to 35 ng/ml by the afternoon.[15] This level of nicotine delivery provides sufficient nicotine intake (regardless of the Federal Trade Commission's so-called rating of the cigarette's nicotine delivery) to produce a cascade of physiologic and behavioral effects that culminate in the disorder of dependence.[16]

The effects of nicotine that are associated with dependence include increased expression of brain nicotine receptors and diverse additional effects, including changes in regional brain glucose metabolism, electroencephalographic changes, the release of catecholamines, tolerance, and physiologic dependence.[17] These effects increase the compulsion to smoke by producing positive reinforcement (with the administration of nicotine) and withdrawal symptoms that start within a few hours of the last cigarette. More dependent cigarette smokers have their first cigarette more quickly on waking in the morning, apparently in response to the more strongly onsetting withdrawal symptoms. In fact, time to the first cigarette and number of cigarettes per day are the two strongest predictors of nicotine dependence level.[18]

Two medical disorders are now widely recognized to comprise what is more generally termed tobacco addiction or dependence: 1) nicotine dependence, which is the disorder of maladaptive and chronic tobacco use, and 2) nicotine withdrawal, which is the constellation of withdrawal symptoms which accompany tobacco abstinence.[19] Effects and symptoms of nicotine dependence and withdrawal vary within individuals over time and by factors such as nicotine dose and delivery speed, and there is also considerable variation across individuals. The FDA-approved medical indication for treating tobacco dependence embodies these two disorders through the following language on the labeling of the products in which they are described as "aids to smoking cessation for the relief of nicotine withdrawal symptoms."

An implication of the diverse cascade of neuropharmacologic and endocrine effects of nicotine administration and withdrawal is that therapeutic effects could be achieved by: 1) substituting other forms of nicotine delivery, 2) administering substances which selectively target one or more of these underlying mechanisms, and 3) administering behavioral treatments, acupuncture, and other therapies to address symptoms modulated by these mechanisms.

NICOTINE REPLACEMENT THERAPY

The most widely studied and used pharmacotherapy for managing nicotine dependence and withdrawal is therapeutic use of nicotine-containing medications.[11,20,21] Nicotine medications make it easier to abstain from tobacco by replacing, at least partially, the nicotine formerly obtained from tobacco and thereby providing nicotine-mediated neuropharmacologic effects. There appear to be at least three major mechanisms of action by which nicotine replacement therapy (NRT) medications support smoking cessation efforts.[20,22] First, the medications may reduce either general withdrawal symptoms or at least prominent ones, thus enabling people to function while they learn to live without cigarettes. Second, the medications may also reduce the reinforcing effects of tobacco-delivered nicotine. Finally, nicotine medications may provide some effects for which the patient previously relied on cigarettes, such as sustaining desirable mood and attention states, making it easier to handle stressful or boring situations, and managing hunger and body weight gain. Evidence for the operation of these mechanisms is not conclusive. Nonetheless, all of the approved nicotine replacement medications have been determined by the FDA to be safe and effective aids to smoking cessation.

It should be noted that not all of the reinforcing effects of tobacco are solely attributable to nicotine. Over time, the various sensory stimuli accompanying cigarettes and cigarette smoking become effective at both triggering and relieving tobacco cravings. For example, denicotinized cig-

arettes have been shown to temporarily reduce tobacco craving and some withdrawal symptoms in abstinent smokers,[23] though it has been long known that they are unsatisfactory substitutes for nicotine-containing cigarettes in the long run.[24] Conversely, although even intravenous nicotine can partially substitute for smoking, reduce spontaneous smoking, and reduce urges to smoke, sensory stimuli can be as important if not more important in the short run. For example, in one study comparing the effects of intravenous nicotine, smoking regular cigarettes, and smoking denicotinized cigarettes, administration of intravenous nicotine caused a small suppression of ad libitum smoking behavior; in contrast, denicotinized smoke produced a significantly larger reduction, showing that short-term satiation is more dependent on the presentation of smoke than delivery of nicotine per se.[25] However, denicotinized smoke alone did not have as much effect as puffs from the usual brands of cigarettes. Further, a meta-analysis of studies of denicotinized cigarettes found that ratings of smoking derived from denicotinized cigarettes appear to vary with level of tobacco dependence, suggesting that sensory factors may be more important to highly dependent, compared with less dependent, smokers.[26] Furthermore, nicotine replacement medications such as nicotine gum and patch can substantially reduce most physiological and cognitive withdrawal symptoms while tobacco cravings persist (albeit typically at lower levels).[27,28] A clinical implication of such observations is that nicotine replacement medications should not be viewed as stand-alone medications that make people stop smoking. They reduce withdrawal and dependence, but it may take many months if not years for some people to be able to comfortably manage their cravings in a world filled with tobacco-associated stimuli. Reassurance and guidance from health professionals combined with the medication can be critical for some people to achieve and sustain abstinence.[11,29]

Currently Approved Products

There are six types of nicotine replacement products on the market. These include several brands and types of nicotine transdermal patch systems that deliver nicotine through the skin, nicotine nasal spray, and several products that deliver nicotine through the oral mucosa: gum, lozenge, sublingual tablet, and vapor inhaler. Nicotine patches are applied once per day and thus could be considered a "passive" dosing system. The other products, unlike the nicotine patch, allow the smoker to self-administer a dose of nicotine on an as-needed basis; these will be referred to as "acute" dosing forms here. Passive and acute dosing medications are sometimes combined to provide general craving relief and breakthrough craving relief,[11,30,31] as are sustained release analgesics often combined along with immediate release analgesics to reduce pain and address "breakthrough" pain, respectively, in the management of cancer pain.[32]

The sections below describe the dosing, instructions for use, expected adverse events, and notable characteristics of each dosing form. It should be noted that there are some adverse events that are common to all NRT products including dizziness, nausea, and headache. Therefore, the sections below will only discuss adverse events that are specific to that delivery form.

Transdermal Nicotine Patches

Nicotine patches are applied to the skin and deliver nicotine through the skin at a relatively steady rate. There are currently four patch formulations on the market that vary widely in their design, pharmacokinetics, and duration of wear (ie, 24- and 16-hour wear). The diversity in patch systems has been described in reviews,[33,34] and the differences in pharmacokinetics have been illustrated in a head-to-head clinical trial.[35] All of the patch types are available in a range of dosages. Some formulations and indications also allow for more highly-dependent smokers to use the strongest patches and less-dependent smokers to use a lower dose. For example, the NicoDerm CQ patch (marketed in the United States by GlaxoSmithKline Consumer HealthCare) has 7-, 14-, and 21-mg/day dose strengths and has been shown effective in both 16- and 24-hour use. Smokers who use 10 or less cigarettes per day are instructed to begin with the 14-mg patch, and those who smoke more than 10 per day are instructed to start with 21 mg. For some prod-

ucts, progressively lower doses can be used to provide weaning over a period of several weeks or longer to enable gradual adjustment to lower nicotine levels and ultimately to a nicotine-free state. For example, patient instructions for NicoDerm CQ state that smokers who use more than 10 cigarettes per day should use the 21-mg/day patch for the first 6 weeks, move to the 14-mg/day strength for 2 weeks, then use the 7-mg dose for the final 2 weeks. The Nicotrol patch (marketed in the United States by Pfizer) is similarly labeled, recommending 15 mg for 6 weeks, and 10- and 5-mg patches for 2 weeks each. The Habitrol patch (marketed in the United States by Novartis), is available in the same doses as the NicoDerm CQ system, but users are instructed to use the 21-mg dose for 4 weeks rather than 6 weeks before tapering.

As previously noted, patches differ in their recommended wear time. The NicoDerm CQ and Habitrol systems are designed to be worn for 24 hours, but can be removed after 16 hours and the Nicotrol system is designed for 16 hours of wear (subjects are instructed to remove the patch at bedtime). Wearing the patch overnight appears to have a clinical advantage in the relief of morning craving but may be more likely to induce sleep disturbances—though distinguishing between sleep disturbances related to nocturnal nicotine intake and those related to insufficient nicotine dosing is not always clear. In a clinical trial comparing the NicoDerm CQ patch (21 mg/24 hours) to the Nicotrol patch (15 mg/16 hours), it was found that the 21-mg/24-hour patch yielded consistently better control of craving, not only during the morning hours, but also throughout the day and over the 2-week period of abstinence.[36] Additionally, the 21-mg/24-hour patch yielded greater reductions in anxiety, irritability, and restlessness. Smokers using the 21-mg/24-hour dosing regimen also experienced longer abstinence than those using the 15-mg/16-hour patch. For smokers with persisting insomnia and other sleep-related adverse events (particularly vivid dreams), the patches should be removed before bedtime.

The main advantage of nicotine patches over acute NRT formulations is that compliance is simple: the patient simply places the patch on the body in the morning, rather than actively using a product throughout the day. For this reason, compliance with patch therapy tends to be higher than for other NRT products.[37] Transdermal patches deliver nicotine more slowly than acute NRT formulations, although nicotine plasma concentrations can become higher during the day with patch use than with acute NRT use, especially if the patient does not use the acute NRT product as many times during the day as recommended.[22,38]

Importantly, nicotine patches may not adequately protect against acute craving provoked by smoking-related stimuli for all smokers. For example, in a laboratory study, Tiffany, et al. showed that, even though a nicotine patch reduced background craving compared with placebo, smokers on active patch experienced similar boosts of craving when exposed to a provocative stimulus.[39] For people who experience powerful breakthrough cravings that are not adequately controlled by transdermal nicotine alone, acute therapies may be combined as discussed in the Clinical Practice Guideline and elsewhere.[11,30,31]

Acute Dosing Forms

Acute-dosing products have the benefit that both the amount and timing of doses can be titrated by the user. Thus, smokers with more nicotine tolerance or greater need can get a higher nicotine dose, and smokers who are experiencing acute adverse effects can scale back their intake. Control over the timing of self-dosing is also key, because it enables smokers to use NRT medications as "rescue medication" when they encounter particularly strong cravings or threats to abstinence. This form of use requires some explanation. Abstinence from tobacco causes some tonic disruptions of function, including rises in overall levels of craving. This background level of craving is punctuated, however, by acute episodes of more intense craving.[40] These episodes of "breakthrough craving" are typically provoked by situational stimuli, such as seeing someone smoke, the ringing of the telephone, or experiencing emotional upset.[41] Notably, nicotine patches do not provide the means to immediately respond to breakthrough crav-

ings.[39] These acute craving episodes are particularly problematic for some cigarette smokers and are associated with very high risk of relapse.[41] Thus, an important application of acute NRT products is for use as rescue medications to quickly reduce cravings when such episodes threaten abstinence. They may also be used when the cigarette smoker is going into a situation expected to produce a craving, such as a demanding meeting, rush-hour traffic, commute, or social situation with cigarette smokers.

A common therapeutic mistake by patients is to only use acute products in response to cravings. It is critical for most people to use the products regularly throughout the day, according to the labeling for each (eg, every 1 to 2 hours for gum and nasal spray) to reduce overall cravings and prevent withdrawal symptoms from building. Whereas labeling places limits on the number of doses per day the smoker should use, underdosing is clearly a more common problem. Indeed, underdosing is the single greatest clinical challenge for successful use of these products.

Gum

The first NRT that was made available to consumers was transmucosal-delivered nicotine polacrilex (nicotine gum), which has been available since the early 1980s in Europe and 1984 in the United States. In many countries, including the United States, nicotine gum is available without a prescription, which has made the products much more widely available to consumers.[42,43] Mint-, orange-, and fruit-flavored gums have been marketed in an effort to increase compliance with use instructions among patients who found the original (peppery) flavor to be unpalatable. A new Fresh-Mint flavor has recently been introduced that is sweeter and softer than previous formulations. The gum is available in two doses: 2 mg and 4 mg, delivering approximately 1 mg and 2 mg, respectively.[44] Users are instructed to use a piece of gum every 1 to 2 hours for the first 6 weeks, then to reduce use to one piece every 2 to 4 hours for 3 weeks, and one piece every 4 to 8 hours for 3 weeks. Smokers who need an extra piece between doses may use one to respond to episodes of acute craving. Smokers who use less than 25 cigarettes per day are instructed to use the 2-mg dose, and those who smoke more are instructed to use the 4-mg dose. In highly dependent smokers, the 4-mg is superior to the 2-mg gum.[45,46]

About 50% of the nicotine in gum is absorbed through the buccal mucosa.[44] Thus, when gum is chewed on a fixed schedule of 10 pieces per day, a smoker receives about 10 mg or 20 mg of nicotine per day using the 2-mg or 4-mg gum formulations, respectively. Data suggest that daily consumption of gum is typically far lower than 10 pieces per day.[47] Thus, most gum chewers do not match daily the nicotine levels achieved through the smoking of cigarettes. Furthermore, because of the relatively slow absorption of nicotine from gum compared with smoke inhalation, individual doses do not produce the extremely high arterial levels of nicotine produced by smoke inhalation.[48] Acidic beverages have been shown to interfere with buccal absorption of nicotine;[49] therefore, patients should avoid acidic beverages (eg, soda, coffee, beer) for 15 minutes before and during chewing gum.

Shiffman, et al.[50] demonstrated that nicotine gum could reduce acute craving following exposure to a provocative stimulus. Some initial reductions in craving are likely due to the behavioral effects of chewing gum.[51] However, after about 15 to 20 minutes of chewing, the nicotine itself reduces craving, and nicotine gum significantly reduced craving, compared with placebo gum.

Chewing nicotine gum may cause jaw soreness, which may be reduced by using the "chew-and-park" method of chewing, whereby the smoker chews the gum to release nicotine, then moves the gum between the cheek and gum for a minute or so. Gum use can also cause a mild burning sensation in the mouth and throat which some people find undesirable and others find useful in craving relief.

Lozenge

A 1-mg lozenge has been available in some European countries for some time; however, no efficacy data are available, and the efficacy of

this low dose is in question. A newer nicotine lozenge, available in 2- and 4-mg formulations since 2002, is the most recent NRT to receive approval in the United States for smoking cessation.[52] Unlike nicotine gum in which the smoker chooses the dose based on number of cigarettes, the indication for the lozenge allocates smokers to the 2- or 4-mg dose based on how soon after waking the first cigarette of the day is smoked. Time to first cigarette is considered a simple but powerful index of nicotine dependence[18] and thus potentially a useful way of determining each smoker's nicotine "need." Both in the United States and United Kingdom, this method results in the majority of smokers being directed to the 4-mg dose.

Like nicotine gum, nicotine from the lozenge is absorbed slowly through the buccal mucosa and delivered into systemic circulation. The lozenge should not be chewed and this is considered a benefit by some patients and a weakness by others who enjoying gum chewing. The amount of nicotine absorbed per lozenge is somewhat higher than that delivered by gum. Single dose studies demonstrated 8% to 10% higher C_{max} values and 25% to 27% higher $AUC_{0-\infty}$ values from lozenges compared with gums at both 2- and 4-mg dose levels, which is probably due to the residual nicotine retained in the gum.[53]

Inhaler

The nicotine vapor inhaler is currently marketed as a prescription medication in the United States. The inhaler consists of a mouthpiece and a plastic cartridge containing nicotine. When the inhaler is "puffed," nicotine is drawn through the mouthpiece into the mouth of the smoker. The vapor inhaler was designed to satisfy behavioral aspects of smoking, namely, the hand-to-mouth ritual. For some smokers, this may be a useful adjunct.

Each inhaler cartridge contains 10 mg nicotine, of which 4 mg can be delivered and 2 mg are absorbed.[54] The product is not a true inhaler in that nicotine is not delivered to the bronchi or lungs, but rather deposited and absorbed in the mouth, much like nicotine gum.[55] The majority of nicotine is delivered into the oral cavity (36%) and in the esophagus and stomach (36%),[55] with very little nicotine reaching the lung (4%).

Nicotine delivery is primarily related to the number of inhalations. Labeling states that 80 deep puffs of the inhaler delivers 4 mg of nicotine. Depth of inhalation does not appear to be a major determinant of dosing.[56] The amount of nicotine absorbed from the inhaler is temperature-dependent, with higher ambient air temperatures delivering larger amounts of nicotine and lower temperatures delivering smaller amounts.[56] Thus, physicians should inform patients that using the product in very cold temperatures may prevent them from receiving adequate amounts of nicotine.

According to the package insert, most successful patients in the clinical trials used between 6 and 16 cartridges a day, and the best effect was achieved by frequent bouts of continuous puffing over 20 minutes. The recommended duration of treatment is 3 months, after which patients may be weaned by gradual reduction of the daily dose over the following 6 to 12 weeks. Some patients find the active use requirement too demanding to sustain adequate nicotine levels, whereas for other patients, the frequent puffing and sensory stimuli are an important benefit that helps them manage tobacco cravings.

Nasal Spray

Nicotine nasal spay is marketed as a prescription smoking cessation medication in the United States and most other countries. The nasal spray was designed to deliver doses of nicotine to the smoker more rapidly than other NRTs. The device is a multidose bottle with a pump that delivers 0.5 mg of nicotine per 50-μL squirt. Each dose consists of two squirts, one to each nostril.

Nicotine nasal spray is absorbed into the blood rapidly relative to all other NRT forms.[57] Venous plasma concentrations after a single 1-mg dose range between 5 and 12 ng/mL. Time to peak plasma concentration (T_{max}) with nasal administration is around 11 to 13 minutes for 1-mg doses. This rise time is slower

than for cigarette delivery but faster than the other nicotine treatments.

According to labeling, the dose of nasal spray should be individualized for each patient based on the patient's level of nicotine dependence and the occurrence of symptoms of nicotine excess. Patients should be started with 1 or 2 doses per hour, which may be increased up to the maximum of 40 doses per day.

Being the NRT form with the most rapid delivery, nasal spray should be able to deliver acute craving relief. A study by Hurt, et al. suggests that a 1-mg dose of nicotine nasal spray can relieve spontaneous nicotine withdrawal symptoms, including craving, more rapidly than a single dose of 4-mg nicotine gum.[58]

The nasal spray may cause some nasal irritation, but this effect dissipates with repeated use for most patients.

Sublingual Tablet

A small nicotine tablet has been developed and is currently being marketed in many European countries but is not yet available in the United States. The product is designed to be held under the tongue, where the nicotine in the tablet is absorbed sublingually. The levels of nicotine obtained by use of the 2-mg tablet and 2-mg nicotine gum are similar.[59] Patients who use less than 20 cigarettes per day are instructed to use one tablet every hour, and they may increase to two tablets every hour if one does not relieve cravings. Smokers who use 20 or more cigarettes per day are instructed to use two tablets every hour, not to exceed 40 tablets per day. It is recommended that smokers use the product for at least 12 weeks. After 12 weeks, the number of tablets used should be gradually tapered.

Improving NRT

Increasing the Dose

In typical use, none of the current NRT formulations achieves nicotine levels like those seen during typical smoking, leading to the idea that higher doses may be needed. An early patch efficacy study demonstrated a dose–response curve for nicotine patch, with increased efficacy for a 21-mg dose over a 14-mg dose.[60] The tolerability of doses as high as 63 mg has been demonstrated.[61] Several higher-dose patch regimens have been evaluated, typically in heavy smokers, who are presumed to most need higher dosing.[22] Results have been mixed. Tonnesen, et al. demonstrated a modest benefit of increasing the dose of 16-hour patches from 15 mg to 25 mg.[62] Jorenby, et al. found a substantial increase in efficacy for 44-mg patches vs. 22-mg patches, but only under conditions of minimal contact.[63] However, Hughes, et al. found no incremental benefit of increasing dose from 21 mg to 42 mg.[64] Taken together, these results suggest that higher doses of nicotine patch may provide at best modest improvements in treatment outcomes for highly dependent individuals.

Increasing the Delivery Speed

We have noted that an advantage of acute dosing forms is their potential as rescue medications when smokers face threats to abstinence. Although a study of nicotine gum demonstrated the principle,[50] it also suggested that the effect was relatively slow: nicotine effects were evident in 15 to 20 minutes, whereas acute cravings can lead to relapse in 10 minutes or less.[65] This suggests the need for faster delivery and faster onset of craving relief. A rapid-release gum has been formulated to provide biphasic nicotine delivery, starting with accelerated delivery to promote rapid craving relief and then leveling off to avoid overdosing.[66] In a proof-of-principle study, Niaura, et al. compared this rapid-release gum to the current gum formulation for rapid craving relief following a provocative stimulus.[67] The rapid-release gum achieved faster and more complete craving relief, differentiating itself from current nicotine gum within the first 3 minutes of use. The use of such a product to provide rapid craving relief when a rescue medication is needed could forestall relapse and thus enhance clinical efficacy. This new technology for rapid nicotine delivery via the transmucosal route merits further study in cessation efficacy trials.

There is a vast difference in the pharmacokinetic profiles of cigarettes and currently available nicotine medications. Even nicotine nasal spray, which produces measurable differences in venous blood nicotine levels faster than oral NRT formulations, does not produce the venous levels of cigarettes. Even more importantly, none of the currently available formulations produces spikes in arterial blood mimicking the blood levels that actually enter the brain. Henningfield, et al. demonstrated that the arterial levels achieved by smoking are much higher than levels seen in venous blood, and the nicotine may reach the brain even faster after smoking than after intravenous dosing.[68] The pulmonary route is an efficient method of delivering drugs to the body because of the large surface area of the pulmonary alveoli. Such higher levels undoubtedly contribute to the addictiveness of cigarette smoke delivered nicotine.

A true pulmonary inhaler, unlike the currently available nicotine inhaler (which actually delivers nicotine into the mouth for buccal absorption), would deliver nicotine to the lung in a manner more comparable to cigarette smoking. This mode of delivery would be expected to reduce background cravings and withdrawal symptoms, and allow for rapid relief of acute cravings. In theory, because the delivery of nicotine directly to the lung would more effectively mimic the effects of cigarette smoking on a physiologic level, the smoker could more readily eliminate the need for tobacco and subsequently taper the nicotine level over time to alleviate dependence on nicotine altogether.

Technical challenges are not small as the nicotine molecules need to be appropriately condensed onto particles of approximately 1-micron median diameter to enable inhalation into the pulmonary alveoli, and the nicotine particles must be designed so as to prevent the production of unacceptably harsh sensory effects.

Combination Products

One strategy for further improving the efficacy of medications is to combine one medication that allows for passive nicotine delivery (eg, transdermal patch) with another medication that permits acute ad libitum nicotine delivery (eg, gum, nasal spray, inhaler).[30] The rationale for combining NRT medications is that smokers may need both a slow delivery system to achieve a constant concentration of nicotine to relieve cravings and tobacco withdrawal symptoms, as well as a faster acting preparation to function as rescue medication for immediate relief of breakthrough cravings.[30] Thus combining the nicotine patch (which may prevent the appearance of severe withdrawal) with acute dosing forms (which can provide relief in trigger-to-smoke contexts) may provide an excellent treatment option over either therapy alone.

Clinical trials suggest incremental efficacy of patch plus gum compared with either product alone.[69–71] Less research is available on combinations of the patch and other acute NRT formulations, but several studies suggest that combinations with other acute dosing forms also provide a clinical benefit, as would be expected.[72] The fact that adding an acute dosing form to patch regimens yields substantial incremental benefit, whereas adding another patch (above) yields less benefit, suggests that the mechanism is not simply an increase in nicotine dose, but the combination of steady-state dosing and acute dosing to provide for use as rescue medication. Bupropion in combination with nicotine patch appears to be more efficacious than nicotine patch alone,[73] possibly because the two medications act via different pharmacological mechanisms.

Despite the possibility of increased efficacy concluded in the Clinical Practice Guideline,[11] present NRT labeling warns against combination use. Without removal of such warnings, these strategies will be largely limited to smoking cessation specialists and clinics. The complexity of obtaining approval for combination medications, combined with the difficulty of marketing combination products, has slowed attempts by manufacturers to gain regulatory approval for combination therapies.[30]

Use of Pharmacotherapies as Part of a Harm Reduction Strategy

The general goal at the core of tobacco control is to reduce the risks associated with

tobacco and has been deemed tobacco harm reduction (THR).[74] Shiffman, et al. have described nine potential uses of NRT products to facilitate THR.[74] Three of these approaches will be discussed below: relapse prevention, nicotine maintenance, and smoking reduction. A cautionary note is that these are not FDA-approved uses of nicotine replacement medications, and the true health benefits of these strategies have not been established. Thus, clinicians should be wary of recommending these strategies. However, clinicians should be aware of these strategies to be able to answer questions from their patients if asked.

It has been suggested that NRT could be used to reduce rates of relapse after smoking cessation. Relapse prevention using NRT could take place immediately after the recommended treatment period (in labeling or by prescription) or to prevent progression to relapse after an initial lapse. There is substantial continuing lapse risk after the typical NRT treatment period of 3 months (United States) or 6 months (Europe). Some smokers may need prolonged use of pharmacotherapy to manage craving and prevent relapse. For example, one study found that smokers treated with the nicotine patch and the antidepressant nortriptyline were much more likely to maintain abstinence at 1-year postcessation if nortriptyline was continued through the 1-year period than if it was discontinued after the 8-week initial treatment period.[75] In a study of bupropion, 1-year use after the initial cessation period was also shown to prevent relapse compared with those who received placebo after the initial cessation period,[76] suggesting the clinical potential of prolonged pharmacotherapy. With regard to preventing progression to relapse after an initial lapse, data show compellingly that after even a single limited reexposure to smoking (lapse), the probability of complete relapse is very high.[77–79] If NRT could impede this progression, it could have significant clinical benefit. Current labeling seems to imply that users should stop NRT if they start smoking, which would curtail this potential benefit. Shiffman and Scharf[80] showed that continued treatment with high-dose patch had a substantial and significant effect in lowering the risk of progression to relapse. Thus, use of NRT after a lapse to prevent progression may be an effective relapse-prevention strategy.

The goal of smoking cessation treatments with NRT is to enable smokers to cease their use of tobacco and subsequently to withdraw them from nicotine as well. However, some smokers may have developed such a strong need for nicotine over their many years of smoking that it may be difficult for them to withdraw from smoking completely. In those instances, it has been suggested that some smokers could benefit by continuing to use NRT for longer periods of time, even indefinitely, to prevent relapse to smoking.[74,81] This strategy is currently used in methadone maintenance programs for heroin-dependent patients, where patients may be maintained on daily doses of methadone for years. Although nicotine is not entirely without risk, nicotine maintenance is clearly safer than cigarette smoke-delivered nicotine with its myriad of toxins, and continuing nicotine to prevent resumption of smoking may be considered for some individuals.[82]

Nicotine is the main pharmacological driver of tobacco use. Tobacco-related death and disease is a consequence of exposure to toxins in tobacco smoke and therefore may be considered a side effect of nicotine-seeking. The mainstays of attempts to control tobacco-related death and disease have been prevention of smoking initiation and stimulation of cessation by current smokers. With the realization that many smokers are unable or unwilling to quit, some focus has shifted to exploration of strategies to reduce the harm of smoking.[83] One proposed strategy for reducing harm is to promote reduced smoking to reduce exposure to tobacco toxins because there is a dose–response relationship between smoke intake and overall disease risk.[84] Many studies[83,85,86] have shown that smokers tend to resist reductions in nicotine intake and respond to reduced smoking by extracting more nicotine from each cigarette—in the process also exposing themselves to more tar and toxins from other tobacco constituents. NRT medications could potentially be used to facilitate harm reduction

by helping the smoker to achieve real decreases in toxic exposure by replacing some of the nicotine normally obtained by smoking. Fagerstrom and Hughes[87] reviewed and conducted a meta-analysis of 11 studies that provided data on blood nicotine concentrations, carbon monoxide in exhaled air, and number of cigarettes smoked during periods of concurrent use of cigarette and NRT products. With simultaneous use of smoking and acute NRT products (gum and inhaler) the nicotine concentrations were unchanged, whereas they increased (+54%) when smoking occurred in combination with nicotine patches. With both types of NRT products, the number of cigarettes smoked per day was reduced by approximately 50% and carbon monoxide was reduced by 30%. Where smokers had the intention or received instructions to reduce smoking, a greater reduction in cigarettes smoked and exhaled carbon monoxide was observed. Despite substantially increased nicotine concentrations (eg, up to 3 times the highest approved doses or 63 mg per day) there were no serious adverse reactions from any combination.

BUPROPION

Bupropion (Zyban) is a smoking cessation aid that was originally marketed as an antidepressant (Wellbutrin). Bupropion is chemically unrelated to tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). The mechanism of action is unknown; however, it is presumed that the action is mediated by noradrenergic and/or dopaminergic mechanisms. Clinically, it is possible that bupropion acts by alleviating some of the symptoms of nicotine withdrawal, which includes depression. One clinical trial demonstrated that highly nicotine-dependent smokers who receive bupropion are more likely to experience a decrease in depressive symptoms during active treatment.[88]

Animal studies demonstrate that bupropion alters the reinforcing and withdrawal effects of nicotine. One study found that low doses of bupropion reduced the rewarding effects of nicotine and the affective and somatic symptoms of withdrawal.[89] Another study examined the effects of bupropion (5 to 40 mg/kg) on the reinforcing properties of nicotine and food in rats under two different schedules of reinforcement.[90] The authors found that pretreatment with the highest dose of bupropion (40 mg/kg) resulted in a 50% reduction of nicotine intake in rats self-administering 0.03 mg/kg/infusion of nicotine under a fixed-ratio (FR) schedule. However, pretreatment with bupropion did not affect the self-administration of nicotine under a progressive-ratio (PR) schedule. These findings are challenging to interpret but may indicate that a high dose of bupropion decreases the reinforcing properties of nicotine under conditions where doses can be obtained at regular and relatively short intervals, while leaving intact the motivation to work for nicotine when doses are more widely spaced. It has also been shown that acute[91] and chronic[92] administration of bupropion increase extracellular levels of nicotine in the nucleus accumbens, a pathway that has been hypothesized to play a key role in nicotine addiction. Taken together, these results suggest that bupropion has several actions demonstrated in animals that could explain its ability to increase rates of cessation in humans.

Like NRT products, bupropion has been endorsed by the US Clinical Practice Guideline[11] as a first-line therapy. Bupropion has been shown to approximately double rates of cessation compared with placebo, and the medication is equally effective for men and women.[93] In a 2-week study, 300 mg of bupropion significantly reduced abstinence-associated increases in rated depression, difficulty concentrating, and irritability, and attenuated a decrease in positive effect, relative to placebo.[94] The results also suggested that bupropion might have a positive effect on performance measures during the withdrawal period. No effects were observed on craving, anxiety, restlessness, or hunger. It has also been shown that bupropion combined with nicotine replacement medications may increase cessation rates relative to bupropion alone.[73] The recommended and maximum dose of bupropion is 300 mg/day, given as 150 mg twice daily. Dry mouth and insomnia are the most common adverse events associated with use. There is a very small risk of seizure, which can be reduced by not prescribing

the medication to persons with a history of seizure or a predisposition toward seizure.

OTHER MEDICATIONS

Besides NRT products and bupropion, two medications (nortriptyline and clonidine) are endorsed by the US Clinical Practice Guideline[11] as second-line therapies, and additional medications are under development. Other medications have been reported in the literature, but cannot be generally recommended.[95] This section will discuss nortriptyline and clonidine, as well as three products in development: rimonabant, varenicline, and nicotine vaccines.

Nortriptyline

In addition to bupropion, several other antidepressants have been tested for efficacy in smoking cessation.[95-97] Of these, the tricyclic antidepressants appear to be the most promising. Nortriptyline has been listed by the Agency for Health Research Quality as a second-line therapy.[11] Several clinical trials have demonstrated the potential efficacy of nortriptyline for smoking cessation in smokers without history of major depression[98] or with such history.[99] Nortriptyline in combination with transdermal nicotine was also shown to enhance the cessation rates above levels seen with transdermal nicotine alone.[100] The tricyclic antidepressant doxepin has also been shown in a small human study to improve cessation rates;[101] however, larger studies are clearly needed to verify these findings. Other studies have shown that doxepin significantly reduces postcessation tobacco withdrawal symptoms and cigarette craving.[102,103] The most commonly encountered side effects associated with nortriptyline include fast heart rate, blurred vision, urinary retention, dry mouth, constipation, weight gain or loss, and low blood pressure on standing.

Clonidine

Clonidine is an alpha-2-noradrenergic agonist used in the treatment of hypertension. Clonidine has been shown to diminish symptoms of both opiate and alcohol withdrawal symptoms.[104,105] On the other hand, the Agency for Health Research Quality has given clonidine a B-level of evidence, indicating that there is some evidence of efficacy.[11] For example, one study of heavy smokers who had failed in previous quit attempts found that those treated with clonidine had twice the rate of abstinence as those treated with placebo at the end of the 4-week treatment.[106] This effect continued through the 6-month follow up. These results suggest that clonidine may be efficacious in the treatment of tobacco dependence, but the conditions under which it is most appropriately used are not well defined. The most common side effects of clonidine are constipation, dizziness, drowsiness, dryness of mouth, and unusual tiredness or weakness. However, there are more severe side effects that could potentially occur that clinicians and patients should be aware of, such as allergic reaction, decreased heart rate, or unusually elevated or decreased blood pressure, as well as contraindications and drug interactions that should be evaluated before prescription.

Rimonabant

The cannabinoid receptor system plays a role in the regulation of appetitive behavior (eg, food and water consumption, drug self-administration). For example, one study found that cannabinoid receptor agonists stimulate food consumption in animals and humans.[107] Further, the cannabinoid receptor system appears to at least partially mediate central nervous system effects of nicotine in rodents. For example, in an extensive evaluation of its motivational effects, rimonabant decreased nicotine self-administration even though it was not functioning as a "substitute" with respect to physiological and other behavioral effects.[108] The results suggest that activation of the cannabinoid receptor system may participate in the motivational and dopamine-releasing effects of nicotine.

STRATUS-US is the first of three studies of rimonabant for smoking cessation to be completed and the findings of this study were pre-

sented at the 2004 American College of Cardiology annual meeting.[109] The study found that the medication was efficacious for smoking cessation. Also, consistent with the role of cannabinoid receptors in the regulation of appetitive behavior was the finding that smokers who quit in the rimonabant group gained less weight than those that quit in the placebo group. The most common side effects where incidence was higher with rimonabant 20 mg than placebo were nausea and upper respiratory tract infection. No cardiovascular safety concerns were identified with rimonabant.

It also appears that rimonabant is efficacious for weight control independently of its use in smoking cessation. Smokers who quit smoking tend to gain weight and the average weight gain has been reported to be as much as 13 pounds after 1 year of continuous abstinence.[110] Further, many smokers report weight gain to be one of the factors associated with relapse.[111] Thus a medication that reduces the weight gain associated with cessation may decrease the likelihood of relapse during a quit attempt.

Varenicline

A partial agonist is a compound that, even at high doses, does not produce the same intensity of response as a full agonist. Varenicline is a partial agonist of nicotinic receptors. Because there is a ceiling on the effects of a partial agonist, it is plausible that varenicline would have an even lower risk of nicotine-related side effects than nicotine containing medications. A variety of nicotinic acetylcholine receptor subtypes have been identified with distinct structural and functional properties. The subtype that has generally been identified as being associated with the addictive (reinforcing) effects of nicotine is the alpha-4 beta-2. It is plausible that a compound that binds with a high degree of specificity, or with a greater affinity, to this subtype relative to nicotine itself, will have a higher level of safety, and possibly a higher level of efficacy. However, to the extent that other subtypes might be associated with reinforcing effects, the efficacy could be muted compared with nicotine, which is less specific in its receptor binding.

Varenicline selectively binds to the alpha-4 beta-2 (nicotinic) receptor type. Phase II clinical trials of varenicline suggest that the medication is efficacious for smoking cessation.[112] This trial also demonstrated few adverse events associated with the medication and no serious adverse events. Whereas the full range of potential benefits and risks of varenicline have not been fully evaluated in clinical trials and practice, such approaches to treating tobacco dependence and withdrawal are promising and may allow patients who are refractory to current medications to improve their success in achieving and sustaining abstinence from tobacco.

Nicotine Vaccines

There are at least three companies in early clinical development of an antinicotine vaccine: Xenova (TA-NIC), Nabi (NicVAX), and Cytos (Nicotine-Qbeta).[113] Results of Phase I studies of TA-NIC and NicVAX reported as conference abstracts suggest that these vaccines are safe, well tolerated, and immunogenic.[114] Cytos has successfully completed a Phase I study with 40 healthy nonsmoking volunteers. So far, results of a Phase I trial by Cytos have shown no unexpected toxicities and Phase II trials have started in Switzerland (Cytos).[113] Preliminary results of the Phase II study indicate that the strength of the immunological response to the vaccine varies among individuals. Among individuals with antibody responses in the highest tertile, continuous abstinence rates were significantly higher and cigarette consumption was significantly lower than among subjects who received a placebo vaccine. Abstinence rates and cigarette consumption among subjects with antibody responses in the middle or lower tertiles were not significantly different from the placebo group.[115]

A vaccine against nicotine induces antibodies against the nicotine molecule that prevents the drug from reaching neural receptors that produce the effects normally associated with smoking. For example, in one study[116] rats received either active or placebo vaccine, and

30 minutes later received intravenous nicotine at 0.03 mg/kg, equivalent on a milligram/kilogram basis to the nicotine intake from two cigarettes by a smoker. Compared with control, the active vaccine reduced the brain nicotine concentration in a dose-related manner (65% reduction at the highest dose of vaccine). Pretreatment with active vaccine also reduced the distribution to brain of 5 repeated doses of nicotine (equivalent to the nicotine intake from 10 cigarettes) administered over 80 minutes. Because vaccines reduce the amount of nicotine that reaches the brain and neural receptors, it would be predicted that the reinforcing effects of nicotine would be reduced substantially. For example, one study found that immunization with a nicotine vaccine prevented the nicotine-induced increase in dopamine release in the shell of the nucleus accumbens, a biochemical correlate to the rewarding properties of nicotine.[117] Another study found that exposure to nicotine after a period of extinction did not reinstate self-administration of nicotine among immunized rats, suggesting a muted reinforcing effect of nicotine.[118]

Taken together, these results suggest that immunization using a nicotine vaccine could be used for smoking cessation. In theory, by eliminating the nicotine that reaches the brain, one would reduce the reinforcing efficacy of tobacco smoking, eventually leading to extinction of the behavior (smoking). However, because the amount of nicotine that reaches the brain is reduced rather than completely eliminated, it is possible that some smokers would actually increase tobacco consumption, at least in the short term, to achieve the levels of nicotine normally obtained during smoking. Results also suggest that a nicotine vaccine would be useful as a relapse prevention treatment. The animal study[118] that found that nicotine did not reinstate self-administration of nicotine after extinction suggests that among people who quit smoking, a lapse (a single smoking bout) may not result in a full-blown relapse because of the reduced reinforcing value of smoking due to the reduced amount of nicotine that reaches the brain. Finally, although nicotine vaccines could theoretically be used in adolescents to prevent initiation of tobacco use, the risks, benefits, and ethical implications of such an intervention will undoubtedly require much more thorough evaluation before such application could be recommended.[119]

IMPROVING THE PUBLIC HEALTH IMPACT OF PHARMACOTHERAPIES

In addition to individual patient benefits, the treatment of tobacco dependence is lauded by the US Public Health Service, the World Health Organization, and many other organizations as a critical component to improving public health in the United States and throughout the world.[11,13,120] This is because, despite the fact that the majority of persons who achieve tobacco abstinence on any given quit attempt will resume smoking, treatment generally doubles the odds of lasting cessation relative to self-quitting or so-called cold turkey.[11] Furthermore, repeated treatment enables more people to achieve lasting abstinence over time. Thus, treatment of tobacco dependence can contribute powerfully to improved public health. This is important for clinicians to understand because they may become as frustrated with their patients at times by the fact that remission from smoking will so often be short-lived.

To further improve the public health benefits of tobacco dependence treatment, there are several barriers that have yet to be addressed. These include underutilization of the full range of treatment options as well as failure to treat long enough and flexibly enough to meet the needs of individuals. Health professionals may need to work with many of their patients just as they would in trying to find the best medication to control hypertension or depression: trying alternative medications and suggesting behavioral strategies in search of a combination that is acceptable and effective for each patient.

Ideally, smokers who would like to quit could be offered a "menu" of treatment options and a medication could be selected that would best suit the needs of an individual smoker. The available options already allow

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smokers some level of flexibility. For smokers with trouble complying with acute NRT products, for example, transdermal nicotine and bupropion are options. For smokers who require the ability to respond to acute cravings but who are unable to chew gum, the nicotine lozenge offers a viable option. For those who need something to do with their hands while quitting, the inhaler offers some of the behavioral elements involved in smoking. For those who require rapid delivery of nicotine, the nasal spray may be the best choice. Bupropion is available for those smokers who wish to give up nicotine altogether and all at once. Recent research in pharmacogenetics explores how genetic variation in drug-metabolizing enzymes and drug targets modifies response to pharmacotherapy.[121] These discoveries could someday help practitioners to further individualize the type, dosage, and duration of tobacco-dependence treatment based on genotype, and maximize the efficacy.

The over the-counter (OTC) availability of nicotine gum, lozenge, and several patches potentially increases the options of patients, but many will need guidance from their health professional to find the treatment and therapeutic regimen that is best for them. Increasing the availability of these medications has been shown to impact the number of smokers who try to quit smoking, as well as the number who succeed. For example, one study examined the impact of switching nicotine patch and nicotine gum from prescription-only status to OTC in the United States.[43] The authors compared the number of quit attempts using nicotine replacement therapy products, the number of smokers who quit smoking with OTC NRT or with NRT still sold by prescription, and incremental quits attributable to OTC NRT. The authors found that in the year after the FDA approved nicotine medications for OTC sale, use of the medications increased by 152% compared with prior prescription use. With increased use of an efficacious treatment, OTC nicotine medications are estimated to yield from 114,000 to 304,000 new former smokers annually in the United States. Despite this increase in availability, however, less than one in five smokers making a quit attempt do so with the benefit of NRT.[122]

The cost of smoking cessation medications is often perceived as being too high for many smokers who want to quit. In reality, however, they are not much more expensive than cigarettes when being used, and in the long run, save individual and health care providers enormously by enabling smoking cessation.[14,123] Thus, clinicians should make an effort to explain to smokers who want to quit that the costs are not much higher than if they continued to smoke, that the costs of medication would only be a burden for the duration of therapy, and that any incremental, short-term costs would be greatly outweighed by the costs of continued smoking. For example, a person who smokes a pack of cigarettes per day would smoke 36 cartons of cigarettes per year. At $30 per carton, this would amount to more than $1,000 a year. Furthermore, the costs of tobacco use will continue to rise as states continue to increase tobacco taxes to pay for the cost imposed by tobacco-caused disease and lost productivity.[14] Nonetheless, reducing economic costs and administrative barriers to obtaining tobacco dependence treatment also have potential to increase treatment utilization and subsequent benefits.[124] Reducing costs to patients is increasingly plausible following several strategies, including reducing the daily cost of the medication itself, decreasing the size of packaging, and by encouraging insurance carriers, health maintenance organizations, and government-sponsored health care plans (eg, Medicare, Medicaid) to provide coverage for smokers on purchasing these medications. Indeed, coverage for smoking cessation by managed care organizations has been shown to be cost-effective.[125]

CONCLUSIONS AND RECOMMENDATIONS

Until 1991, nicotine gum was the only FDA-approved pharmacotherapy for the treatment of tobacco dependence to aid smoking cessation, and it was available by prescription only in the 2-mg dose and in one flavor. Today, nicotine gum, patches, and lozenges are available OTC in two doses and several flavor variations. Additional nicotine replacement

medications and bupropion are available by prescription, as are several second-line medications. More medications are in development and health professionals can expect the pipeline of effective pharmacotherapies and strategies to continue for many years to come. This situation appears analogous to the pipeline of antibiotic development over the mid to late 20th century, which greatly expanded the range of types of disease and individual needs that could be addressed, even though any given medication was not the generally effective and tolerable "answer" for all infections.

The increasing diversity of medication types and applications increases the importance of health professionals becoming familiar with them to be better able to address the questions and needs of tobacco users who appear to be increasingly interested in smoking cessation. This includes being familiar with the OTC medications, which are not necessarily any less effective than prescription medications and may be the best choices for some individuals. How to choose and how to use will become increasingly more challenging for individuals as the public health goals of expanded access and options are achieved.

Furthermore, health professionals can contribute powerfully to the motivation of their patients to attempt and sustain cessation by offering encouragement, advice, and assistance according to the structured guidance of the US Clinical Practice Guidelines.[11] For patients who are not yet ready to make a quit attempt, such advice can move them further toward that point.[11] Showing a willingness to help and being able to provide assistance can be very important in giving cigarette smokers the motivation and confidence that can be important in quitting, as well as the reassurance that a knowledgeable health professional stands ready to offer guidance and support. This can be rewarding for health professionals, lifesaving for their patients, and an important contribution to the health of the community and nation. Understanding the benefits and limitations of the available medications provides an important foundation for such a contribution to individual and public health.

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