CHAPTER 1
Smoking Cessation

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Overview

Tobacco use is a public health issue of enormous importance, and smoking is the primary risk factor for the development of lung cancer. Considerable knowledge has been gained with respect to biobehavioral factors leading to smoking initiation and development of nicotine dependence. Smoking cessation provides extensive health benefits for everyone. State-of-the-art treatment for smoking cessation includes behavioral counseling in conjunction with one or more FDA-approved pharmaceutical aids for cessation. The US Public Health Service *Clinical Practice Guideline for Treating Tobacco Use and Dependence* advocates a five-step approach to smoking cessation (Ask about tobacco use, Advise patients to quit, Assess readiness to quit, Assist with quitting, and Arrange follow-up). Health care providers are encouraged to provide at least brief interventions at each encounter with a patient who uses tobacco.

Introduction

More than two decades ago, the former US Surgeon General C. Everett Koop stated that cigarette smoking is the "chief, single, avoidable cause of death in our society and the most important public health issue of our time" [1]. This statement remains true today. In the United States, cigarette smoking is the primary known cause of preventable deaths [2], resulting in nearly 440,000 deaths each year [3]. The economic implications are enormous: more than $75 billion in medical expenses and over $81 billion in loss of productivity as a result of premature death are attributed to smoking each year [4–8]. While the public often associates tobacco use with elevated cancer risk, the negative health consequences are much broader. The 2004 Surgeon General's Report on the health consequences of smoking [9] provides compelling evidence of the adverse impact of smoking and concluded that smoking harms nearly every organ in the body (Table 1.1). In 2000, 8.6 million persons in the United States were living with an estimated 12.7 million smoking-attributable medical conditions [10]. There is convincing evidence that stopping smoking is associated with immediate as well as long-term health benefits, including reduced cumulative risk for cancer. This is true even in older individuals, and in patients who have been diagnosed with cancer [11].

Smoking and lung cancer

In the United States, approximately 85% of all lung cancers are in people who smoke or who have smoked [3]. Lung cancer is fatal for most patients. The estimated number of deaths of lung cancer will exceed 1.3 million annually early in the third millennium [12]. Lung cancer is the leading cause of cancer-related deaths among Americans of both genders, with 174,470 estimated newly diagnosed cases and 162,460 deaths [13,14]. The number of deaths due to lung cancer exceeds the

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Table 1.1 Health consequences of smoking.

Cancer	Acute myeloid leukemia
	Bladder
	Cervical
	Esophageal
	Gastric
	Kidney
	Laryngeal
	Lung
	Oral cavity and pharyngeal
	Pancreatic
Cardiovascular diseases	Abdominal aortic aneurysm
	Coronary heart disease (angina pectoris, ischemic heart disease, myocardial infarction, sudden death)
	Cerebrovascular disease (transient ischemic attacks, stroke)
	Peripheral arterial disease
Pulmonary diseases	Acute respiratory illnesses
	Pneumonia
	Chronic respiratory illnesses
	Chronic obstructive pulmonary disease
	Respiratory symptoms (cough, phlegm, wheezing, dyspnea)
	Poor asthma control
	Reduced lung function in infants exposed (in utero) to maternal smoking
Reproductive effects	Reduced fertility in women
	Pregnancy and pregnancy outcomes
	Premature rupture of membranes
	Placenta previa
	Placental abruption
	Preterm delivery
	Low infant birth weight
	Infant mortality (sudden infant death syndrome)
Other effects	Cataract
	Osteoporosis (reduced bone density in postmenopausal women, increased risk of hip fracture)
	Periodontitis
	Peptic ulcer disease (in patients who are infected with *Helicobacter pylori*)
	Surgical outcomes
	Poor wound healing
	Respiratory complications

Source: Reference [9].

annual number of deaths from breast, colon, and prostate cancer combined [15]. Recent advances in technology have enabled earlier diagnoses, and advances in surgery, radiation therapy, imaging, and chemotherapy have produced improved responses rates. However, despite these efforts, overall survival has not been appreciably affected in 30 years, and only 12–15% of patients with lung cancer are being cured with current treatment approaches [16]. The prognosis of lung cancer depends largely on early detection and immediate, premetastasis stage treatment [17]. Prevention of lung cancer is the most desirable and cost-efficient approach to eradicating this deadly condition. Numerous epidemiologic studies consistently define smoking as the major risk factor for lung cancer (e.g. [18–20]). The causal role of cigarette smoking in lung cancer mortality has been irrefutably established in longitudinal studies, one of which lasted as long as 50 years [21]. Tobacco smoke, which is inhaled either directly or as second-hand smoke, contains an estimated 4000 chemical compounds, including over 60 substances that are known to cause cancer [22]. Tobacco irritants and carcinogens damage the cells in the lungs, and over time the damaged cells may become cancerous. Cigarette smokers have lower levels of lung function than nonsmokers [9,23], and quitting smoking greatly reduces cumulative risk for developing lung cancer [24].

The association of smoking with the development of lung cancer is the most thoroughly documented causal relationship in biomedical history [25]. The link was first observed in the early 1950s through the research of Sir Richard Doll, whose pioneering research has, perhaps more so than any other epidemiologist of his time, altered the landscape of disease prevention and consequently saved millions of lives worldwide. In two landmark US Surgeon Generals' reports published within a 20-year interval (in 1964 [26] and in 2004 [9]), literature syntheses further documented the strong link between smoking and cancer. Compared to never smokers, smokers have a 20-fold risk of developing lung cancer, and more than 87% of lung cancers are attributable to smoking [27]. The risk for developing lung cancer increases with younger age at initiation of smoking, greater number of cigarettes smoked, and greater number of years smoked [11]. Women smoking the

same amount as men experience twice the risk of developing lung cancer [28,29].

Second-hand smoke and lung cancer

While active smoking has been shown to be the main preventable cause of lung cancer, second-hand smoke contains the same carcinogens that are inhaled by smokers [30]. Consequently, there has been a concern since release of the 1986 US Surgeon General's report [31] concluding that second-hand smoke causes cancer among nonsmokers and smokers. Although estimates vary by exposure location (e.g., workplace, car, home), the 2000 National Household Interview Survey estimates that a quarter of the US population is exposed to second-hand smoke [32]. Second-hand smoke is the third leading cause of preventable deaths in the United States [33], and it has been estimated that exposure to second-hand smoke kills more than 3000 adult nonsmokers from lung cancer [34]. According to Glantz and colleagues, for every eight smokers who die from a smoking-attributable illness, one additional nonsmoker dies because of second-hand smoke exposure [35].

Since 1986, numerous additional studies have been conducted and summarized in the 2006 US Surgeon General's report on "*The Health Consequences of Involuntary Exposure of Tobacco Smoke*." The report's conclusions based on this additional evidence are consistent with the previous reports: exposure to second-hand smoke increases risk of lung cancer. More than 50 epidemiologic studies of nonsmokers' cigarette smoke exposure at the household and/or in the workplace showed an increased risk of lung cancer associated with second-hand smoke exposure [34]. This means that 20 years after second-hand smoke was first established as a cause of lung cancer in lifetime nonsmokers, the evidence supporting smoking cessation and reduction of second-hand smoke exposure continues to mount. Eliminating second-hand smoke exposure at home, in the workplaces, and other public places appears to be essential for reducing the risk of lung cancer development among nonsmokers.

Smoking among lung cancer patients

Tobacco use among patients with cancer is a serious health problem with significant implications for morbidity and mortality [36–39]. Evidence indicates that continued smoking after a diagnosis with cancer has substantial adverse effects on treatment effectiveness [40], overall survival [41], risk of second primary malignancy [42], and increases the rate and severity of treatment-related complications such as pulmonary and circulatory problems, infections, impaired would healing, mucositis, and Xerostomia [43,44].

Despite the strong evidence for the role of smoking in the development of cancer, many cancer patients continue to smoke. Specifically, about one third of cancer patients who smoked prior to their diagnoses continue to smoke [45] and among patients received surgical treatment of stage I nonsmall cell lung cancer [46] found only 40% who were abstinent 2 years after surgery. Davison and Duffy [47] reported that 48% of former smokers had resumed regular smoking after surgical treatment of lung cancer. Therefore, among patients with smoking-related malignancies, the likelihood of a positive smoking history at and after diagnosis is high.

Patients who are diagnosed with lung cancer may face tremendous challenges and motivation to quit after a cancer diagnosis can be influenced by a range of psychological variables. Schnoll and colleagues [48] reported that continued smoking among patients with head and neck and lung cancer is associated with lesser readiness to quit, having relatives who smoke at home, greater time between diagnoses and assessment, greater nicotine dependence, lower self-efficacy, lower risk perception, fewer perceived pros and greater cons to quitting, more fatalistic beliefs, and higher emotional distress. Lung cancer patients should be advised to quit smoking, but once they are diagnosed, some might feel that there is nothing to be gained from quitting [49]. Smoking cessation should be a matter of special concern throughout cancer diagnosis, treatment, and the survival continuum, and the diagnosis of cancer should be used as a "teachable moment" to encourage smoking cessation among patients, family members, and significant others [37]. The

Table 1.2 Percentage of current cigarette smokers[a] aged ≥18 years, by selected characteristics—National Health Interview Survey, United States, 2005.

Characteristic	Category	Men ($n = 13,762$)	Women ($n = 17,666$)	Total ($n = 31,428$)
Race/ethnicity[b]	White, non-Hispanic	24.0	20.0	21.9
	Black, non-Hispanic	26.7	17.3	21.5
	Hispanic	21.1	11.1	16.2
	American Indian/Alaska Native	37.5	26.8	32.0
	Asian[c]	20.6	6.1	13.3
Education[d]	0–12 years (no diploma)	29.5	21.9	25.5
	GED[e] (diploma)	47.5	38.8	43.2
	High school graduate	28.8	20.7	24.6
	Associate degree	26.1	17.1	20.9
	Some college (no degree)	26.2	19.5	22.5
	Undergraduate degree	11.9	9.6	10.7
	Graduate degree	6.9	7.4	7.1
Age group (yrs)	18–24	28.0	20.7	24.4
	25–44	26.8	21.4	24.1
	45–64	25.2	18.8	21.9
	≥65	8.9	8.3	8.6
Poverty level[f]	At or above	23.7	17.6	20.6
	Below	34.3	26.9	29.9
	Unknown	21.2	16.1	18.4
Total		23.9	18.1	20.9

[a]Persons who reported having smoked at least 100 cigarettes during their lifetime and at the time of the interview reported smoking every day or some days; excludes 296 respondents whose smoking status was unknown.
[b]Excludes 314 respondents of unknown or multiple racial/ethnic categories or whose racial/ethnic category was unknown.
[c]Excludes Native Hawaiians or other Pacific Islanders.
[d]Persons aged ≥25 years, excluding 339 persons with unknown level of education.
[e]General Educational Development.
[f]Calculated on the basis of US Census Bureau 2004 poverty thresholds.
Source: Reference [7].

medical, psychosocial, and general health benefits of smoking cessation for cancer patients provide a clear rationale for intervention.

Forms of tobacco

Smoked tobacco

Cigarettes have been the most widely used form of tobacco in the United States for several decades [51], yet in recent years, cigarette smoking has been declining steadily among most population subgroups. In 2005, just over half of ever smokers reported being former smokers [3]. However, a considerable proportion of the population continues to smoke. In 2005, an estimated 45.1 million adult Americans (20.9%) were current smokers; of these, 80.8% reported to smoking every day, and 19.2% reported smoking some days [7]. The prevalence of smoking varies considerably across populations (Table 1.2), with a greater proportion of men (23.9%) than women (18.1%) reporting current smoking. Persons of Asian or Hispanic origin exhibit the lowest prevalence of smoking (13.3 and 16.2%, respectively), and American Indian/Alaska natives exhibit the highest prevalence (32.0%). Also, the prevalence of smoking among adults varies widely across the United States, ranging from 11.5% in Utah to

28.7% in Kentucky [51]. Twenty-three percent of high school students report current smoking, and among boys, 13.6% report current use of smokeless tobacco, and 19.2% currently smoke cigars [52]. These figures are of particular concern, because nearly 90% of smokers begin smoking before the age of 18 years [53].

Other common forms of burned tobacco in the United States include cigars, pipe tobacco, and bidis. Cigars represent a roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco [54]. Cigars' popularity has somewhat increased over the past decade [55]. The latter phenomenon is likely to be explained by a certain proportion of smokers switching cigarettes for cigars and by adolescents' experimentation with cigars [56]. In 1998, approximately 5% of adults had smoked at least one cigar in the past month [57]. The nicotine content of cigars sold in the United States ranged from 5.9 to 335.2 mg per cigar [58] while cigarettes have a narrow range of total nicotine content, between 7.2 and 13.4 mg per cigarette [59]. Therefore, one large cigar, which could contain as much tobacco as an entire pack of cigarettes is able to deliver enough nicotine to establish and maintain physical dependence [59].

Pipe smoking has been declining steadily over the past 50 years [60]. It is a form of tobacco use seen among less than 1% of Americans [60]. Bidi smoking is a more recent phenomenon in the United States. Bidis are hand-rolled brown cigarettes imported mostly from Southeast Asian countries. Bidis are wrapped in a *tendu* or *temburni* leaf [61]. Visually, they somewhat resemble marijuana joints, which might make them attractive to certain groups of the populations. Bidis are available in multiple flavors (e.g., chocolate, vanilla, cinnamon, strawberry, cherry, mango, etc.), which might make them particularly attractive to younger smokers. A survey of nearly 64,000 people in 15 states in the United States revealed that young people (18–24 years of age) reported higher rates of ever (16.5%) and current (1.4%) use of bidis then among older adults (ages 25 plus years). With respect to sociodemographic characteristics, the use of bidis is most common among males, African Americans, and concomitant cigarette smokers [62]. Although featuring less tobacco than standard cigarettes, bidis expose their smokers to considerable amounts of hazardous compounds. A smoking machine-based investigation found that bidis deliver three times the amount of carbon monoxide and nicotine and almost five times the amount of tar found in conventional cigarettes [63].

Smokeless tobacco

Smokeless tobacco products, also commonly called "spit tobacco," are placed in the mouth to allow absorption of nicotine through the buccal mucosa. Spit tobacco includes chewing tobacco and snuff. Chewing tobacco, which is typically available in loose leaf, plug, and twist formulations, is chewed or parked in the cheek or lower lip. Snuff, commonly available as loose particles or sachets (resembling tea bags), has a much finer consistency and is generally held in the mouth and not chewed. Most snuff products in the United States are classified as moist snuff. The users park a "pinch" (small amount) of snuff between the cheek and gum (also known as dipping) for 30 minutes or longer. Dry snuff is typically sniffed or inhaled through the nostrils; it is used less commonly [64].

In 2004, an estimated 3.0% of Americans 12 years of age and older had used spit tobacco in the past month. Men used it at higher rates (5.8%) than women (0.3%) [60]. The prevalence of spit tobacco is the highest among 18- to 25-year-olds and is substantially higher among American Indians, Alaska natives, residents of the southern states, and rural residents [61,66]. The consumption of chewing tobacco has been declining since the mid-1980s; conversely, in 2005, snuff consumption increased by approximately 2% over the previous year [66], possibly because tobacco users are consuming snuff instead of cigarettes in locations and situations where smoking is banned.

Factors explaining tobacco use

Smoking initiation

In the United States, smoking initiation typically occurs during adolescence. About 90% of adult smokers have tried their first cigarette by 18 years

of age and 70% of daily smokers have become regular smokers by that age [67,68]. Because most adolescents who smoke at least monthly continue to smoke into adulthood, youth-oriented tobacco preventions and cessation strategies are warranted [67,68]. Since the mid-1990s, by 2004, the past-month prevalence had decreased by 56% in 8th graders, 47% in 10th graders, and 32% in 12th graders [69]. In recent years, however, this downward trend has decelerated [69]. The downward trend is unlikely to be sustained without steady and systematic efforts by health care providers in preventing initiation of tobacco use and assisting young smokers in quitting.

A wide range of sociodemographic, behavioral, personal, and environmental factors have been examined as potential predictors of tobacco experimentation and initiation of regular tobacco use among adolescents. For example, it has been suggested that the prevalence of adolescent smoking is related inversely to parental socioeconomic status and adolescent academic performance [68]. Other identified predictors of adolescent smoking include social influence and normative beliefs, negative affect, outcome expectations associated with smoking, resistance skills (self-efficacy), engaging in other risk-taking behaviors, exposure to smoking in movies, and having friends who smoke [70–75].

Although numerous studies have been successful in identifying predictors of smoking initiation, few studies have identified successful methods for promoting cessation among youth, despite the finding that in 2005, more than half of high school cigarette smokers have tried to quit smoking in the past year and failed [52]. These results confirm the highly addictive nature of tobacco emphasizing the need for more effective methods for facilitating cessation among the young.

Nicotine addiction

Nicotine has come to be regarded as a highly addictive substance. Judging by the current diagnostic criteria, tobacco dependence appears to be quite prevalent among cigarette smokers; more than 90% of smokers meet the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for nicotine dependence [76]. Research has shown that nicotine acts on the brain to produce a number of effects [77,78] and immediately after exposure, nicotine induces a wide range of central nervous system, cardiovascular, and metabolic effects. Nicotine stimulates the release of neurotransmitters, inducing pharmacologic effects, such as pleasure and reward (dopamine), arousal (acetylcholine, norepinephrine), cognitive enhancement (acetylcholine), appetite suppression (norepinephrine), learning and memory enhancement (glutamate), mood modulation and appetite suppression (serotonin), and reduction of anxiety and tension (β-endorphin and GABA) [78]. Upon entering the brain, a bolus of nicotine activates the dopamine reward pathway, a network of nervous tissue in the brain that elicits feelings of pleasure and stimulates the release of dopamine.

Although withdrawal symptoms are not the only consequence of abstinence, most cigarette smokers do experience craving and withdrawal on cessation [79], and, therefore, relapse is common [80]. The calming effect of nicotine reported by many users is usually associated with a decline in withdrawal effects rather than direct effects on nicotine [53]. This rapid dose-response, along with the short half-life of nicotine ($t^1/_2 = 2$ h), underlies tobacco users' frequent, repeated administration, thereby perpetuating tobacco use and dependence. Tobacco users become proficient in titrating their nicotine levels throughout the day to avoid withdrawal symptoms, to maintain pleasure and arousal, and to modulate mood. Withdrawal symptoms include depression, insomnia, irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, increased appetite/weight gain, and decreased heart rate [81,82].

The assumption that heavy daily use (i.e., 15–30 cigarettes per day), is necessary for dependence to develop is derived from observations of "chippers," adult smokers who have not developed dependence despite smoking up to five cigarettes per day for many years [83,84]. Chippers do not tend to differ from other smokers in their absorption and metabolism of nicotine, causing some investigators to suggest that this level of consumption may be too low to cause nicotine dependence. However, these atypical smokers are usually eliminated from most

studies, which are routinely limited to smokers of at least 10 cigarettes per day [83].

Signs of dependence on nicotine have been reported among adolescent smokers, with approximately one fifth of them exhibiting adult-like dependence [85]. Although, lengthy and regular tobacco use has been considered necessary for nicotine dependence to develop [68], recent reports have raised concerns that nicotine dependence symptoms can develop soon after initiation, and that these symptoms might lead to smoking intensification [79,86]. Adolescent smokers, who use tobacco regularly, tend to exhibit high craving for cigarettes and substantial levels of withdrawal symptoms [87].

Genetics of tobacco use and dependence

As early as 1958, Fisher hypothesized that the link between smoking and lung cancer could be explained at least in part by shared genes that predispose individuals to begin smoking as young adults and to develop lung cancer later in adulthood [88]. More recently, tobacco researchers have begun to explore whether genetic factors do in fact contribute toward tobacco use and dependence.

Tobacco use and dependence are hypothesized to result from an interplay of many factors (including pharmacologic, environmental and physiologic) [77]. Some of these factors are shared within families, either environmentally or genetically. Studies of families consistently demonstrate that, compared to family members of nonsmokers, family members of smokers are more likely to be smokers also. However, in addition to shared genetic predispositions, it is important to consider environmental factors that promote tobacco use—siblings within the same family share many of the same environmental influences as well as the same genes. To differentiate the genetic from the environmental influences, epidemiologists use adoption, twin, twins reared apart, and linkage study designs [89].

Key to the adoption studies is the assumption that if a genetic link for tobacco use exists, then tobacco use behaviors (e.g., smoking status, number of years smoked, number of cigarettes smoked per day) will be more similar for persons who are related genetically (i.e., biologically) than for persons who are not related genetically. Hence, one would expect to observe greater similarities between children and their biological parents and siblings than would be observed between children and their adoptive parents or adopted siblings. Indeed, research has demonstrated stronger associations (i.e., higher correlation coefficients) between biologically-related individuals, compared to nonbiologically-related individuals, for the reported number of cigarettes consumed [90]. In recent years, it has become more difficult to conduct adoption studies, because of the reduced number of intranational children available for adoption [91]. Additionally, delayed adoption (i.e., time elapsed between birth and entry into the new family) is common with international adoptions and might lead to an overestimation of genetic effects if early environmental influences are attributed to genetic influences [92].

In twin studies, identical (monozygotic) twins and fraternal (dizygotic) twins are compared. Identical twins share the same genes; fraternal twins, like ordinary siblings, share approximately 50% of their genes. If a genetic link exists for the phenomenon under study, then one would expect to see a greater concordance in identical twins than in fraternal twins. Thus, in the case of tobacco use, one would expect to see a greater proportion of identical twins with the same tobacco use behavior than would be seen with fraternal twins. Statistically, twin studies aim to estimate the percentage of the variance in the behavior that is due to (1) genes (referred to as the "heritability"), (2) shared (within the family) environmental experiences, and (3) nonshared (external from the family) environmental experiences [91]. A number of twin studies of tobacco use have been conducted in recent years. These studies have largely supported a genetic role [91,93]; higher concordance of tobacco use behavior is evident in identical twins than in fraternal twins. The estimated average heritability for smoking is 0.53 (range, 0.28–0.84) [93,94]; approximately half of the variance in smoking appears to be attributable to genetic factors.

Recent advances in the mapping of the human genome have enabled researchers to search for genes associated with specific disorders, including tobacco use. Using a statistical technique called linkage analysis, it is possible to identify genes that predict a trait or disorder. This process is not based on prior knowledge of a gene's function, but rather it is determined by examining whether the trait or disorder is coinherited with markers found in specified chromosomal regions. Typically, these types of investigations involve collection of large family pedigrees, which are studied to determine inheritance of the trait or disorder. This method works well when a single gene is responsible for the outcome; however, it becomes more difficult when multiple genes have an impact, such as with tobacco use. In linkage studies of smoking, it is common for investigators to identify families, ideally with two or more biologically-related relatives that have the trait or disorder under study (referred to as affected individuals, in this case, smokers) and other unaffected relatives. For example, data from affected sibling pairs with parents is a common design in linkage analysis. A tissue sample (typically blood) is taken from each individual, and the sample undergoes genotyping to obtain information about the study participant's unique genetic code. If a gene in a specific region of a chromosome is associated with smoking, and if a genetic marker is linked (i.e., in proximity), then the affected pairs (such as affected sibling pairs) will have increased odds for sharing the same paternal/maternal gene [91].

As genetic research moves forward, new clues provide insight into which genes might be promising "candidates" as contributors to tobacco use and dependence. Currently, there are two general lines of research related to candidate genes for smoking. One examines genes that affect nicotine pharmacodynamics (the way that nicotine affects the body) and the other examines genes that affect nicotine pharmacokinetics (the way that the body affects nicotine). A long list of candidate genes are being examined—some of the most extensively explored involve (a) the dopamine reward pathway (e.g., those related to dopamine synthesis, receptor activation, reuptake, and metabolism) and (b) nicotine metabolism via the cytochrome P450 liver enzymes (specifically, CYP2A6 and CYP2D6).

In summary, each of these types of study designs supports the hypothesis that genetics influence the risk for a wide range of tobacco-related phenotypes, such as ever smoking, age at smoking onset, level of smoking, ability to quit, and the metabolic pathways of nicotine (e.g., see [45,89,95–99]). But given that there are many predictors of tobacco use and dependence, of which genetic predisposition is just one piece of a complex puzzle, it is unlikely that society will move toward widespread genotyping for early identification of individuals who are at risk for tobacco use. Perhaps a more likely use of genetics as related to tobacco use is its potential for improving our treatment for dependence [91]. If genetic research leads to new knowledge regarding the mechanisms underlying the development and maintenance of dependence, it is possible that new, more effective medications might be created. Furthermore, through pharmacogenomics research we might gain improved knowledge as to which patients, based on their genetic profiles, would be best treated with which medications. Researchers are beginning to examine how DNA variants affect health outcome with pharmacologic treatments, with a goal of determining which genetic profiles respond most favorably to specific pharmaceutical aids for cessation (e.g. [98,100–103]).

Benefits of quitting

The reports of the US Surgeon General on the health consequences of smoking, released in 1990 and 2004, summarize abundant and significant health benefits associated with giving up tobacco [9,104]. Benefits noticed shortly after quitting (e.g., within 2 weeks to 3 months), include improvements in pulmonary function and circulation. Within 1–9 months of quitting, the ciliary function of the lung epithelium is restored. Initially, patients might experience increased coughing as the lungs clear excess mucus and tobacco smoke particulates. In several months, smoking cessation results in measurable improvements of lung function. Over time, patients experience decreased coughing, sinus

congestion, fatigue, shortness of breath, and risk for pulmonary infection and 1 year postcessation, the excess risk for coronary heart disease is reduced to half that of continuing smokers. After 5–15 years, the risk for stroke is reduced to a rate similar to that of people who are lifetime nonsmokers, and 10 years after quitting, an individual's chance of dying of lung cancer is approximately half that of continuing smokers. Additionally, the risk of developing mouth, larynx, pharynx, esophagus, bladder, kidney, or pancreatic cancer is decreased. Finally, 15 years after quitting, a risk for coronary heart disease is reduced to a rate similar of that of people who have never smoked. Smoking cessation can also lead to a significant reduction in the cumulative risk for death from lung cancer, for males and females.

Smokers who are able to quit by age 35 can be expected to live an additional 6–9 years compared to those who continue to smoke [105]. Ossip-Klein *et al*. [106] recently named tobacco use a "geriatric health issue." Indeed, a considerable proportion of tobacco users continue to smoke well into their 70s and 80s, despite the widespread knowledge of the tobacco health hazards. Elderly smokers frequently claim that the "damage is done," and it is "too late to quit;" however, a considerable body of evidence refutes these statements. Even individuals who postpone quitting until age 65 can incur up to four additional years of life, compared with those who continued to smoke [24,106]. Therefore, elderly smokers should not be ignored as a potential target for cessation efforts. Health care providers ought to remember that it is never too late to advise their elderly patients to quit and to incur health benefits.

A growing body of evidence indicates that continued smoking after a diagnosis of cancer has substantial adverse effects. For example, these studies indicate that smoking reduces the overall effectiveness of treatment, while causing complications with healing as well as exacerbating treatment side effects, increases risk of developing second primary malignancy, and decreases overall survival rates [36–38,107–109]. On the other hand, the medical, health, and psychosocial benefits of smoking cessation among cancer patients are promising. Gritz *et al*. [37] indicated that stopping smoking prior to diagnosis and treatment can have a positive influence on survival rates. Although many smoking cessation interventions are aimed at primary prevention of cancer, these results indicate that there can be substantial medical benefits for individuals who quit smoking after they are diagnosed with cancer.

Smoking cessation interventions

Effective and timely administration of smoking cessation interventions can significantly reduce the risk of smoking-related disease [110]. Recognizing the complexity of tobacco use is a necessary first step in developing effective interventions and trials for cessation and prevention. The biobehavioral model of nicotine addiction and tobacco-related cancers presents the complex interplay of social, psychological, and biological factors that influence tobacco use and addiction (Figure 1.1). These factors in turn mediate dependence, cessation, and relapse in most individuals, and treatment has been developed to address many of the factors noted in the model [38].

The health care provider's role and responsibility

Health care providers are uniquely positioned to assist patients with quitting, having both access to quitting aids and commanding a level of respect that renders them particularly influential in advising patients on health-related issues. To date, physicians have received the greatest attention in the scientific community as providers of tobacco cessation treatment. Although less attention has been paid to other health care providers such as pharmacists and nurses, they too are in a unique position to serve the public and situated to initiate behavior change among patients or complement the efforts of other providers [64,111].

Fiore and associates conducted a meta-analysis of 29 investigations in which they estimated that compared with smokers who do not receive an intervention from a clinician, patients who receive a tobacco cessation intervention from a physician clinician or a nonphysician clinician are 2.2 and 1.7 times as likely to quit smoking at 5 or more months postcessation, respectively [112]. Although brief advice from a clinician has been shown to

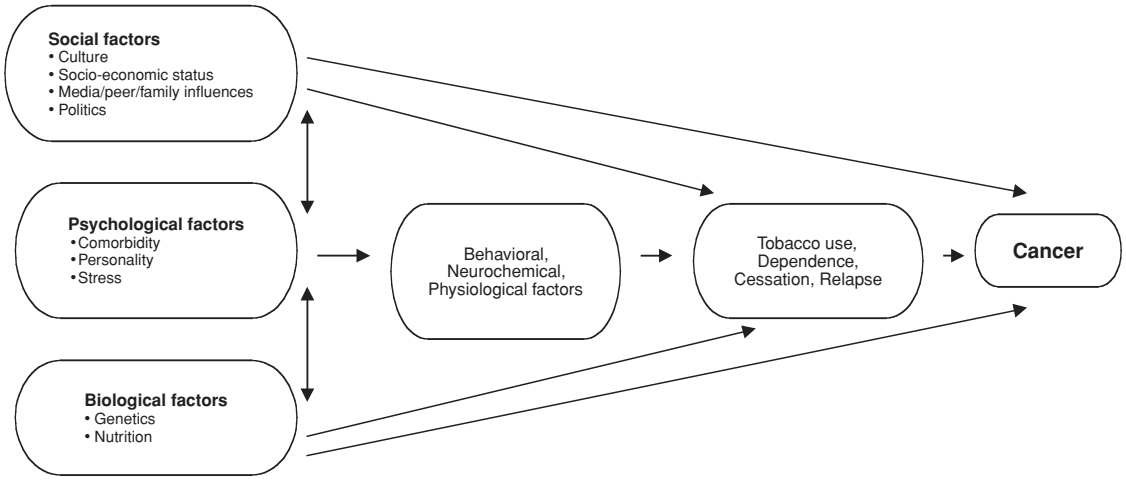

Figure 1.1 Biobehavioral model of nicotine addiction and tobacco-related cancers. (Adapted from [38].)

lead to increased likelihood of quitting, more intensive counseling leads to more dramatic increases in quit rates [112]. Because the use of pharmacotherapy agents approximately doubles the odds of quitting [7,112], smoking cessation interventions should consider combining pharmacotherapy with behavioral counseling.

To assist clinicians and other health care providers in providing cessation treatment, the US Public Health Service has produced a *Clinical Practice Guideline for the Treatment of Tobacco Use and Dependence* [112]. The *Guideline* is based on a systematic review and analysis of scientific literature which yields a series of recommendations and strategies to assist health care providers in delivering smoking cessation treatment. The *Guideline* emphasizes the importance of systematic identification of tobacco users by health care workers and offering at least brief treatment interventions to every patient who uses tobacco. Among the most effective approaches for quitting are behavioral counseling and pharmacotherapy, used alone or, preferably, in combination [112].

Behavioral counseling

Behavioral interventions play an integral role in smoking cessation treatment, either alone or in conjunction with pharmacotherapy. These interventions, which include a variety of methods ranging from self-help materials to individual cognitive–behavioral therapy, enable individuals to more effectively recognize high-risk smoking situations, develop alternative coping strategies, manage stress, improve problem-solving skills, and increase social support [113]. The *Clinical Practice Guideline* outlines a five-step framework that clinicians can apply when assisting patients with quitting. Health care providers should: (a) systematically identify all tobacco users, (b) strongly advise all tobacco users to quit, (c) assess readiness to make a quit attempt, (d) assist patients in quitting, and (e) arrange follow-up contact. The steps have been described as the 5 A's: Ask, Advise, Assess, Assist, and Arrange follow-up (Table 1.3). Due to the possibility of relapse, health care providers should also provide patients with brief relapse prevention treatment. Relapse prevention reinforces the patient's decision to quit, reviews the benefits of quitting, and assists the patient in resolving any problems arising from quitting [112]. The outlined strategy has been termed the 5 R's (Table 1.3): Relevance, Risks, Rewards, Roadblocks, and Repetition. In the absence of time or expertise for providing more comprehensive counseling, clinicians are advised to (at a minimum), ask about tobacco use, advise tobacco users to quit, and refer these patients to other resources for quitting, such as a toll-free tobacco cessation quitline (1-800-QUIT NOW, in the US).

Table 1.3 The 5 A's and 5 R's for smoking cessation interventions.

5 A's	Ask about tobacco use	Identify and document tobacco use status for every patient at every visit
	Advise to quit	Urge every tobacco user to quit in a clear, strong, and personalized manner
	Assess readiness to make a quit attempt	Assess whether or not the tobacco user is ready to make a quit attempt in the next 30 days
	Assist in quit attempt	Use counseling and/or pharmacotherapy with the patient willing to make a quit attempt to help him or her quit
	Arrange follow-up	Schedule follow-up contact, preferably within the first week after the quit date
5 R's	Relevance	Encourage the patient to indicate why quitting is personally relevant, being specific as possible
	Risk	Ask the patient to identify the negative consequences of tobacco use, including acute risks (e.g., short breath), long-term risks (e.g., cancer, and environmental risks, e.g., cancer among family)
	Rewards	Request that the patient identify potential benefits of stopping tobacco use (e.g., improved health)
	Roadblocks	Ask the patient to identify barriers or impediments to quitting and note the elements of treatment that could address such barriers (e.g., withdrawal symptoms, fear of failure, lack of support)
	Repetition	Repeat the motivational intervention every time an unmotivated patient visits the clinic setting

Adapted from [112].

Pharmaceutical aids for smoking cessation

According to the *Clinical Practice Guideline* [112], all patients attempting to quit should be encouraged to use one or more effective pharmacotherapy agents for cessation except in the presence of special circumstances. These recommendations are supported by the results of more than 100 controlled trials demonstrating that patients receiving pharmacotherapy are approximately twice as likely to remain abstinent long-term (greater than 5 mo) when compared to patients receiving placebo (Figure 1.2). Although one would argue that pharmacotherapy is costly and might not be a necessary component of a treatment plan for each patient, it is the most effective known method for maximizing the odds of success for any given quit attempt, particularly when combined with behavioral counseling [112].

Currently, seven marketed agents have an FDA-approved indication for smoking cessation in the US: five nicotine replacement therapy (NRT) formulations (nicotine gum, nicotine lozenge, transdermal nicotine patches, nicotine nasal spray, and nicotine oral inhaler), sustained-release bupropion, and varenicline tartrate. These are described in brief below, and summaries of the prescribing information for each medication are provided in Table 1.4.

Nicotine replacement therapy

In clinical trials, patients who use NRT products are 1.77 times as likely to quit smoking than are those who receive placebo [7]. The main mechanism of action of NRT products is thought to be a stimulation of nicotine receptors in the ventral tegmental area of the brain, which results in dopamine release in the nucleus accumbens. The use of NRT is to reduce the physical withdrawal symptoms and to alleviate the physiologic symptoms of withdrawal, so the smoker can focus on the behavioral and psychological aspects of quitting before fully abstaining nicotine. Key advantages of NRT are that patients are not exposed to the carcinogens and other toxic compounds found in tobacco and tobacco smoke, and NRT provides slower onset of action than nicotine delivered via cigarettes, thereby eliminating the near-immediate reinforcing effects of nicotine obtained through smoking (Figure 1.3). NRT products

Table 1.4 FDA-approved medications for smoking cessation.

	Nicotine replacement therapy (NRT) formulations						Bupropion SR	Varenicline
	Gum	Lozenge	Transdermal preparations[1]		Nasal spray	Oral inhaler		
Product	**Nicorette[2], Generic** OTC 2 mg, 4 mg; original, FreshMint[2], Fruit Chill[2], mint, orange[2]	**Commit[2], Generic** OTC 2 mg, 4 mg mint	**Nicoderm CQ[2]** OTC 24-hour release 7 mg, 14 mg, 21 mg	**Generic Patch** OTC/Rx (formerly Habitrol) 24-hour release 7 mg, 14 m g, 21 mg	**Nicotrol NS[3]** Rx Metered spray 0.5 mg nicotine in 50 μL aqueous nicotine solution	**Nicotrol inhaler[3]** Rx 10 mg cartridge delivers 4 mg inhaled nicotine vapor	**Zyban[2], Generic** Rx 150 mg sustained-release tablet	**Chantix[3]** Rx 0.5 mg, 1 mg tablet
Dosing	*≥25 cigarettes/day*: 4 mg *<25 cigarettes/day*: 2 mg Week 1–6: 1 piece q 1–2 hours Week 7–9: 1 piece q 2–4 hours Week 10–12: 1 piece q 4–8 hours • Maximum, 24 pieces/day • Chew each piece slowly • Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews) • Resume chewing when taste or tingle fades • Repeat chew/park steps until most of the nicotine is gone (taste or tingle does not return; generally 30 min) • Park in different areas of mouth • No food or beverages 15 min before or during use • Duration: up to 12 weeks	*1st cigarette ≤30 minutes after waking*: 4 mg *1st cigarette >30 minutes after waking*: 2 mg Week 1–6: 1 lozenge q 1–2 hours Week 7–9: 1 lozenge q 2–4 hours Week 10–12: 1 lozenge q 4–8 hours • Maximum, 20 lozenges/day • Allow to dissolve slowly (20–30 min) • Nicotine release may cause a warm, tingling sensation • Do not chew or swallow • Occasionally rotate to different areas of the mouth • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks	*>10 cigarettes/day*: 21 mg/day × 6 weeks 14 mg/day × 2 weeks 7 mg/day × 2 weeks *≤10 cigarettes/day:* 14 mg/day × 6 weeks 7 mg/day × 2 weeks • May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime) • Duration: 8–10 weeks	*>10 cigarettes/day:* 21 mg/day × 4 weeks 14 mg/day × 2 weeks 7 mg/day × 2 weeks *≤10 cigarettes/day:* 14 mg/day × 6 weeks 7 mg/day × 2 weeks • May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime) • Duration: 8 weeks	1–2 doses/hour (8–40 doses/day) One dose = 2 sprays (one in **each** nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa • Maximum – 5 doses/hour – 40 doses/day • For best results, initially use at least 8 doses/day • Patients should not sniff, swallow, or inhale through the nose as the spray is being administered • Duration: 3–6 mo	6–16 cartridges/day; individualized dosing • Initially, use at least 6 cartridges/day • Best effects with continuous puffing for 20 minutes • Nicotine in cartridge is depleted after 20 minutes of active puffing • Patient should inhale into back of throat or puff in short breaths • Do not inhale into the lungs (like a cigarette) but "puff" as if lighting a pipe • Open cartridge retains potency for 24 hours • Duration: up to 6 months	150 mg po q AM × 3 days, then increase to 150 mg pobid • Do not exceed 300 mg/day • Treatment should be initiated while patient is still smoking • Set quit date 1–2 weeks **after** initiation of therapy • Allow at least 8 hours between doses • Avoid bedtime dosing to minimize insomnia • Dose tapering is not necessary • Can be used safely with NRT • Duration: 7–12 weeks, with maintenance up to 6 months in selected patients	Days 1–3: 0.5 mg po q AM Days 4 –7: 0.5 mg po bid Weeks 2–12: 1 mg po bid • Patients should begin therapy 1 week prior to quit date • Take dose after eating with a full glass of water • Dose tapering is not necessary • Nausea and insomnia are side effects that are usually temporary • Duration: 12 weeks; an additional 12 week course may be used in selected patients
Adverse effects	• Mouth/jaw soreness • Hiccups • Dyspepsia • Hypersalivation • Effects associated with incorrect chewing technique: – Lightheadedness – Nausea/vomiting – Throat and mouth irritation	• Nausea • Hiccups • Cough • Heartburn • Headache • Flatulence • Insomnia	• Local skin reactions (erythema, pruritus, burning) • Headache • Sleep disturbances (insomnia) or abnormal/vivid dreams (associated with nocturnal nicotine absorption)		• Nasal and/or throat irritation (hot, peppery, or burning sensation) • Rhinitis • Tearing • Sneezing • Cough • Headache	• Mouth and/or throat irritation • Unpleasant taste • Cough • Rhinitis • Dyspepsia • Hiccups • Headache	• Insomnia • Dry mouth • Nervousness/difficulty concentrating • Rash • Constipation • Seizures (risk is 1/1000 [0.1%])	• Nausea • Sleep disturbances (insomnia, abnormal dreams) • Constipation • Flatulence • Vomiting

	Nicotine replacement therapy (NRT) formulations							
	Gum	Lozenge	Transdermal preparations		Nasal spray	Oral inhaler	Bupropion SR	Varenicline
			Nicoderm CQ	Generic Patch				
Advantages	• Gum use might satisfy oral cravings • Gum use may delay weight gain • Patients can titrate therapy to manag e withdrawal symptoms	• Lozenge use might satisfy oral cravings • Patients can titrate therapy to manage withdrawal symptoms	• Provides consistent nicotine levels over 24 hours • Easy to use and conceal • Once-a-day dosing associated with fewer compliance problems		• Patients can titrate therapy to manage withdrawal symptoms	• Patients can titrate therapy to manage withdrawal symptoms • Mimics hand-to-mouth ritual of smoking	• Easy to use; oral formulation might be associated with fewer compliance problems • Can be used with NRT • Might be beneficial in patients with depression	• Easy to use; oral formulation might be associated with fewer compliance problems • Offers a new mechanism of action for patients who have failed other agents
Disadvantages	• Gum chewing may not be socially acceptable • Gum is difficult to use with dentures • Patients must use proper chewing technique to minimize adverse effects	• Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome	• Patients cannot titrate the dose • Allergic reactions to adhesive might occur • Patients with dermatologic conditions should not use the patch		• Nasal/throat irritation may be bothersome • Dependence can result • Patients must wait 5 minutes before driving or operating heavy machinery • Patients with chronic nasal disorders or severe reactive airway disease should not use the spray	• Initial throat or mouth irritation can be bothersome • Cartridges should not be stored in very warm conditions or used in very cold conditions • Patients with underlying bronchospastic disease must use the inhaler with caution	• Seizure risk is increased • Several contraindications and precautions preclude use (see *Precautions*, above)	• May induce nausea in up to one third of patients • Post-marketing surveillance data not yet available
Cost/day[4]	2 mg: $3.28–$6.57 (9 pieces) 4 mg: $4.31–$6.57 (9 pieces)	2 mg: $3.66–$5.26 (9 pieces) 4 mg: $3.66–$5.26 (9 pieces)	$2.24–$3.89 (1 patch)	$1.90–$2.94 (1 patch)	$3.67 (8 doses)	$5.29 (6 cartridges)	$3.62–$6.04 (2 tablets)	$4.00–$4.22 (2 tablets)

From: Rx for Change: [8] Copyright © 1999–2007, with permission.
[1]Transdermal patch formulations previously marketed, but no longer available: Nicotrol 5 mg, 10 mg, 15 mg delivered over 16 hours (Pfizer) and generic patch (formerly Prostep) 11 mg and 22 mg delivered over 24 hours.
[2]Marketed by GlaxoSmithKline.
[3]Marketed by Pfizer.
[4]Average wholesale price from 2006 Drug Topics Redbook. Montvale, NJ: Medical Economics Company, Inc., June 2007.
Abbreaviations : Hx, history; MAO, monoamine oxidase; NRT, nicotine replacement therapy; OTC, (over-the-counter) non-prescription product; Rx, prescription product.
For complete prescribing information, please refer to the manufacturers' package inserts.

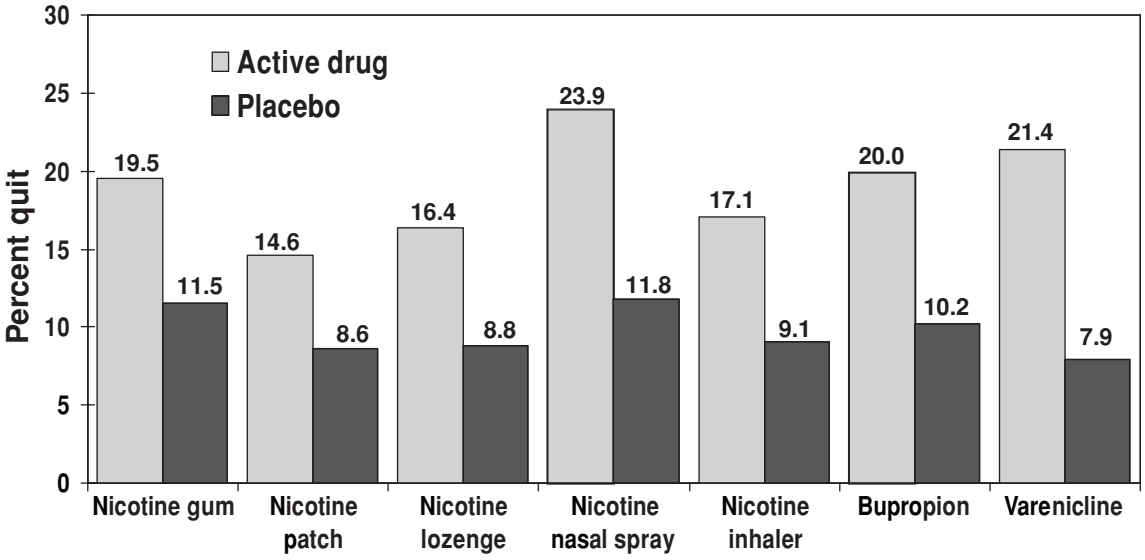

Figure 1.2 Long-term (≥6 mo) quit rates for FDA-approved medications for smoking cessation. (Data adapted from [4–7].) (*From Rx for Change*: [114] Copyright © 1999–2007, with permission.)

should be used with caution in patients who have underlying serious arrhythmias, serious or worsening angina pectoris, or a recent (within 2 weeks) myocardial infarction [112]. Animal data suggest that nicotine is harmful to the developing fetus, and as such prescription formulations of nicotine are classified by the Food and Drug Administration as pregnancy category D agents. Yet despite these concerns, most experts perceive the risks of NRT to be small relative to the risks of continued smoking. Use of NRT may be appropriate in patients with underlying cardiovascular disease or in women who

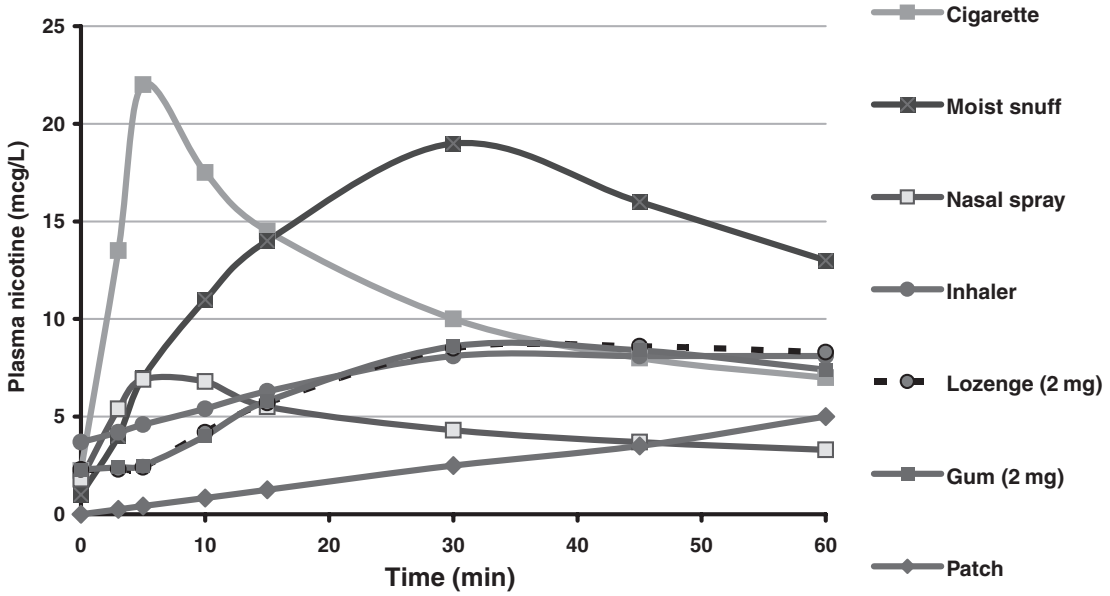

Figure 1.3 Plasma nicotine concentrations for various nicotine-containing products. (*From Rx for Change*: [114];) Copyright © 1999–2007, with permission.)

are pregnant if these patients are under medical supervision [112]. Patients with temporomandibular joint disease should not use the nicotine gum, and patients smoking fewer than 10 cigarettes daily should initiate NRT with caution and generally at reduced dosages [112]. The safety and efficacy of NRT have not been established in adolescents, and currently none of the NRT products are indicated for use in this population [112,115].

Sustained-release bupropion (Zyban)

Initially marketed as an atypical antidepressant, sustained-release bupropion is hypothesized to promote smoking cessation by inhibiting the reuptake of dopamine and norepinephrine in the central nervous system [116] and acting as a nicotinic acetylcholine receptor antagonist [117]. These neurochemical effects are believed to modulate the dopamine reward pathway and reduce the cravings for nicotine and symptoms of withdrawal [112].

Because seizures are a dose-related toxicity associated with bupropion, this medication is contraindicated in patients with underlying seizure disorders and in patients receiving concurrent therapy with other forms of bupropion (Wellbutrin, Wellbutrin SR, and Wellbutrin XL). Bupropion also is contraindicated in patients with anorexia or bulimia nervosa and in patients who are undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines) due to the increased risk for seizures. The concurrent administration of bupropion and a monoamine oxidase (MAO) inhibitor is contraindicated and at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion [118]. Although seizures were not reported in the smoking cessation clinical trials, the incidence of seizures with the sustained-release formulation (Wellbutrin) used in the treatment of depression was 0.1% among patients without a previous history of seizures [119]. For this reason, bupropion should be used with extreme caution in patients with a history of seizure, cranial trauma, patients receiving medications known to lower the seizure threshold, and patients with underlying severe hepatic cirrhosis. Bupropion is classified as a pregnancy category C drug, meaning that either (a) animal studies have demonstrated that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or (b) no studies are available in either animals or women. Correspondingly, the manufacturer recommends that this agent be used during pregnancy only if clearly necessary [118].

Varenicline tartrate (Chantix)

The efficacy of varenicline, a partial agonist selective for the a4b2 nicotinic acetylcholine receptor [120,121), is believed to be the result of sustained, low-level agonist activity at the receptor site combined with competitive inhibition of nicotine binding. The partial agonist activity induces modest receptor stimulation, which leads to increased dopamine levels, thereby attenuating the symptoms of nicotine withdrawal. In addition, by competitively blocking the binding of nicotine to nicotinic acetylcholine receptors in the central nervous system, varenicline inhibits the surges of dopamine release that occur following the inhalation of tobacco smoke. The latter effect might be effective in preventing relapse by reducing the reinforcing and rewarding effects of smoking [120]. The FDA classifies varenicline as a pregnancy category C drug, and the manufacturer recommends that this medication be used during pregnancy only if the potential benefit justifies the potential risk to the fetus [121].

Summary

Tobacco use remains prevalent among the population and represents a matter of special public health concern. It is the primary risk factor for the development of lung cancer. It has been shown to cause malignancies in other locations, as well as numerous other diseases. The body of knowledge of various aspects of smoking behavior has largely increased over the past two decades. Studies of factors predisposing to smoking initiation among youth may provide important clues for the development of feasible and effective smoking prevention activities. The knowledge of biobehavioral factors leading to development of nicotine dependence may assist in providing more effective treatments to patients who use tobacco products. The five A's approach (Ask about tobacco use, Advise patients to quit, Assess readiness to quit, Assist with quitting, and Arrange follow-up) is described in the US Public Health Service

Clinical Practice Guideline for Treating Tobacco Use and Dependence. Health care providers are encouraged to implement at least brief interventions at each encounter with a patient who uses tobacco.

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