CHAPTER 1
Smoking Prevention and Cessation

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Overview

It is well established that tobacco use is a leading cause of disease and death worldwide, and smoking is the primary risk factor for the development of lung cancer [1]. A considerable body of knowledge has been gained with respect to environmental, personal, and behavioral factors leading to smoking initiation and development of tobacco dependence. Two key elements of successful tobacco control are prevention and cessation. According to the 2012 Surgeon General's Report, prevention of tobacco use among adolescents and young adults is a matter of particular importance [2]. The dramatic downward trends in tobacco use rates among youth, observed since the mid-1990s, have stalled; furthermore, the use of smokeless tobacco is increasing among some age groups [2]. A variety of strategies, including policy change and education, have been shown to positively impact tobacco prevention [3]. Cessation of tobacco use provides extensive health benefits for everyone, regardless of age, sex, ethnicity, or health status [4]. Evidence-based 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) [5]. Systematic referral of patients who use tobacco to helpful resources, such as telephone quitlines, is recently emerging as a feasible and promising approach. Health care providers are encouraged to provide at least brief interventions at each encounter with a patient who uses tobacco [5].

Introduction

In 2011, an estimated 19% of adults in the United States were cigarette smokers [6], and in 2012, 17% of high-school seniors smoked at least 1 cigarette in the past 30 days [7]. This is despite the fact that five 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" [8]. Cigarette smoking is associated with nearly 443 000 deaths each year, including more than 49 000 deaths from exposure to secondhand smoke [9]. The economic implications are enormous: more than $75 billion in medical expenses and $81 billion in loss of productivity, as a result of premature death, are attributed to smoking each year [10]. While the public often associates tobacco use with elevated cancer risk, the

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negative health consequences are much broader. The 2004 Surgeon General's Report on the health consequences of smoking provides compelling evidence of the adverse impact of smoking and concluded that smoking harms nearly every organ in the body [11] (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 [12]. 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 among older individuals and among patients who have been diagnosed with cancer [13].

Of key importance, often undermined by health professionals, is the primary prevention of smoking initiation among youth. Indeed, 99% of first use of tobacco occurs by 26 years of age [2]. Thus, nearly all tobacco use starts in childhood or adolescence. Although a substantial decline in tobacco use rates among youth has been observed since the mid-1990s, this favorable trend appears to have stalled in the recent years, especially in smokeless tobacco use [7]. Tobacco use among adolescents is not just a social phenomenon. Rapidly developing physiological dependence on nicotine prevents many adolescents from quitting tobacco products; as such, about 80% of adolescent smokers will smoke into adulthood [2]. Each year, more than 1 million new tobacco users emerge in the United States. In his foreword to the 2012 Surgeon General's report, the Director of the Centers for Disease Control and Prevention, Dr Thomas R. Frieden, indicated that preventing smoking and smokeless tobacco use among young people is crucial to ending the epidemic of tobacco use [2].

Table 1.1 Health consequences of smoking (USDHHS SGR report, 2004)

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 – Pre-term 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: [11].

Tobacco and lung cancer

In the United States, approximately 85% of all lung cancers occur among people who smoke or who have smoked [14]. Lung cancer is fatal for most patients, with the estimated number of deaths of lung cancer projected to exceed 1.3 million annually early in the third millennium [15]. Lung cancer is the leading cause of cancer-related deaths

among both men and women in the USA, with 174 470 estimated newly diagnosed cases and 162 460 deaths each year [16,17]. The number of deaths due to lung cancer exceeds the annual number of deaths from breast, colon, and prostate cancer combined [18]. 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 [19]. The prognosis of lung cancer depends largely on early detection and immediate, premetastatic stage treatment [20]. Prevention of lung cancer is the most desirable [21]. 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 [15]. Tobacco smoke, which is inhaled either directly or as secondhand smoke, contains an estimated 4000 chemical compounds, including 69 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 [23, 24], and quitting smoking greatly reduces cumulative risk for developing lung cancer [25, 26].

The association of smoking with the development of lung cancer is the most thoroughly documented causal relationship in biomedical history [27]. The link was first observed in the early 1950s through the research of Sir Richard Doll [28], 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 40-year interval (in 1964 and in 2004), literature syntheses further documented the strong link between smoking and cancer. Compared to never-smokers, smokers have a 15–30 times elevated risk of developing lung cancer, and more than 90% of lung cancers are attributable to smoking [29]. 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 [30]. Findings are mixed in regards to the susceptibility of developing lung cancer in males or females for a given history of smoking [31].

Secondhand smoke and lung cancer

While active smoking has been shown to be the main preventable cause of lung cancer, secondhand smoke contains the same carcinogens that are inhaled by smokers [22, 32]. Consequently, there has been a concern since the release of the 1986 US Surgeon General's Report, which concluded that secondhand smoke causes cancer among nonsmokers and smokers. Although estimates vary by exposure location (e.g., workplace, home), the 2006 Surgeon General's Report estimates that 60% of children and 40% of nonsmoking adults were exposed to secondhand smoke [33]. Secondhand exposure to tobacco smoke kills more than 3000 adult nonsmokers from lung cancer [33]. According to Glantz and colleagues, for every eight smokers who die from a smoking-attributable illness, one additional nonsmoker dies because of secondhand smoke exposure [34].

Since 1986, numerous additional studies have been conducted and are 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 secondhand 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 secondhand smoke exposure [33]. This means that 20 years after secondhand smoke was first established as a cause of lung cancer in lifetime nonsmokers, the evidence supporting smoking cessation and reduction of secondhand smoke exposure continues to mount. Eliminating secondhand 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 [33].

Smoking among lung cancer patients

Tobacco use among patients with cancer is a serious health problem with significant implications for morbidity and mortality [35]. Evidence indicates that continued smoking after a diagnosis of cancer has substantial adverse effects on treatment effectiveness [36, 37], overall survival [38], risk of second primary malignancy [39, 40], and increases the rate and severity of treatment-related complications such as pulmonary and circulatory problems, infections, impaired wound healing, mucositis, and xerostomia [41].

Despite the strong evidence for the role of smoking in the development of cancer, many cancer patients continue to smoke [42, 43]. Specifically, about one third of cancer patients who smoked prior to their diagnoses continue to smoke, and among patients who received surgical treatment of lung cancer 30% were abstinent at follow-up [44]. It is estimated that more than one half of former smokers resume regular smoking after surgical treatment for lung cancer [45]. Therefore, among patients with smoking-related malignancies, the likelihood of a positive smoking history at and after diagnosis is high [46].

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 [47]. Schnoll and colleagues reported that continued smoking among patients with head, neck, or 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 for 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 [48]. 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 [43].

Forms of tobacco

Smoked tobacco

Cigarettes have been the most widely used form of tobacco in the United States for several decades, yet in recent years, cigarette smoking has been declining steadily among most population subgroups [6]. The number of former US smokers has exceeded the number of current smokers since 2002 [49]. Nineteen percent (43.8 million) of US adults were current cigarette smokers in 2011; of these, 77.8% (34.1 million) smoked every day, and 22.2% (9.7 million) smoked some days [6]. The prevalence of smoking varies considerably across populations (Table 1.2), with a greater proportion of men (21.5%) than women (16.5%) reporting current smoking. Persons of Asian or Hispanic origin exhibited the lowest prevalence of smoking (9.9 and 12.9%, respectively). American Indian/Alaska natives exhibited the highest prevalence (31.5%). Also, the prevalence of smoking among adults varies widely across the regions in the United States, ranging from 15.0% in the West to 21.8% in the Midwest [6]. According to the 2012 Monitoring the Future report, 17% of high school students reported smoking in the past 30 days [7]. Data from the 2011 National Youth Tobacco Survey indicated that among high-school males reported 12.9% used smokeless tobacco and 15.7% smoked cigars. These figures are of particular concern because nearly 90% of smokers begin smoking before the age of 18 years [50].

Other common forms of smoked 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 [51]. Popularity of cigars has somewhat increased over the past decade [50]. The latter phenomenon is likely to be explained by a certain proportion of smokers switching cigarettes for cigars and by adolescents' experimentation with cigars [50]. In 1998, approximately 5% of adults had smoked at least one

Table 1.2 Percentage of persons aged ≥ 18 years who were current cigarette smokers,[a] by selected characteristics – National Health Interview Survey, United States, 2011

Characteristic	Category	Men (n = 14,811)	Women (n = 18,203)	Total (n = 33,014)
Age group (yrs)	18–24	21.3	16.4	18.9
	25–44	24.5	19.7	22.1
	45–64	24.4	18.5	21.4
	≥ 65	8.9	7.1	7.9
Race/ethnicity[b]	White	22.5	18.8	20.6
	Black	24.2	15.5	19.4
	Hispanic	17.0	8.6	12.9
	American Indian/Alaska Native	34.4	29.1	31.5
	Asian[c]	29.7	5.5	9.9
Education[d]	0–12 years (no diploma)	30.5	25.1	25.5
	GED[e]	47.5	45.2	45.3
	High school graduate	27.9	23.8	23.8
	Associate degree	21.4	17.5	19.3
	Some college (no degree)	25.2	20.0	22.3
	Undergraduate degree	9.8	8.7	9.3
	Graduate degree	5.2	4.8	5.0
Poverty level[f]	At or above	20.2	15.6	20.6
	Below	33.6	25.7	29.9
	Unknown	19.4	11.4	18.4
Total		21.6	16.5	19

[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 86 respondents whose smoking status was unknown.
[b]Excludes 61 respondents of unknown race. Unless indicated otherwise, all racial/ethnic groups are non-Hispanic; Hispanics can be of any race.
[c]Excludes Native Hawaiians or Other Pacific Islanders.
[d]Persons aged ≥25 years, excluding 173 persons whose educational level was unknown.
[e]General Educational Development Certificate.
[f]Calculated on the basis of US Census Bureau 2010 poverty thresholds.
Source: [52].

cigar in the past month [53]. The nicotine content of cigars sold in the United States ranges from 5.9 to 335.2 mg per cigar [54], while cigarettes have a narrow range of total nicotine content, between 7.2 and 13.4 mg per cigarette [55]. 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 [56].

Pipe smoking has been declining steadily over the past 50 years [57]. It is a form of tobacco use seen among less than 1% of Americans [57]. Bidi smoking is a more recent phenomenon in the United States. Bidis are hand-rolled brown cigarettes, imported mostly from Southeast Asian countries, that are wrapped in a *tendu* or *temburni* leaf [58]. Visually, they somewhat resemble marijuana joints, which might make them attractive to certain population groups. 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 than 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 [59]. 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 [60].

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. Snus, 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 snus 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. In contrast dry snus, which is typically sniffed or inhaled through the nostrils, is used less commonly [61].

In 2004, an estimated 3.0% of Americans 12 years of age or older had used spit tobacco in the past month, with males using it at higher rates (5.8%) than women (0.3%) [62]. 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 [63]. The consumption of chewing tobacco has been declining since the mid-1980s; conversely, in 2005, snus consumption increased by approximately 5% over the previous year [63], possibly because tobacco users are consuming snus instead of cigarettes in locations and situations where smoking is banned.

While cigarette consumption in the United States continues to decline, promotion for and consumption of smokeless tobacco products is increasing [64]. A recent report indicated that between 2005 and 2011, sales of moist snus products increased by 65.6%. Sales of pouched and flavored forms of moist snus increased by 333.8% and 72.1%, respectively, and contributed to 28% and 59.4% of the total growth in the moist snus category respectively. Increased sales of flavored and discounted snuff raise concerns about use and appeal to youth [64] and warrant strong prevention programs addressing these tobacco products.

Recent developments on the tobacco market

Over the past decade, the tobacco industry has substantially increased its repertoire of potentially harmful products. The industry is broadly advertising new potentially reduced-exposure tobacco products (PREPs). These products are typically marketed as an "alternative to conventional cigarettes," implying that they are likely to cause less harm than traditional forms of tobacco (i.e., cigarettes) or decrease exposure to toxic compounds in the PREPs' smoke. These PREPs include modified-tobacco cigarettes (e.g., Omni, Advance), cigarette-like items (e.g., Accord, Eclipse), and smokeless tobacco products (e.g., Ariva, Exalt) [65].

The oral formulations of tobacco are available as small sachets of flavored tobacco (Camel Snus, Marlboro Snus), lozenges containing compressed low-nitrosamine tobacco powder (Ariva, Stonewall), or a dissolvable of finely grained tobacco with additives (Camel Orbs, Strips, and Sticks) that are often marketed as cigarette substitutes for situations where smoking is prohibited. Smokeless tobacco products reduce exposure to the harmful products associated with combustion, but do not substitute for a smoker's own brand of cigarette. Research has shown that non-combustible PREP use for typical smokers does not offer sufficient nicotine to suppress withdrawal symptoms, and therefore smokers are unlikely to switch from cigarettes [66]. Overall, no sufficient evidence has been obtained regarding these products' harmful effects [67]. It is clear, however, that all these nicotine-containing products possess addition potential. This, in turn, makes them dangerous

with respect to engaging young people in tobacco use and possibly lifelong nicotine dependence.

There is public health concern about smoking tobacco through hookah (aka waterpipe, shisha, narghile, qalyan, etc.). In this smoking device, tobacco smoke passes through water in a special container before it is inhaled. Hookah smoking is becoming rapidly widespread in the United States, especially among young people [68–74]. For example, among college students, hookah smoking rates are second to the frequency of conventional cigarette use [75]. Importantly, many hookah users believe that this type of smoking is safer than cigarettes [76]. Research indicates though that hookah use is no less harmful than cigarette smoke, it may lead to the known tobacco-attributable diseases, and can interfere with successful quitting due to nicotine addiction [77].

Electronic cigarettes (or e-cigarettes) are another rapidly spreading form of unregulated nicotine delivery in the United States. An e-cigarette is a battery-operated device containing nicotine, various flavors, and other chemicals. The e-cigarette appearance resembles that of conventional cigarettes. Once switched on, the e-cigarette turns the chemical compounds into a vapor that is inhaled by the user in a way similar to smoking a regular cigarette. The laboratory analysis has detected toxic compounds such as diethylene glycol (used in antifreeze) and carcinogens (including nitrosamines) [78]. The particular public health concern regarding this type of product is in the appeal to modern youth who are highly interested in technology [79]. Young e-cigarette users are likely to develop nicotine addiction and may switch to conventional cigarettes later in life.

Factors explaining tobacco use

Smoking initiation

In the United States, smoking initiation typically occurs during adolescence. From mid-1990 to 2004, the past-month prevalence had decreased by 56% in 8th graders, 47% in 10th graders, and 32% in 12th graders [80]. In recent years, however, this downward trend has decelerated [80]. 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 [81]. 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 [82–87].

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 [88]. These results confirm the highly addictive nature of tobacco emphasizing the need for more effective methods for facilitating cessation among the young.

Smoking prevention

After decades of research, it became clear that only comprehensive, concerted efforts may lead to successful prevention of tobacco use among youth. Among the major conclusions of the 2012 Surgeon General's report, there is one that states the following: "Coordinated, multicomponent interventions that combine mass media campaigns, price increases including those that result from tax increases, school-based policies and programs, and statewide or community-wide changes in smoke-free policies and norms are effective in reducing the initiation, prevalence, and intensity of smoking among youth and young adults" [2]. Indeed, it "takes a village" to prevent tobacco use successfully,

and healthcare providers represent a key group in this multicomponent system.

There are multiple ways for a healthcare provider to be engaged in smoking prevention among youth. First and foremost, efforts to prevent tobacco use should be applied routinely in the medical practice. Asking about tobacco use, advising to quit or not to start and assisting in adopting a nonsmoking tobacco lifestyle through evidence-based materials and resources should become an indispensable component of patient care. It is essential to work with parents of young children to eliminate all secondhand smoke from the children's environment. A recent study, conducted among a predominantly low-socioeconomic status Mexican-American community, indicated very low knowledge about secondhand smoke exposure and associated health consequences [89]. A series of culturally sensitive, printed materials effectively increased this knowledge and practically eliminated secondhand smoke from the targeted Mexican-American households [89]. In addition to these direct health-enhancing effects, such elimination is likely to help in prevention of smoking initiation among children and adolescents.

Because young people do not seem to respond positively to telephone tobacco quitlines [90], it would be important to consider alternative resources designed specifically for the young audiences. Among them, Internet-based resources should be considered [91]. Healthcare providers need to be familiar with contemporary approaches to helping young patients make the right decisions to avoid initiation of tobacco use. Referral to these resources should be integrated into healthcare practice. Furthermore, as highly respected members of their communities, healthcare providers are positioned to make a difference in tobacco use prevention among youth beyond their medical practices. One possible highly rewarding direction of their activities could be advocating for smoking prevention programs in schools. Despite the criticism of school-based education programs aimed at prevention of tobacco use [92], these programs appear to represent an indispensable part of the systematic, comprehensive approach to reducing tobacco use among youth. It is imperative to realize that children, adolescents, and young adults are special population groups with unique needs and requirements that are often simply unmet or underappreciated.

In his systematic review of school-based programs, Dr Brian Flay, an internationally recognized expert in the area of smoking prevention among youth, outlined several key characteristics of effective school-based programs that were able to produce long-term effects [93]. He concluded that school-based programs can have long-term effects of practical importance if they: (a) include 15 or more educational sessions over multiple years, including sessions in high school; (b) use the social influence model and interactive delivery methods; (c) include components on norms, commitment not to use, intentions not to use, and training and practice in the use of refusal and other life skills; and (d) use peer leaders in some role. Such programs, Dr Flay concludes, are able to reduce smoking onset by 25–30%. A combination of school-based programs with community programs can dramatically reduce smoking onset (by 35–40%) by the time teens graduate from high school.

We would like to add to this analysis that the school-based programs should to be culturally sensitive, to better resonate of the needs with the culturally diverse adolescent populations in the United States. Program developers should be mindful of literacy levels in general, and health literacy in particular, among their target populations. The latter notion is of particular importance due to the fact that youth with the lowest literacy skills tend to be at the highest risk for smoking initiation and lifelong nicotine dependence. Finally, it is critically important to realize that we live in the era of technology. Therefore, using the interactive multimedia programs delivered via Internet, use of social networks (Facebook, Twitter, YouTube, etc.) highly popular among young populations, as well as programs and apps for smart phones, is becoming absolutely essential and standard for making smoking prevention programs attractive, effective, and sustainable. Our own evidence-based bilingual (English and Spanish) smoking prevention and cessation program for youth, called ASPIRE (A Smoking Prevention InteRactive Experience;

www.mdanderson.org/aspire), is based on many of the aforementioned principles [91, 94, 95]. It is currently being disseminated to 29 states in the United States with consistently positive feedback from the participating communities. For example, of the nearly 15 000 student participants, 92% said they learned new tobacco facts, 83% said the program influenced their decision not to use tobacco, 91% said they have a greater understanding of the effects of tobacco, and 77% said they would recommend ASPIRE to a friend/family member.

Nicotine addiction

Nicotine, the addictive component of tobacco, reaches the brain rapidly (within 10–20 seconds) [96] and produces a wide range of pharmacologic effects [97, 98]. 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 (3-endorphin and GABA) [99]. 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.

In the absence of nicotine, the dependent patient experiences symptoms of withdrawal that can range from mild to severe. Although withdrawal symptoms are not the only consequence of abstinence, most quitters do experience withdrawal and cravings upon cessation [100], and relapse is common [101]. In general, most withdrawal symptoms manifest within 1–2 days after quitting, peak within the first week, and subside within 2–4 weeks [100]. The near-immediate calming effect of nicotine reported by many users is usually associated with alleviation of withdrawal effects rather than the direct effects of nicotine. This rapid dose-response, along with the short half-life of nicotine (approximately 2 hours), underlies tobacco users' frequent, repeated administration, thereby perpetuating tobacco use and establishment of 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 can include irritability/frustration/anger, anxiety, difficulty concentrating, restlessness/impatience, depressed mood/depression, insomnia, impaired performance, increased appetite/weight gain, and cravings [100].

Tobacco initiation, use, and dependence are hypothesized to result from an interplay of many factors (including pharmacologic, genetic, social and environmental, and learned/conditioned factors) [98]. 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. Because a myriad of factors contribute to tobacco use and dependence, tobacco control initiatives (e.g., community-based efforts) as well as tobacco cessation counseling services (provided at the individual level) should be multi-faceted [102].

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 [11, 103]. 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 while the lungs clear excess mucus and tobacco smoke particulates. With just a few months, smoking cessation leads to measurable improvements in lung function. Over time, patients experience decreased

coughing, sinus congestion, fatigue, shortness of breath, and risk for pulmonary infection. One year post-cessation, 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.

A growing body of evidence indicates that continued smoking after a cancer diagnosis has substantial adverse effects. Smoking reduces the overall effectiveness of treatment, causing complications with healing, exacerbating treatment side effects, increasing risk of developing second primary malignancy, and decreasing overall quality of life and survival rates. As such, smoking cessation should be considered an essential component of cancer treatment for all types of cancer – including, but not limited to, cancers of the lung [42].

Smoking cessation interventions

Effective and timely administration of smoking cessation interventions can significantly reduce the risk of smoking-related disease. Recognizing the complexity of tobacco use is a necessary first step in developing effective interventions and trials for cessation and prevention.

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, nurses, and respiratory therapists, they too are in a unique position to assist with quitting and are situated to initiate behavior change among patients or complement the efforts of other providers.

A meta-analysis of 29 studies determined 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 post-cessation, respectively [101]. To assist clinicians with providing cessation treatment, the US Public Health Service has published a *Clinical Practice Guideline for the Treatment of Tobacco Use and Dependence* [101]. The *Guideline* is based on a systematic review and analysis of relevant scientific literature, yielding a series of recommendations and strategies to assist clinicians with delivering treatment for tobacco use and dependence. The update emphasizes the importance of identification of tobacco users by health care providers 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 [101]. Effectiveness of the various behavioral and pharmaceutical strategies for cessation is shown in Table 1.3.

Behavioral counseling

Behavioral interventions play an integral role in smoking cessation treatment, either alone or in conjunction with pharmacotherapy [101]. 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. 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

Table 1.3 Efficacy of treatment methods for tobacco use and dependence

Treatment method	Estimated odds ratio[a] (95% CI)	Estimated abstinence[b] rate (95% CI)
Behavioral interventions		
Advice to quit		
No advice to quit	1.0	7.9
Physician advice to quit	1.3 (1.1–1.6)	10.2 (8.5–12.0)
Clinician intervention		
No counseling by a clinician	1.0	10.2
Counseling by a nonphysician	1.7 (1.3–2.1)	15.8 (12.8–18.8)
Counseling by a physician	2.2 (1.5–3.2)	19.9 (13.7–26.2)
Format of smoking cessation counseling		
No format	1.0	10.8
Self-help	1.2 (1.0–1.3)	12.3 (10.9–13.6)
Proactive telephone counseling[c]	1.2 (1.1–1.4)	13.1 (11.4–14.8)
Group counseling	1.3 (1.1–1.6)	13.9 (11.6–16.1)
Individual counseling	1.7 (1.4–2.0)	16.8 (14.7–19.1)
Pharmacotherapy interventions		
Placebo	1.0	13.8
First-line agents		
Bupropion SR	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Nicotine gum (6–14 weeks)	1.5 (1.2–1.7)	19.0 (16.5–21.9)
Nicotine inhaler	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Nicotine lozenge (2 mg)	2.0 (1.4–2.8)	24.2[d]
Nicotine patch (6–14 weeks)	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Nicotine nasal spray	2.3 (1.7–3.0)	26.7 (21.5–32.7)
Varenicline (2 mg/day)	3.1 (2.5–3.8)	33.2 (28.9–37.8)
Second-line agents[e]		
Clonidine	2.1 (1.2–3.7)	25.0 (15.7–37.3)
Nortriptyline	1.8 (1.3–2.6)	22.5 (16.8–29.4)
Combination therapy		
Patch (>14 weeks) + *ad lib* nicotine (gum or nasal spray)	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Nicotine patch + bupropion SR	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Nicotine patch + nortriptyline	2.3 (1.3–4.2)	27.3 (17.2–40.4)
Nicotine patch + nicotine inhaler	2.2 (1.2–3.6)	25.8 (17.4–36.5)

[a]Estimated relative to referent group.

[b]Abstinence percentages for specified treatment method.

[c]A quitline that responds to incoming calls and makes outbound follow-up calls. Following an initial request by the smoker or via a fax-to-quit program, the clinician initiates telephone contact to counsel the patient.

[d]One qualifying randomized trial; 95% CI not reported in 2008 *Clinical Practice Guideline*.

[e]Not approved by the US Food and Drug Administration as a smoking cessation aid; recommended by the USPHS *Guideline* as a second-line agent for treating tobacco use and dependence.

Data from [101].

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. 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. 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 United States).

Tobacco quitlines are telephone services that provide tobacco cessation counseling, generally at no cost, to the caller. Quitlines have proliferated in recent years, providing comprehensive interventions that can reach patients who might otherwise have limited access to medical treatment because of geographic location, financial resources or lack of insurance. In clinical trials, telephone counseling services for which at least some of the contacts are initiated by the quitline counselor have been shown to be effective in promoting abstinence [101, 104], and these results have been shown to translate into real-world effectiveness [105]. The addition of medication to quitline counseling significantly improves abstinence rates compared to medication alone [106]. In some states, clinicians can submit a fax-referral form, on behalf of a patient, to the quitline. This form initiates a process whereby a quitline counselor then contacts the patient directly. Up to 30% success rates have been shown for patients who complete all follow-up sessions. However, most physicians are unfamiliar with quitline services, and clinician referrals are low – yet even the busiest of clinicians can serve an important role by simply asking about tobacco use, advising patients who smoke to quit, and referring patients who are ready to quit to a quitline for more comprehensive counseling (Ask-Advise-Refer) [107].

Clinicians should also attempt to become familiar with local, community-based resources for tobacco cessation, such as group programs that might be offered through local hospitals or clinics. For some patients, an internet-based cessation program might be preferred, such as www.quitnet.com, an online quitting community where quitters can share experiences and support each other in achieving their cessation goals. Patients now have more options for obtaining assistance; clinicians should advise patients to utilize as many services as needed to achieve long-term success.

Our group has recently developed QuitMedKit©, a free iOS app, designed to assist healthcare providers in effective counseling and treatment of tobacco dependence among their patients. This program provides state-of-the-art knowledge on behavioral counseling, pharmacological treatments for nicotine dependence and is based on the *Clinical Practice Guideline*. QuitMedKit© is available in the Apple iTunes store and is compatible with iPhone, iPod touch, and iPad. It requires iOS 4.3 or later and is optimized for iPhone 5.

Pharmaceutical aids for smoking cessation

According to the *Clinical Practice Guideline for Treating Tobacco Use and Dependence* [101], 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 months) when compared to patients receiving placebo (Table 1.3) [101, 108]. Although one could 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 [101].

Currently, seven marketed agents have an FDA-approved indication for smoking cessation in the United States: 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. These are described in brief below, and summaries of the prescribing information for each medication are provided in Table 1.4. For more details, readers are referred to the manufacturer's prescribing information.

Table 1.4 FDA-approved medications for smoking cessation

	Nicotine Replacement Therapy (NRT) Formulations						
	Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler	Bupropion SR	Varenicline
Product	**Nicorette[1], Generic** OTC 2 mg, 4 mg original, cinnamon, fruit, mint, orange	**Nicorette Lozenge,[1] Nicorette Mini Lozenge,[1] Generic** OTC 2 mg, 4 mg cherry, mint	**NicoDerm CQ[1], Generic** OTC (NicoDerm CQ, generic) Rx (generic) 7 mg, 14 mg, 21 mg (24-hour release)	**Nicotrol NS[2]** Rx Metered spray 0.5 mg nicotine in 50 mcL aqueous nicotine solution	**Nicotrol Inhaler[2]** Rx 10 mg cartridge delivers 4 mg inhaled nicotine vapor	**Zyban[1], Generic** Rx 150 mg sustained-release tablet	**Chantix[2]** Rx 0.5 mg, 1 mg tablet
Precautions	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Temporomandibular joint disease • Pregnancy[3] and breastfeeding • Adolescents (<18 years)	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy[3] and breastfeeding • Adolescents (<18 years)	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Pregnancy[3] (Rx formulations, category D) and breastfeeding • Adolescents (<18 years)	• Recent (≤2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis) • Severe reactive airway disease • Pregnancy[3] (category D) and breastfeeding • Adolescents (<18 years)	• Recent (≤ 2 weeks) myocardial infarction • Serious underlying arrhythmias • Serious or worsening angina pectoris • Bronchospastic disease • Pregnancy[3] (category D) and breastfeeding • Adolescents (<18 years)	• Concomitant therapy with medications or medical conditions known to lower the seizure threshold • Severe hepatic cirrhosis • Pregnancy[3] (category C) and breastfeeding • Adolescents (<18 years) **Warning:** • Black-boxed warning for neuropsychiatric symptoms[4] **Contraindications:** • Seizure disorder • Concomitant bupropion (e.g., Wellbutrin) therapy • Current or prior diagnosis of bulimia or anorexia nervosa • Simultaneous abrupt discontinuation of alcohol or sedatives/benzodiazepines • MAO inhibitor therapy in previous 14 days	• Severe renal impairment (dosage adjustment is necessary) • Pregnancy[3] (category C) and breastfeeding • Adolescents (<18 years) **Warnings:** • Black-boxed warning for neuropsychiatric symptoms[4] • Cardiovascular adverse events in patients with existing cardiovascular disease

(*continued*)

Table 1.4 (*Continued*)

	Nicotine Replacement Therapy (NRT) Formulations						
	Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler	Bupropion SR	Varenicline
Dosing	*1st cigarette ≤30 minutes after waking:* 4 mg *1st cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 piece q 1–2 hours Weeks 7–9: 1 piece q 2–4 hours Weeks 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 tingle fades • Repeat chew/park steps until most of the nicotine is gone (tingle does not return; generally 30 min)	*1st cigarette ≤30 minutes after waking:* 4 mg *1st cigarette >30 minutes after waking:* 2 mg Weeks 1–6: 1 lozenge q 1–2 hours Weeks 7–9: 1 lozenge q 2–4 hours Weeks 10–12: 1 lozenge q 4–8 hours • Maximum, 20 lozenges/day • Allow to dissolve slowly (20–30 minutes for standard; 10 minutes for mini) • 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 × 4 weeks (generic) 6 weeks (NicoDerm CQ) 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	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 or – 40 doses/ day • For best results, initially use at least 8 doses/day • Do not sniff, swallow, or inhale through the nose as the spray is being administered • Duration: 3–6 months	6–16 cartridges/day Individualize dosing; initially use 1 cartridge q 1–2 hours • Best effects with continuous puffing for 20 minutes • Initially use at least 6 cartridges/day • Nicotine in cartridge is depleted after 20 minutes of active puffing • 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 • No food or beverages 15 minutes before or during use • Duration: 3–6 months	150 mg po q AM x 3 days, then 150 mg po bid • Do not exceed 300 mg/day • Begin therapy 1–2 weeks prior to quit date • 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 • Begin therapy 1 week prior to quit date; alternatively, the patient can begin therapy and then quit smoking between days 8–35 of treatment • Take dose after eating and with a full glass of water • Dose tapering is not necessary • Dosing adjustment is necessary for patients with severe renal impairment • Duration: 12 weeks; an additional 12-week course may be used in selected patients

	• Park in different areas of mouth • No food or beverages 15 minutes before or during use • Duration: up to 12 weeks						
Adverse Effects	• Mouth/jaw soreness • Hiccups • Dyspepsia • Hypersalivation • Effects associated with incorrect chewing technique: – Lightheaded-ness – Nausea/ vomiting – Throat and mouth irritation	• Nausea • Hiccups • Cough • Heartburn • Headache • Flatulence • Insomnia	• Local skin reactions (erythema, pruritus, burning) • Headache • Sleep disturbances (insomnia, 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 • Cough • Headache • Rhinitis • Dyspepsia • Hiccups	• Insomnia • Dry mouth • Nervousness/ difficulty concentrating • Rash • Constipation • Seizures (risk is 0.1%) • Neuropsychiatric symptoms (rare; see Precautions)	• Nausea • Sleep disturbances (insomnia, abnormal/vivid dreams) • Constipation • Flatulence • Vomiting • Neuropsychiatric symptoms (rare; see Precautions)
Advantages	• Might satisfy oral cravings • Might delay weight gain • Patients can titrate therapy to manage withdrawal symptoms • Variety of flavors are available	• Might satisfy oral cravings • Might delay weight gain • Easy to use and conceal • Patients can titrate therapy to manage withdrawal symptoms • Variety of flavors are available	• Provides consistent nicotine levels over 24 hours • Easy to use and conceal • Once daily dosing associated with fewer compliance problems	• Patients can titrate therapy to rapidly manage withdrawal symptoms	• Patients can titrate therapy to manage withdrawal symptoms • Mimics hand-to-mouth ritual of smoking (could also be perceived as a disadvantage)	• Easy to use; oral formulation might be associated with fewer compliance problems • Might delay weight gain • 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

(*continued*)

Table 1.4 (*Continued*)

	Nicotine Replacement Therapy (NRT) Formulations						
	Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler	Bupropion SR	Varenicline
Disadvantages	• Need for frequent dosing can compromise compliance • Might be problematic for patients with significant dental work • Patients must use proper chewing technique to minimize adverse effects • Gum chewing may not be socially acceptable	• Need for frequent dosing can compromise compliance • Gastrointestinal side effects (nausea, hiccups, heartburn) might be bothersome	• Patients cannot titrate the dose to acutely manage withdrawal symptoms • Allergic reactions to adhesive might occur • Patients with dermatologic conditions should not use the patch	• Need for frequent dosing can compromise compliance • Nasal/throat irritation may be bothersome • 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	• Need for frequent dosing can compromise compliance • 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 with caution	• Seizure risk is increased • Several contraindications and precautions preclude use in some patients (see Precautions) • Patients should be monitored for potential neuropsychiatric symptoms[4] (see Precautions)	• May induce nausea in up to one third of patients • Patients should be monitored for potential neuropsychiatric symptoms[4] (see Precautions)
Cost/day[5]	2 mg or 4 mg: $1.89–$5.48 (9 pieces)	2 mg or 4 mg: $3.05–$4.38 (9 pieces)	$1.52–$3.40 (1 patch)	$4.12 (8 doses)	$7.35 (6 cartridges)	$2.38–$6.22 (2 tablets)	$5.96–$6.50 (2 tablets)

[1]Marketed by GlaxoSmithKline.

[2]Marketed by Pfizer.

[3]The US Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and theoretical concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit.

[4]In July 2009, the FDA mandated that the prescribing information for all bupropion- and varenicline-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a healthcare provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped due to neuropsychiatric symptoms, patients should be monitored until the symptoms resolve.

[5]Wholesale acquisition cost from Red Book Online. Thomson Reuters, September 2012.

Abbreviations: 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.

Nicotine replacement therapy

In clinical trials, use of an NRT significantly increases quitting rates, compared to placebo [101]. 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 rationale for 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 from nicotine. Key advantages of NRT are that patients are not exposed to the carcinogens or other toxic compounds found in tobacco and tobacco smoke. NRT provides slower onset of action than nicotine delivered via cigarettes, thereby eliminating the near-immediate reinforcing effects of nicotine obtained through smoking (Figure 1.1).

Because the efficacy of the various NRT formulations (gum, lozenge, transdermal patch, inhaler, nasal spray) are similar [101], selection should be based on patient preference. With the exception of the nicotine patch, which is dosed once a day, all NRT formulations require frequent administration to ensure adequate concentrations of nicotine to alleviate withdrawal. To maximize chances for success, clinicians should advise patients to take the full recommended number of doses each day and continue to adhere to the recommended regimen for the entire course of therapy. There are no specific contraindications to NRT use, but because nicotine stimulates the sympathetic nervous system and leads to increases in heart rate, myocardial contractility, and blood pressure, NRT products should be used with caution in patients who have serious arrhythmias, underlying serious or worsening angina pectoris, or a recent (within 2 weeks) myocardial infarction [101]. Because the blood levels of nicotine associated with the recommended doses of NRT products are generally lower than those attained through smoking, most experts contend that the risks associated with NRT use in patients with cardiovascular disease are minimal relative to the significant risks associated with continued smoking [112].

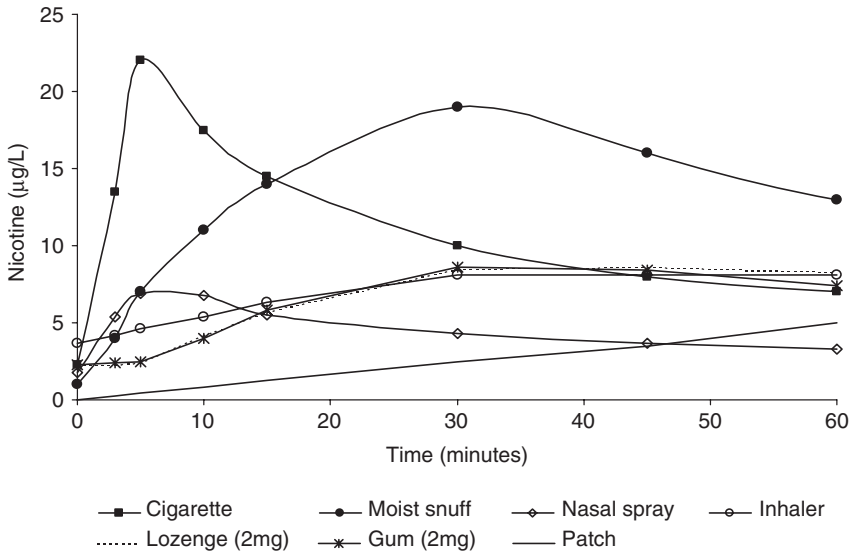

Figure 1.1 Plasma nicotine concentrations for various nicotine-containing products. *Source:* Reprinted from [108], with permission. Copyright © 1999–2014 The Regents of the University of California. All rights reserved. Plasma nicotine concentration curves derived from references [109–111].

Sustained-release bupropion

Initially marketed as an atypical antidepressant, sustained-release bupropion is hypothesized to facilitate smoking cessation by inhibiting the reuptake of dopamine and norepinephrine in the central nervous system [101] and acting as a nicotinic acetylcholine receptor antagonist [113]. These neurochemical effects are believed to modulate the dopamine reward pathway and reduce the cravings for nicotine and symptoms of withdrawal [101].

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. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion [114]. The incidence of seizures associated with the recommended 300 mg/day dose of the sustained-release formulation when used in the treatment of depression was 0.1% (1/1000) among patients without a previous history of seizures. 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.

In July 2009, the FDA mandated that the prescribing information for all bupropion-containing products include a black-boxed warning to highlight the risk of serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide. All patients being treated with bupropion should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. Patients should be advised to stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. Ongoing monitoring and supportive care should be provided until symptoms resolve [114].

Varenicline

The efficacy of varenicline, a partial agonist selective for the α4β2 nicotinic acetylcholine receptor [115, 116], 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 [116].

Similar to bupropion, in 2009 the FDA mandated that the prescribing information for varenicline include a black-boxed warning to highlight the risk of serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt and completed suicide. All patients being treated with varenicline should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. Patients should be advised to stop taking varenicline and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior [117].

More recently, a warning/precaution related to use among patients with known cardiovascular

disease was added to the manufacturer's labeling for varenicline. Specifically, patients should be instructed to notify their health care provider if they notice any new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. Although a meta-analysis of 15 clinical trials (including a trial in patients with stable cardiovascular disease) demonstrated that cardiovascular events were infrequent overall, some were reported more frequently in patients treated with varenicline, and these events occurred primarily among patients with known cardiovascular disease. In both the clinical trial and meta-analysis, however, all-cause and cardiovascular mortality was lower among patients treated with varenicline [117].

Combination therapy

While the use of a cessation medication approximately doubles the likelihood that a patient will successfully quit smoking, improvements in long-term quit rates are needed. Based on data from eight clinical trials, the 2008 *Clinical Practice Guideline* [101] recommends that clinicians consider the use of combination pharmacotherapy as a first-line treatment approach for patients during a quit attempt. Combination therapy approaches, which typically include a long-acting formulation (e.g., nicotine patch) in combination with a short-acting formulation (e.g., gum, lozenge, inhaler, or nasal spray) are being increasingly utilized. The long-acting formulation helps to prevent the onset of severe withdrawal symptoms while the short-acting formulation is used as needed to control situational cravings. Furthermore, the optimal combinations, dosages, and duration of dual NRTs are not yet known.

Use of medications in pregnancy

The *Clinical Practice Guideline* [101] states that pregnant smokers should be encouraged to quit without medication, because of insufficient evidence of effectiveness and hypothetical concerns with safety.

Animal data suggest that nicotine is harmful to the developing fetus. As such prescription formulations of NRT are classified by the FDA as pregnancy category D agents. Bupropion and varenicline are classified as a pregnancy category C drug. Correspondingly, the manufacturers recommend that this agent be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus [114, 117].

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 several 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 5 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 prevent smoking initiation among youth and implement at least brief interventions (Ask-Advise-Refer) at each encounter with a patient who uses tobacco.

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