

# Smoking and Health Hazards to all Generations: Everybody Matters

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## Introduction

Tobacco use remains the world's leading preventable cause of death and morbidity. Cigarette smoking has been identified as the most important source of preventable morbidity and premature mortality worldwide. The World Health Organization (WHO) reported that smoking killed 100 million people worldwide in the 20th century and warned that it could be the primary cause of death for one billion smokers in the 21st century.<sup>1</sup> The global tobacco death toll, currently at 5.4 million deaths every year, is expected to be more than 8 million deaths annually by 2030.<sup>1,2,3</sup>

In 1998, a historic legal landmark, the Master Settlement Agreement (MSA), was signed by the attorney generals of 46 states with the four largest tobacco companies in the United States (Brown & Williamson, Lorillard, Philip Morris and R.J. Reynolds Companies). This agreement was to reduce smoking initiation and prohibit tobacco advertising targeting people younger than 18 years of age. Unfortunately, this agreement appears to have had little effect on cigarette advertising in magazines and on the exposure of young people to these advertisements.<sup>4</sup> The supporting evidence on both sides of this battleground is that 90 percent of all adult smokers begin while in their teens, or earlier, and two-thirds become regular, daily smokers before they reach the age of 19. As many as 21.6 percent of high-school students are current smokers by the time they leave high school.<sup>5,6</sup>

Tobacco is a tall plant of the genus *Nicotiana*, with large, sticky leaves. Interestingly, the tobacco plant is closely related to the tomato and potato. The leaves of cultivated tobacco are chopped, dried, processed in preparation for use as smokeless tobacco (snuff or chew) or for smoking (cigarettes, cigars, small cigars or pipes). One species, *Nicotiana tabacum*, or common tobacco, is native to tropical America, Mexico and the West Indies, where it is widely cultivated for its leaves. It is the main source of commercial tobacco used to make cigarettes.<sup>7</sup>

The major states with extensive tobacco farming, and often cigarette manufacturing, are North Carolina, Kentucky, Virginia, South Carolina, Tennessee and Georgia. In 2008, the state with the highest tobacco tax was New York at \$2.75 per pack, and the lowest was South Carolina at 7 cents per pack.<sup>8</sup>

Tobacco use in the United States has passed through many stages of use. Native Americans commonly used tobacco in religious ceremonies. The colonists adopted tobacco for secular use and established it as a trading merchandise. Cigarettes were introduced around the mid-1700s. Toward the end of the 19th century, the more common types of smoking tobacco were cigars, pipes or roll-your-own cigarettes. At the end of the 19th century, less than 3 percent of all tobacco consumed was in the form of manufactured cigarettes, while more than 50 percent was consumed as chewing tobacco. By the mid-1900s, cigarette smoking became the most popular way to use tobacco. This increase in acceptance of cigarette smoking was due to changing social acceptance of the manufactured product as well as usage of milder, blended tobaccos, beginning around 1913. These changes allowed tobacco users to more efficiently absorb nicotine through inhalation than by the more classic absorption through the oral mucosa.

Smokeless tobacco (ST) use increased in the 1970s and early 1980s following the landmark 1964 Surgeon General's Report that identified tobacco smoking as the major cause of lung cancer. This report resulted in decreased smoking rates. As a result, tobacco companies increased advertising of smokeless tobacco, and the public was left with the message that smokeless tobacco was a safe alternative to smoking. In the United States, it has been estimated that 7.8 million people 12 years and older, regularly use smokeless tobacco.<sup>9</sup> Smokeless tobacco is associated with significant health risks and is not a safe alternative to smoking cigarettes. It contains the same chemicals as cigarettes (nicotine, carcinogens, pesticides) and can lead to nicotine addiction and dependence.<sup>10</sup> Holding one pinch of

smokeless tobacco in the mouth for 30 minutes delivers as much nicotine as three to four cigarettes.<sup>9</sup> Tobacco industries have also produced several products to circumvent federal and state laws in order to expand their market with new customers, youth and women.

**Tobacco Ingredients**

Cigarette smoke contains over 4,800 chemical substances, 69 of which are known to cause cancer.<sup>11</sup> Cigars contain the same addictive, toxic and carcinogenic compounds found in cigarettes. A single large cigar contains as much tobacco as an entire pack (20 per pack) of cigarettes.<sup>12</sup> Secondhand smoke is a mixture of the smoke given off by the burning end of a cigarette, pipe or cigar and the smoke exhaled from the lungs of smokers. Secondhand smokers are exposed to more than 250 chemicals known to be toxic or carcinogenic, including formaldehyde, benzene, vinyl chloride, arsenic, ammonia and hydrogen cyanide.<sup>13</sup> People exposed to environmental tobacco smoke (ETS), or sidestream smoke, are more vulnerable to higher exposures of toxic substances from the secondhand tobacco smoke. The average sidestream-to-mainstream ratios for the 15 brands of Canadian cigarettes (the declared tar yields range from 0.7 to 17 mg per cigarette) were 3.5, 6.6 and 6.8 for tar, nicotine and carbon monoxide, respectively. Interestingly, the highest yields of sidestream substances were obtained from the brands with the lowest mainstream yields. These findings emphasize the significant health effects of secondhand smoke regardless of the presence of a filter tip. Cigarettes with ventilated filters, on average, have mainstream tar, nicotine and carbon monoxide deliveries significantly lower than the non-ventilated brands. Contrary to these findings, most of the 15 brands tested (including unvented and ventilated filter) produced considerably higher yields of toxins in the sidestream than in the mainstream smoke (Table 1).<sup>14</sup>

Not only does smoking affect the health of firsthand smokers, but it also impacts the health of the secondhand smoker as shown in Table 2.

Chewing tobacco (plug and loose leaf ) and snuff (oral and

**Table 2. The dangers of secondhand smoke.<sup>15</sup>**

Health effects of secondhand smoke	The estimated annual excess number in the USA
Smoking in pregnancy:	
Low birth weight	24,500
Pre-term delivery	71,900
Asthma in children: Episodes	202,300
New cases	8,000-26,000 from OEHHA(1997)
Exacerbations	400,000-1,000,000 from OEHHA(1997)
Lower respiratory illness	150,000-300,000 from OEHHA(1997)
Otitis media visits	790,000
SIDS	430
Coronary artery disease death	46,000 (range 22,700-69,600)
Lung cancer death	3,400
Breast cancer: diagnosis in younger, primarily premenopausal women	Approximately 68-120 percent increased risk

\*OEHHA State of California Office of Environmental Health Hazards.

nasal) are the two most common forms of ST used in the United States. Chewing tobacco consists of the tobacco leaf with the stem removed and various sweeteners and flavor additives such as honey, licorice and rum. Oral snuff consists of an entire tobacco leaf that's dried and powdered or finely cut, with menthol, peppermint oil, camphor or aromatic additives such as attar of roses or oil of cloves. The user places a pinch between cheek and gum, and nicotine is then absorbed through the buccal mucosa. Nasal snuff is a fine tobacco powder that is sniffed into the nostrils. Flavoring may be added to nasal snuff during fermentation, while perfumes may be added after grinding.

Several carcinogens have been identified in ST: volatile and nonvolatile nitrosamines; polynuclear aromatic hydrocarbons; polonium-210 ( <sup>210</sup> Po); tobacco-specific N-nitrosamines (TSNAs) including N'-nitrosornicotine (NNN); and 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNN and NNK, the two most carcinogenic forms of the TSNAs, are formed during curing, aging and especially during fermentation of tobacco. The concentration of strongly carcinogenic TSNAs is higher in snuff than in other ST products.<sup>16</sup> Hoffman and

**Table 1. The average sidestream-to-mainstream ratio.**

The average sidestream-to-mainstream ratio for	Non-ventilated brands	Ventilated brands	All 15 brands
Tar	1.4	6.6	3.5
Nicotine	3.2	10.4	6.6
Carbon monoxide	3.1	11	6.8

Djordjevic found that the three leading snuff brands in the United States contain far higher concentrations of nicotine, unprotonated nicotine and TSNA than the less popular brands. They conclude that the leading U.S. snuff brands are the strongest inducers of nicotine dependence and also have the highest carcinogenic potential.<sup>17</sup> There are lower TSNA levels in Swedish brands of ST, which have only 2 percent of the TSNA amount compared to their U.S. counterparts. Swedish ST has maintained lower levels of TSNA over time, in contrast to the products sold in the United States due to lack of uniform manufacturing codes.<sup>18</sup> Unfortunately, there is no regulation and few restrictions on the advertising of ST products in the United States.

### *The pathogenesis of tobacco smoke and substances to health hazards*

#### **Nicotine Addiction**

Nicotine is recognized as the major inducer of tobacco dependence. Most of the nicotine is pyrolyzed during formation of tobacco smoke, which produces a sufficient dose to cause mild physical dependency and mild to strong psychological dependency. Harmane, one of the monoamine-oxidase-A (MAO-A) inhibitors, is formed from acetaldehyde in cigarette smoke and plays an important role in addiction by blocking MAO-A. MAO-A is the enzyme which breaks down dopamine, so blocking this enzyme eventually results in an increase in brain dopamine. Nicotine has a chemical structure similar to acetylcholine. Nicotine use has a pleasurable effect that triggers positive reinforcement by increasing release of dopamine in the brain, especially in the mesolimbic pathway, nucleus accumbens. This is the same neuro-reward circuit activated by abused drugs such as heroin and cocaine.<sup>19</sup> Nicotine probably facilitates dopamine release in the brain via cholinergic receptors. Nicotine tolerance may be explained by changes in both the number and sensitivity of cholinergic receptors in the regular nicotine user. The beta subunit of the cholinergic receptor plays a critical role in mediating the pleasurable effects of nicotine. Nicotine has both somatic and psychological effects. Compared to ethanol, cocaine and heroin withdrawal effects, nicotine has a lower potential for somatic dependence. In contrast, nicotine's potential for psychological dependency exceeds all other studied drugs.<sup>20</sup> This is the main reason for difficulty in quitting smoking, despite well known harmful and even lethal effects. In fact, at least 90 percent of current smokers would like to quit, but fewer than 10 percent who try are actually successful each year. The important message from all the studies supports prevention programs against

tobacco use.

#### **Carcinogenicity**

The most important families of carcinogens in tobacco are polycyclic aromatic hydrocarbons, aromatic amines, nitroso compounds including nitrosamines, volatile compounds such as benzene, and radioelements such as polonium-210.

Molecular techniques have been applied to the epidemiology of tobacco-related cancer and have made three general types of measurements:

1. Internal exposure, including the dose at the presumed target tissue (DNA);
2. Early biological effects, particularly mutations and cytogenetic damage, likely to be predictive of cancer; and
3. Variations in individual susceptibility to carcinogens, mainly via metabolic polymorphisms.

The TSNA, substances formed from nicotine during tobacco processing and smoking, as well as the minor tobacco alkaloids including NNN, NNK, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), have been shown to be significant carcinogens. TSNA are procarcinogens, agents which require metabolic activation to become carcinogenic. The active forms of TSNA react with cellular components, including DNA and hemoglobin. Several pyrolysis products of tobacco smoke bind to DNA and can cause genetic mutations. Polynuclear aromatic hydrocarbons (PAH) in smoke are changed to mutagenic epoxides which can irreversibly attach to DNA killing the cell or causing a genetic mutation. Among the respiratory carcinogens known as PAHs, benzopyrene associated with smoking forms adducts with DNA in cells in the lung.<sup>21</sup> These adducts in the guanine bases of DNA are in accordance with the main type of mutations (G to T transversions) found in the K-ras oncogene and p53 tumor-suppressor gene in some cancers.

Several lines of evidence indicate that aromatic amines from tobacco smoke are relevant to bladder carcinogenesis,<sup>22</sup> especially in air-cured tobacco, which is higher in arylamines (4-aminobiphenyl and 2-naphthylamine) when compared to flue-cured tobacco.<sup>23</sup> About 50 percent of bladder cancers in men living in Western countries are attributable to smoking.<sup>24</sup> Cancers of the esophagus, larynx, pharynx and oral cavity are also more strongly associated with air-cured (higher concentrations of NNN and NNK) than flue-cured tobacco smoking.<sup>25,26,27</sup> The finding of increased DNA adducts in the cervical epithelium of smokers suggests a potential mechanism for the increased

Table 3. Detail of correlation of cancers, carcinogens and genetic derangements.

Types of cancer	Known carcinogens or precursor lesions	Genetic derangement / Oncogenes	Time consequences
Lung especially adenocarcinoma	PAHs, NNK, and other carcinogens	DNA adducts induce mutations: <i>K-ras</i> , <i>MYC</i> , <i>p53</i> tumor suppressor gene, <i>p16</i> , <i>RB</i> , <i>FHIT</i>	Lag or latent period about 20 years
Oral cavity and pharyngeal cancers	Erythroplasia and leukoplakia are precursor lesions	Chromosome loss at 9p21, inactivation of <i>p16/INK 4a</i> , increase <i>p53</i> protein levels, loss of 3p21 region, amplification of <i>cyclin D1</i>	Dose-response (snuff type smokeless tobacco and smoke), no definite lag period, synergist with alcohol drinking.
Esophageal cancer	Premalignant lesions, Barrett's esophagitis	Loss of chromosome region 9p21, <i>p16 INK 4a</i> , increase <i>p53</i> protein level	Dose-response, no definite lag period, synergist with alcohol drinking.
Pancreatic cancer	NNK, aromatic amines	K-ras mutation	Dose-response, no definite lag period, synergist with alcohol drinking.
Bladder and kidney cancers	N-nitrosodimethylamine	P53 mutation	Dose-response, no definite lag period
Cervical cancer	Nicotine, NNK	DNA adducts	Dose-response, no definite lag period
Stomach cancer	Susceptible to <i>H.Pyrol</i> , benzo(a) pyrene, dibenz(a,h)anthracene, 7H-dibenzo(c,g)carbarole, n-nitrosodi-n-butylamine, and n-nitrosodi-ethylamine	P53 mutation, deleted DCC gene, <i>DPC4</i> and <i>madd</i>	Dose-response, no definite lag period

Adapted from Surgeon General Report 2004.<sup>29</sup>

risk of cervical cancer in these patients.<sup>28</sup> A summary of carcinogenic activity related to tobacco is shown in Table 3.

### Cardiovascular Effects

Inhaling cigarette smoke increases both heart rate and blood pressure. Atherosclerosis is the consequence of a complex pathogenic process whose clinical expression results from multiple events occurring at the vascular wall. The presence and extent of atherosclerosis is quantitatively related to smoking, which appears to accelerate the atherogenic process in both a dose- and duration-dependent manner.<sup>30,31</sup> Atherosclerosis is the main pathophysiologic process of most clinically significant manifestations of cardiovascular disease (CVD), including coronary artery disease (CAD) or coronary heart disease (CHD), stroke (cerebrovascular disease) and peripheral arterial disease

(PAD). The increase in blood pressure and peripheral vascular resistance seen immediately after smoking one cigarette, which is more pronounced with aging, is directly proportional to the increase in plasma nicotine concentration.<sup>32</sup> This hemodynamic effect is largely secondary to nicotine, of which 50 to 150 micrograms are absorbed with each puff. Nicotine acts as an adrenergic agonist mediating catecholamine release, with nicotine exposure resulting in increased circulating norepinephrine and epinephrine levels.<sup>33</sup> Other than CHD, cigarette smoking is a major cause of sudden death, stroke, peripheral vascular disease and aortic aneurysm.<sup>34-37</sup>

Cigarette smoking acts synergistically with two other major CHD risk factors, hypertension and hyperlipidemia, to markedly increase the risk of CHD. Oral contraceptive use is

also synergistic with smoking to substantially increase the risk of myocardial infarction, subarachnoid hemorrhage and stroke in women.<sup>38,39</sup>

Smoking causes endothelial dysfunction, dyslipidemia (decreased high-density lipoprotein cholesterol [HDL], hypertriglyceridemia and increased oxidation of low-density lipoprotein cholesterol [LDL]) and platelet activation. As a result, tobacco smokers are prone to a prothrombotic state. Smoking two cigarettes increases platelet activation over 100 fold.<sup>40</sup> The continuous stimulation of intimal cells by oxidized LDL leads to development of atherosclerosis. Smoking also increases emerging CHD risk factors such as fibrinogen levels, highly sensitive C-reactive protein, insulin resistance and risk of diabetes mellitus. The beneficial effects of statins and antioxidants are counteracted by

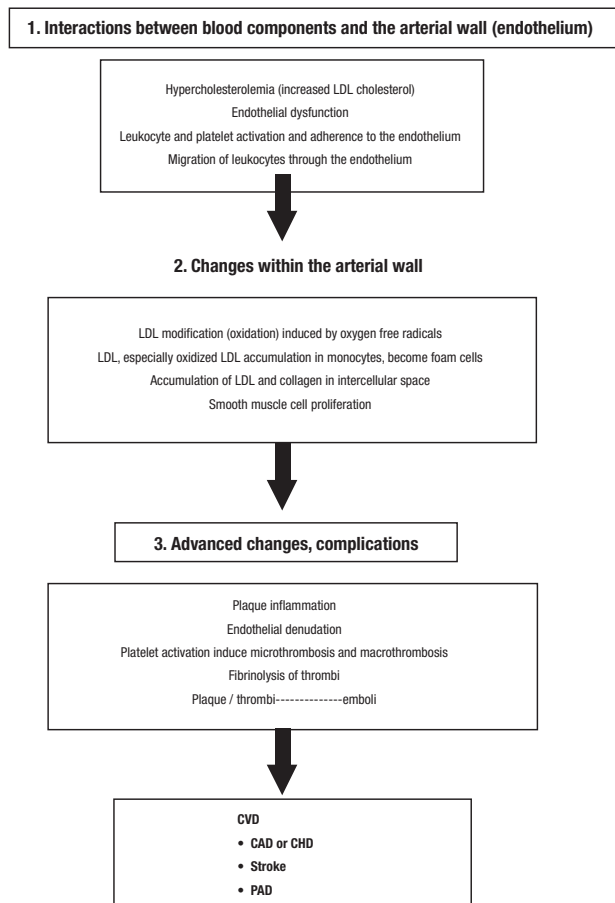
smoking. Smoking also induces alterations in growth molecules and gene expression which can accelerate the progression of atherosclerosis. Nicotine stimulates the release of catecholamines by free radicals and aromatics, then diminishes the endothelial synthesis of nitric oxide which causes impaired relaxation of arteries, the earliest signs of endothelial dysfunction.<sup>41</sup> According to “The Strong Heart Study,” the lower prevalence of CHD among Indians in Arizona is distinctive in view of their higher rates of diabetes, obesity, hypertension and albuminuria. This may be partly explained by their lower frequency of smoking and lower concentrations of total and low-density lipoprotein cholesterol.<sup>42</sup> This finding supports the importance of tobacco smoking contributing to other risk factors of CHD.

The effects of tobacco smoke on the body’s circulation produce a substantial shift in the hemostatic balance at the endothelium, leading to atherosclerosis and its thrombotic complications. The summary of basis pathogenesis of atherosclerosis is shown in Figure 1. In addition to direct effects of tobacco smoke on the vascular endothelium, it also diminishes the ability of blood to carry oxygen (carbon monoxide) and increases the physiologic demand of the myocardium. The net result of the above mechanisms is a reduction in oxygen delivery to the heart and peripheral tissues.

**Respiratory System**

Smoking has adverse health effects on the entire lung – affecting every aspect of lung structure and function – including impairing lung defenses against infection and causing sustained lung injury by damaging airways and alveoli that lead to chronic obstructive pulmonary disease (COPD). The mechanisms of smoking-induced COPD are a complex interplay among a number of biologic processes including oxidative stress, inflammation, protease-antiprotease imbalance, unbalanced repair processes and genetic variations that control these processes. The inhalation of tobacco smoke exposes the lungs to high concentrations of oxidants and free radicals, which can induce cellular injury. This epithelial injury results in the release of several proinflammatory mediators such as cytokines from epithelial cells, as well as an influx of inflammatory cells, such as lymphocytes and macrophages, in the airway walls. This process initiates an inflammatory cascade within the lung. If this injury is sustained, permanent change occurs in the structure and function of small airways which is fundamental to the development of smoke-induced COPD. An imbalance between proteases and antiproteases causes the inflammatory processes to extend into the peribronchiolar

Figure 1. Basic pathogenesis of atherosclerosis.<sup>29</sup>



alveoli and destroy the alveolar walls, which is a hallmark of emphysema. Smoking is related to chronic coughing and wheezing among adults. Smokers are more likely to have upper- and lower-respiratory tract infections because smoking suppresses immune function. In general, smokers’ lung function declines faster than that of nonsmokers.<sup>29</sup>

**Pregnancy and Fetus**

Substantial evidence shows that pregnant women who smoke have babies with lower birth weight compared to nonsmoking women at an average of 200 g Preterm delivery – adjusted odd ratio (OR) of 1.27 – spontaneous abortion (OR 1.2 for each 10 cigarettes per day), increased perinatal mortality, abruptio placenta (ORs range 1.4 to 2.4), placenta previa (OR 1.3 to 4.4), bleeding, ectopic pregnancy, and premature rupture of the membranes (ORs range from 1.6 to 2.1) are all increased in pregnant women who smoke. There is a strong dose-response relationship between smoking and the above conditions.<sup>29</sup>

Maternal smoking exerts a direct, growth-retarding effect

on the fetus, which is partly explained by decreasing intervillous blood flow. Maternal smoking also increases the risk for perinatal mortality – both stillbirth and neonatal deaths – and the risk for sudden infant death syndrome (SIDS). Umbilical arteries from the umbilical cords of infants born to smoking mothers showed endothelial changes when compared to those from nonsmoking mothers. These changes included subendothelial edema or swelling, widening of the intercellular junctions, distension of endoplasmic reticulum, and increased numbers of mitochondria.<sup>43,44,45</sup> Umbilical arteries from the placentas of smoking women showed significantly more inter and intracellular holes in the endothelium when compared to nonsmoking women.<sup>46</sup> The other health consequences of maternal smoking have been extensively reviewed and are available online at the Web site of the Surgeon General.

**Tobacco Control and Prevention Program**

In 2003, the WHO’s World Health Assembly unanimously adopted the WHO Framework Convention on Tobacco Control in order to galvanize action against the worldwide tobacco epidemic. The best way to fight tobacco use in any form is preventing initial exposure to tobacco. Once tobacco use is started, it is more difficult to quit using. In addition, polytobacco use is common in adolescents (62 percent in male and 30.9 percent in female).<sup>47</sup> Polytobacco use is associated with being male, middle-school age, residing outside of the Northeast, able to obtain cigarettes from a retailer, subject to peer influence, having favorable beliefs about tobacco, willing to use tobacco promotional items, being exposed to tobacco advertisements and having higher levels of lost autonomy. The overall strategies of tobacco industries to gain more revenue with reduced expense are shown in Figure 2.

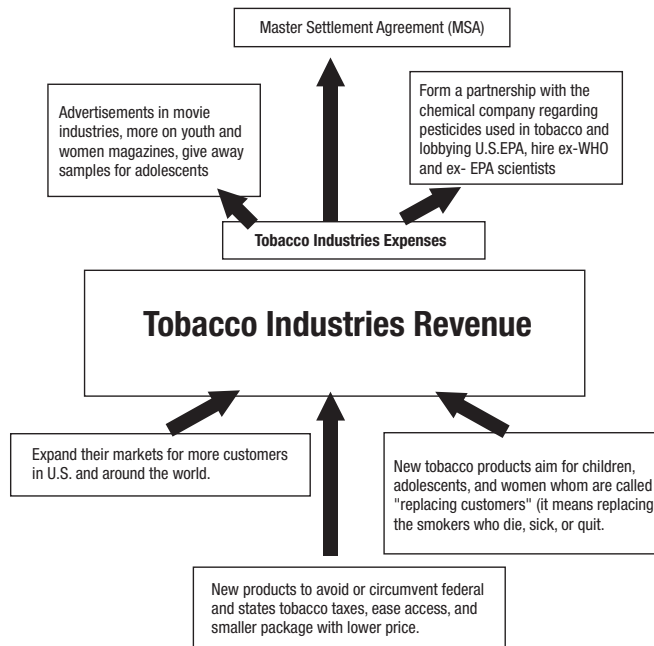
In 2008, the WHO introduced the MPOWER package of six proven policies:

- Monitor tobacco use and prevention policies;
- Protect people from tobacco smoke;
- Offer help to quit tobacco use;
- Warn about the dangers of tobacco;
- Enforce bans on tobacco advertising, promotion, and sponsorship; and
- Raise taxes on tobacco.

With adaptation of the MPOWER policy, the measures can reverse the tobacco epidemic and prevent millions of tobacco-related deaths around the world.

In May 2008, the U.S. Department of Health and Human Services published clinical practice guidelines on treating

**Figure 2. Overview of the tobacco industry's revenue and expenses.**



tobacco use and dependence.<sup>48</sup> Clinicians are in the position to offer and recommend effective tobacco dependence counseling and medications to their patients who use tobacco. Health systems, insurers and purchasers should assist clinicians in making such effective treatment available to smokers. The important messages from these clinical practice guidelines are as follows:

1. Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. This requires clinicians and health care delivery systems to identify, document the status, counsel and encourage the patient to quit and treat every tobacco user seen.
2. Tobacco dependence treatments are effective, even if brief. Two components of counseling (practical counseling and social support) are effective in addition to individual, group and telephone counseling. Several effective medications are available for tobacco dependence, including five nicotine and two non-nicotine first-line medications. These medications are nicotine gum, inhaler, lozenge, nasal spray, patch, bupropion SR and varenicline.
3. Counseling, telephone quit-line counseling and medications are effective in encouraging and treating all tobacco-dependent patients. The treatments are both clinically effective and highly cost-effective. All insurance plans should include the counseling and

effective medications for tobacco dependence as covered benefits.

### Conclusion and Recommendation

The most effective treatment in medicine is prevention. As recent data from the Home Automatic External Defibrillator Trial (HAT) showed, there was no significant reduction in death from any cause with home AED usage. These results suggest that future efforts should focus on education, modification of risk factors and other methods

for primary prevention of heart disease, with less emphasis on improbable resuscitation.<sup>49,50</sup> This suggestion may be applied to tobacco smoke prevention policy – encouraging quitting, treating tobacco-dependent individuals and putting into action laws and regulations to prevent the worldwide tobacco epidemic. As stated by Johann Wolfgang von Goethe (1749-1832), “Knowing is not enough; we must apply. Willing is not enough; we must do.”

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